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A HISTOLOGICAL STUDY OF THE THYROID
GLANDS OF C3H AND C57 MICE

Thesis for the Degree of M. S.
MICHIGAN STATE COLLEGE
Barbara G. Beaman
1952

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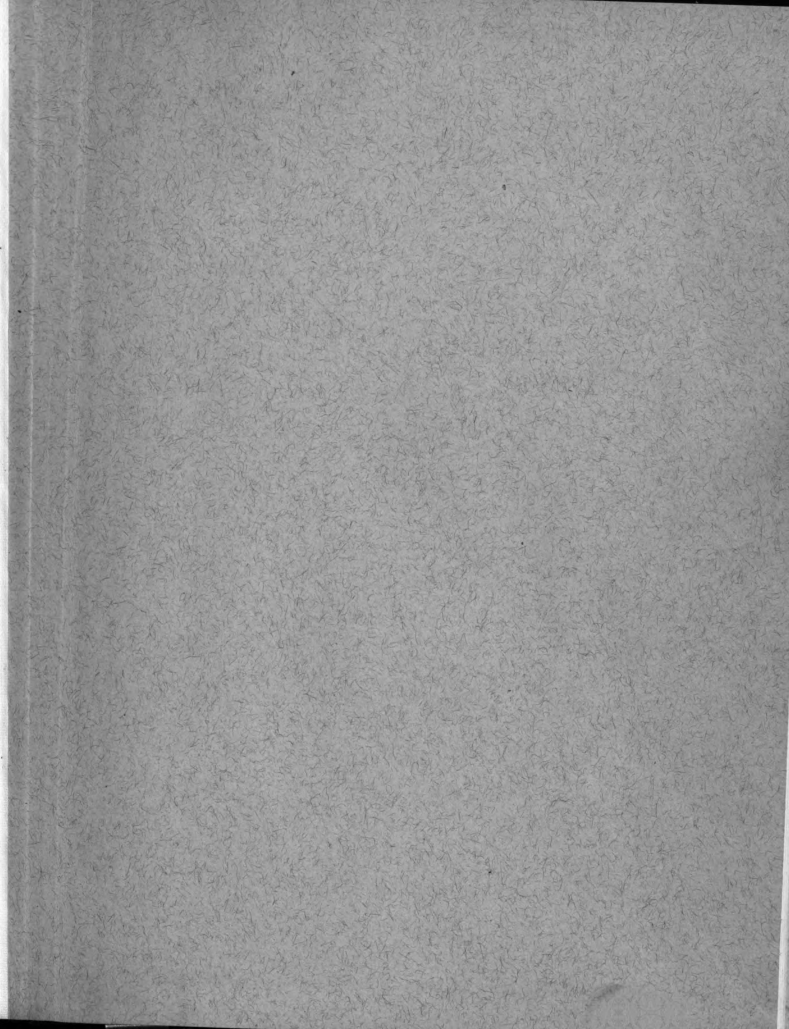
has been accepted towards fulfillment
of the requirements for

M.S. degree in Zoology

R. A. Jennell

Major professor

Date March 14, 1952.



A HISTOLOGICAL STUDY OF THE THYROID GLANDS
OF C3H AND C57 MICE

By

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A THESIS

Submitted to the School of Graduate Studies of Michigan
State College of Agriculture and Applied Science
in partial fulfillment of the requirements
for the degree of

MASTER OF SCIENCE

Department of Zoology

1952

ACKNOWLEDGMENTS

The author wishes to express her sincere appreciation to the staff of the Zoology Department of Michigan State College and especially to Dr. R. A. Fennell, under whose auspices this study was conducted.

Grateful thanks is also due to the staff of The Roscoe B. Jackson Memorial Laboratory and to those that made it possible for most of the research to be conducted there.

Acknowledgment is also due Dr. W. R. Breneman for his advice concerning the statistical analyses.

VITA

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I. INTRODUCTION

The observations of Little et al. (1939) showed a low incidence of mammary tumors in C57 female mice. Later, Andervont (1949) reported a high incidence in breeding C3H females. Husely and Bittner (1946) maintained that the following intricately interrelated factors are important in mammary tumor development: (1) inherited susceptibility; (2) hormonal stimulation of the mammary glands; and (3) the milk factor.

Bischoff et al. (1931 and 1932), Mercier and Gosselin (1935), and Salter et al. (1940) concluded that thyroxine administration did not effect tumor incidence in mice. Histological investigations made on mice supported this view. Twort and Twort (1935) did not demonstrate a relationship between size of the thyroid and tumor incidence. Later Barry and Kennaway (1937), who investigated the thyroid in five strains of mice, maintained that there is no correlation between thyroid appearance and incidence of tumors. Lacassagne (1939) and Haagen-sen et al. (1940) maintained that the thyrotrophic hormone of the pituitary gland failed to prevent mammary tumors in mice. Sugiura (1935), Ferguson et al. (1940), and Smith et al. (1942)

concluded that thyroxine had no effect on tumor proliferation in rats. Lerman (1947) maintained that thyroid function did not influence development and growth of either experimental or human cancer.

The results of Gross and Schwartz (1951) who studied thyroid hormone concentration and elimination (using thyroxine labeled with I^{131}) in both the C3H and C57 strains of mice, suggested that an increased level of thyroxine in C3H mice increased the responsiveness of the mammary glands to gonadal hormones. Support is given to this view by the work of Levine and Kugel (1933), Vasquez-Lopez (1940), Morris and Dubnik (1946), and Dubnik et al. (1950), who demonstrated that administration of antithyroid drugs decreased the development and incidence of mammary tumors in mice. Larinow (1940) found that height of the follicular epithelium was decreased in mice with benzpyrene-induced cancer. McJunken et al. (1936) showed that removal of the thyroids and parathyroids induced regression of sarcoma in rats. Shipata (1929) found that thyroidectomized rabbits showed an increased resistance to epithelial proliferation subsequent to tarring.

Another view in regard to the relationship between thyroxine concentration and tumor incidence was advanced by Gilroy (1930). He concluded that thyroxine inhibited tumor growth. Likewise, Moppet (1937) and Meyer and McTiernan (1933), who studied the effect of thyroxine on transplanted tumors, suggested that tumor growth is retarded by thyroxine administration. This view is supported by the work of Cramer and Horning (1938), who showed that mammary tumor appearance was inhibited by the thyrotrophic hormone of the pituitary gland, and that of Karnicki (1932) who demonstrated an acceleration of tumor growth in thyroparathyroidectemized rats. McClendon (1939) and Chidester (1944) suggested that the thyroxine may play an important role in human cancer development.

It was shown in the preceding paragraphs that three views were presented in regard to the relationship between the thyroid hormone and tumor incidence, i.e., (1) thyroxine did not effect tumor incidence; (2) thyroxine increased tumor proliferation; and (3) thyroxine inhibited tumor development.

It is the objective of this study to compare the thyroid glands in various ages of C3H mice with those of C57 mice of essentially the same ages from the viewpoint of obtaining

additional information about the relationship between histological structure of the thyroid and mammary tumor development.

II. MATERIALS AND METHODS

Breeding pairs of C3H Andervont and C57 black line 6 mice were obtained from the Jackson Memorial Laboratory. Animals were maintained by brother-sister mating. The thyroid gland was removed for histological study from 1-8 animals ranging in age from 1-26 months. If, on autopsy, any pathological condition was found in either males or females other than spontaneous mammary tumors in C3H females, the mouse was discarded.

Mice were killed by severing the spinal cord with pressure applied to the occipitocervical region by means of the thumb and index finger. The skin, underlying fascia, and submaxillary glands, were removed from the ventro-cervical region and then the thyroids were extirpated by severing the trachea above and below the glands (Fig. 1). They were fixed in Bouins' fluid and stained with haematoxylin and eosin.

All follicles measured were in a line through the middle of the gland extending from the medial to the lateral aspect (Fig. 2). A Bausch and Lomb ocular micrometer x 20 and a x 48 objective were used for measurement of the follicular diameter. Height

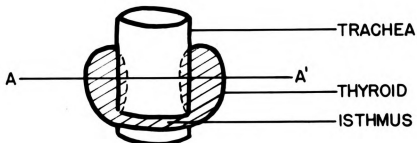


FIG. 1. VENTRAL VIEW OF THYROID AND TRACHEA.

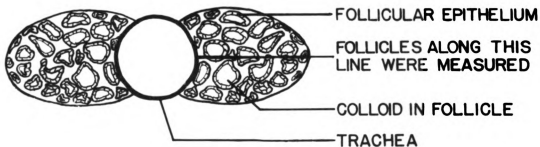


FIG. 2. DIAGRAMMATIC CROSS-SECTION THROUGH A-A' OF FIGURE 1.

of the follicular epithelium was measured with a x 96 objective and a x 20 ocular micrometer. Both follicle diameter and epithelial height were obtained by making ten measurements on each of the one hundred individuals used in this study. The arithmetic means obtained for epithelial heights and diameters of the ten follicles were used in the statistical analyses. Conversion of all measurements to microns was made with a standardized haemocytometer.

III. OBSERVATIONS

General Histology

The thyroid gland in the mouse consists of right and left lobes symmetrically located on the ventral and lateral surfaces of the trachea. The lobes, which are surrounded by a thin fibrous capsule, are connected caudally by an isthmus which transverses the ventral side of the trachea (Fig. 1). The histological structure of the isthmus is essentially the same as that of the gland proper. However, the follicles of the former are smaller and more uniform in size. The homogeneous colloidal material which fills the lumen of the follicle stains well with acid dyes. The cuboidal follicular epithelium exhibits well-defined spherical nuclei with an abundance of chromatin. Follicles are invested by an irregular interfollicular reticular connective tissue which is abundantly supplied with blood and lymph. The height of the follicular epithelium is closely correlated with the secretory activity of the gland, i.e., a high epithelium shows a greater secretory activity than a lower epithelium. The diameter of the follicle (epithelium plus colloid) is inversely related

to the height of the epithelium, i.e., an increased amount of colloidal material is correlated with a decreased epithelial height. In general, follicles in the peripheral portion of the gland were largest, medially located ones were smaller, and those nearest the trachea were smallest.

The parathyroids, which are usually located along the posterior and lateral surfaces of the thyroid and separated from it by connective tissue capsules, consist of densely packed cords of cells.

It was found in this study that tumor-bearing mice and those with other types of pathological manifestations showed thyroids that appeared less vascular than those found in normal animals. One particularly interesting case, not included in the statistical analyses, is worthy of review. Tissue enlargements approximately 2 cm. in diameter and resembling goitres were noted in the thyroid region. An autopsy revealed essentially normal thyroid tissue and cystic lymph nodes at approximately the same location on each submaxillary gland.

The Relation Between Thyroid Morphology, Age, and Sexuality

One hundred individuals were used to ascertain the relation between thyroid morphology, age, and sexuality; namely, 25 C3H females, 21 C3H males, 25 C57 females, and 29 C57 males. The results obtained are presented in Table I and Figures 3-6, inclusive. In some age groups the data were interpolated.

Table I and Figure 3 show that in C3H females epithelial height decreased from 6.17 microns at one month to 4.66 microns at three months, increased to 7.47 microns at six months, decreased to a second minimum of 5.37 microns at nine months, and then increased to a second maximum of 6.89 microns at fourteen months. Correspondingly, in the C3H males there was a decrease in epithelial height from 8.27 microns at one month to 4.44 microns at three months, an increase to a maximum of 8.06 microns at seven months, a decrease to 5.09 microns at ten months, and at fourteen months it increased to a second maximum of 7.63 microns. A t value of 0.400 demonstrated that sexuality did not significantly influence the height of the follicular epithelium in C3H mice.

Table I shows the mean epithelial height and mean diameter of the thyroid follicles in males and females in both C3H (tumor susceptible) and C57 (tumor resistant) strains of mice.

TABLE I

COMPARISON OF MALES AND FEMALES IN C3H AND
C57 LINES OF MICE

(all measurements in microns)

Age in Months	C3H Females			C3H Males		
	No. Ind.	Mv. ^a Fol. ^b Ep. Ht.	Mv. Fol. Diam.	No. Ind.	Mv. Fol. Ep. Ht.	Mv. Fol. Diam.
1	4	6.17	44.44	1	8.27	64.26
2	3	5.65	43.39	3	5.54	49.69
3	1	4.66	34.75	2	4.44	55.93
4	* ^c	5.41	44.03	1	5.09	52.60
5	1	6.15	53.31	1	5.09	45.93
6	2	7.47	56.64	1	6.89	66.16
7	3	6.36	71.16	1	8.06	77.11
8	*	5.87	73.10	1	7.21	55.45
9	3	5.37	75.04	2	6.10	62.95
10	5	6.16	66.35	3	5.69	60.29
11	2	6.30	65.02	2	7.47	76.63
12	*	6.50	76.59	*	7.52	71.56
13	*	6.70	88.16	*	7.58	74.08
14	1	6.89	99.72	1	7.63	69.02
15	0	-	-	1	6.15	70.21
16	0	-	-	0	-	-
18-26	0	-	-	1	7.00	64.74
Total ind.	25			21		
Mv. and S.E. ^d		6.13 =.24	60.29 =3.26		6.28 =	61.26 =1.92
t value ^e		C3H: ep. ht., 0.400; diam, 0.257				

^a Mv., arithmetic mean.^b Fol., thyroid follicle.

TABLE I (Continued)

Age in Months	C57 Females			C57 Males		
	No. Ind.	Mv. Fol. Ep. Ht.	Mv. Fol. Diam.	No. Ind.	Mv. Fol. Ep. Ht.	Mv. Fol. Diam.
1	3	7.88	36.97	3	9.01	46.19
2	2	6.99	36.29	3	6.43	33.16
3	*	6.67	34.27	4	6.54	37.24
4	*	6.36	32.25	*	6.87	39.98
5	1	6.04	30.23	2	7.20	42.72
6	3	7.03	56.17	2	7.52	48.07
7	2	5.83	54.74	2	9.27	47.60
8	2	8.95	51.56	2	10.07	54.93
9	2	8.03	55.21	2	6.68	49.67
10	*	8.04	58.86	*	7.34	51.16
11	*	8.05	62.51	*	7.99	52.65
12	1	8.06	66.16	*	8.65	54.14
13	*	7.24	60.21	*	9.30	55.63
14	2	6.41	54.26	1	9.96	57.12
15	0	—	—	*	9.12	65.81
16	0	—	—	1	8.27	74.49
18-26	7	7.22	52.34	7	7.89	55.18
Total Ind.	25			29		
Mv. and S.E.		7.72 ±.35	49.85 = .61		7.84 =.27	47.96 =2.08
t value		C57: ep. ht., 0.027; diam., 0.566				

^c *, interpolated data.

^d S.E., standard error of mean.

^e t value, Snedecor (1946).

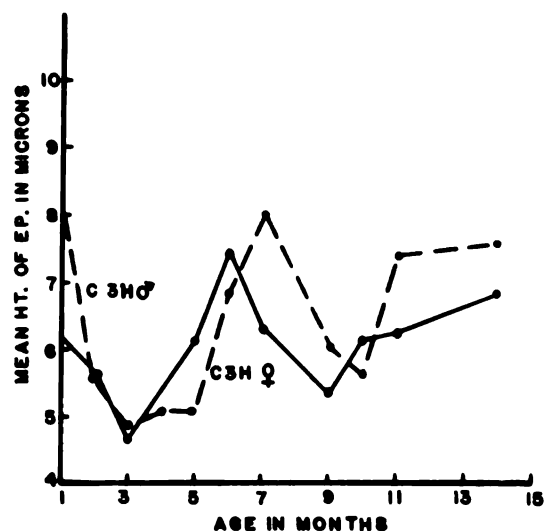


FIG. 3. EPITHELIAL HEIGHT OF THYROID FOLLICLES OF C3H MALES AND FEMALES.

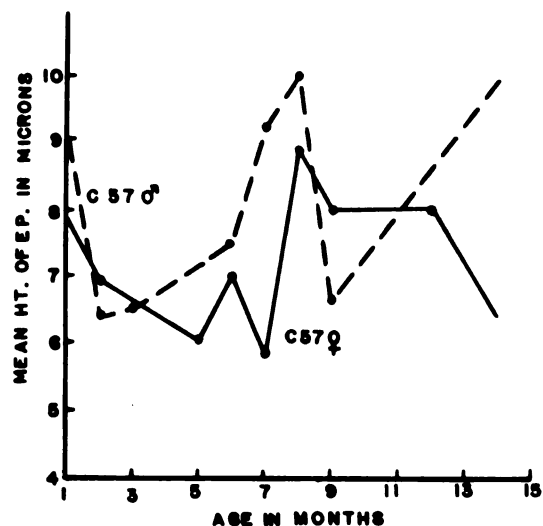


FIG. 4. EPITHELIAL HEIGHT OF THYROID FOLLICLES OF C57 MALES AND FEMALES.

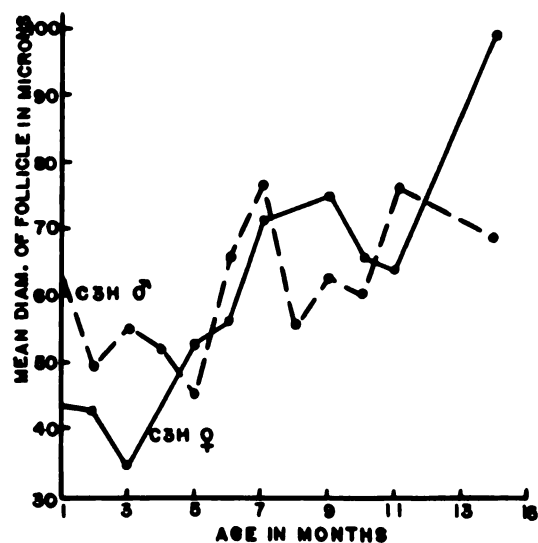


FIG. 5. THYROID FOLLICLE DIAMETERS OF C3H MALES AND FEMALES.

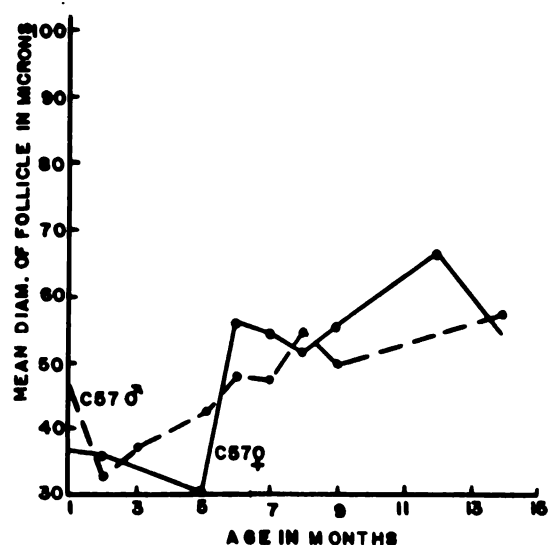


FIG. 6. THYROID FOLLICLE DIAMETERS OF C57 MALES AND FEMALES.

A comparison of Figure 3 with Figure 4 shows that epithelial height in C3H and C57 males and females exhibited the same pattern of variability at corresponding ages. A *t* value of 0.027 demonstrated that epithelial height in C57 males and females was essentially the same.

Table I and Figure 5 show that in C3H females the diameter of the thyroid follicles decreased from 44.44 microns at one month to 34.75 microns at three months, increased to a maximum of 75.04 microns at nine months, and after decreasing again at eleven months, increased to a second maximum of 99.72 microns at fourteen months. Likewise, the C3H males manifested a decrease from 64.26 microns at one month to 45.93 microns at five months, increased to a maximum of 77.11 microns at seven months, decreased to 55.02 microns at eight months, and then it increased to a second maximum of 76.63 at eleven months. A *t* value of 0.257 obtained from this data showed that sexuality did not influence the diameter of the thyroid follicles in C3H mice. The follicle diameters in C57 males and females (Fig. 6) followed the same trends as those in C3H mice, i.e., they showed essentially similar age variations and were not influenced by the sex of the individuals.

The Relation Between Strain Difference and Thyroid Morphology

Table II and Figures 7 and 8 show the results obtained in the comparison of 46 C3H mice with 54 C57 mice. The height of the epithelium and the diameter of the follicles followed essentially the same trends as noted in the preceding comparisons of males and females, since the present analyses were made after combining the data obtained from these males and females. Age played a consistent and important role; however, the data could not be fitted into a linear or curvilinear regression. Some significance is attached to the t values derived from the data in Table II, i.e., t equaled 1.23 and 5.68 for epithelial height and diameter respectively.

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Comparison of Three Corresponding Age Groups in C3H and C57 Mice

In Table III and Figures 9 and 10 the animals are divided into three age groups, i.e., groups I, II, and III represent mice 1-4, 5-7, and 8-16 months of age, respectively. Each group consists of 9-21 individuals.

It is evident in Table III and Figures 9 and 10 that the height of the follicular epithelium in C57 mice of age groups

Table II shows the mean epithelial height and mean diameter of the thyroid follicles of C3H and C57 Mice.

TABLE II
COMPARISON OF THE THYROID GLANDS OF
C3H AND C57 MICE
(all measurements in microns)

Age in Months	No. C3H Indiv.	No. C57 Indiv.	Mean Ep. Ht.		Mean Diameter	
			C3H	C57	C3H	C57
1	5	6	6.59	8.45	54.35	41.58
2	6	5	5.60	6.66	46.59	34.73
3	3	4	4.80	6.54	45.34	37.24
4	1	*	5.00	6.72	52.60	36.86
5	2	3	5.62	6.82	49.62	36.48
6	3	5	7.26	7.23	61.40	52.12
7	4	4	6.86	7.55	74.14	51.17
8	1	4	7.21	9.52	55.45	53.25
9	5	4	5.66	7.61	68.99	52.44
10	8	*	5.99	7.76	63.32	57.01
11	4	*	6.89	7.91	70.83	61.58
12	*	1	7.01	8.06	75.34	66.16
13	*	*	7.14	7.83	79.85	60.93
14	2	3	7.26	7.60	84.37	55.69
15	1	*	6.15	7.94	70.21	65.24
16	0	1	—	8.27	—	74.79
18-26	1	14	7.00	7.56	64.74	53.76
Total	46	54				
Mean and standard error			6.19 ±.18	7.78 ±.21	60.73 ±9.73	48.83 ±1.63
t value			1.23		5.68	

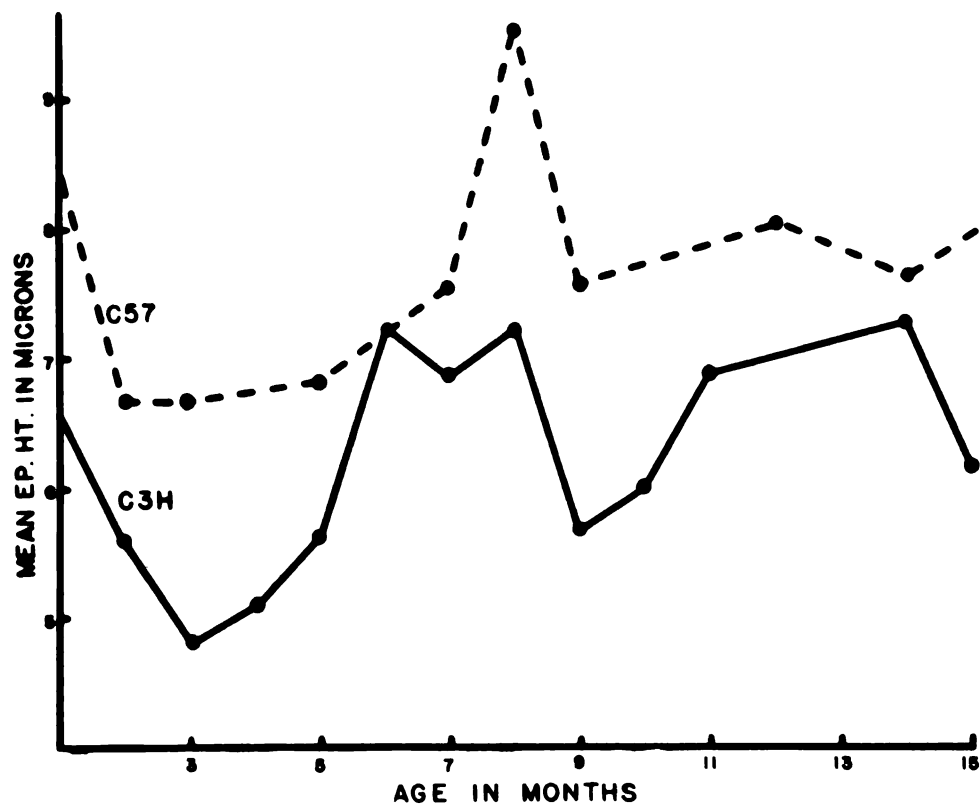


FIG. 7. EPITHELIAL HEIGHT OF THE THYROID FOLLICLES OF C3H AND C57 MICE.

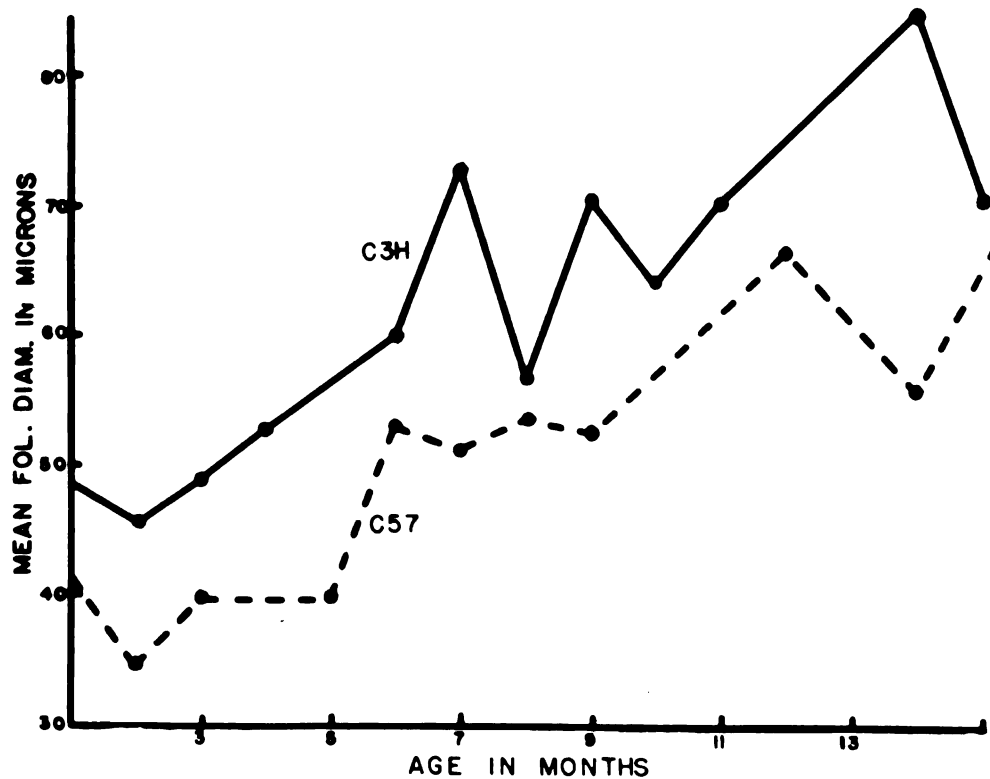


FIG. 8. DIAMETER OF THE THYROID FOLLICLES OF C3H AND C57 MICE.

Table III presents the mean epithelial height and mean diameter of the thyroid follicles of three age groups of C3H and C57 mice.

TABLE III
COMPARISON OF THE THYROIDS IN THREE AGE GROUPS OF C3H AND C57 MICE
(all measurements in microns)

	Group											
	I (1-4 months)				II (5-7 months)				III (8-16 months)			
	Ep. Ht.	Diameter			Ep. Ht.	Diameter			Ep. Ht.	Diameter		
	C3H	C57	C3H	C57	C3H	C57	C3H	C57	C3H	C57	C3H	C57
No. ind.	15	15	15	15	9	12	9	12	21	13	21	13
Avg. age in months	2.06	1.86	2.06	1.86	6.22	6.08	6.22	6.08	10.47	10.61	10.47	10.61
Mv.	5.74	7.34	48.03	38.03	6.73	8.08	63.25	48.91	6.27	8.28	68.54	56.08
S.E.	±.36	±.34	±2.04	±2.67	±.31	±.58	±4.03	±3.58	±.27	±.42	±2.26	±.81
t value	3.24		2.99		2.05		2.66		4.03		5.21	

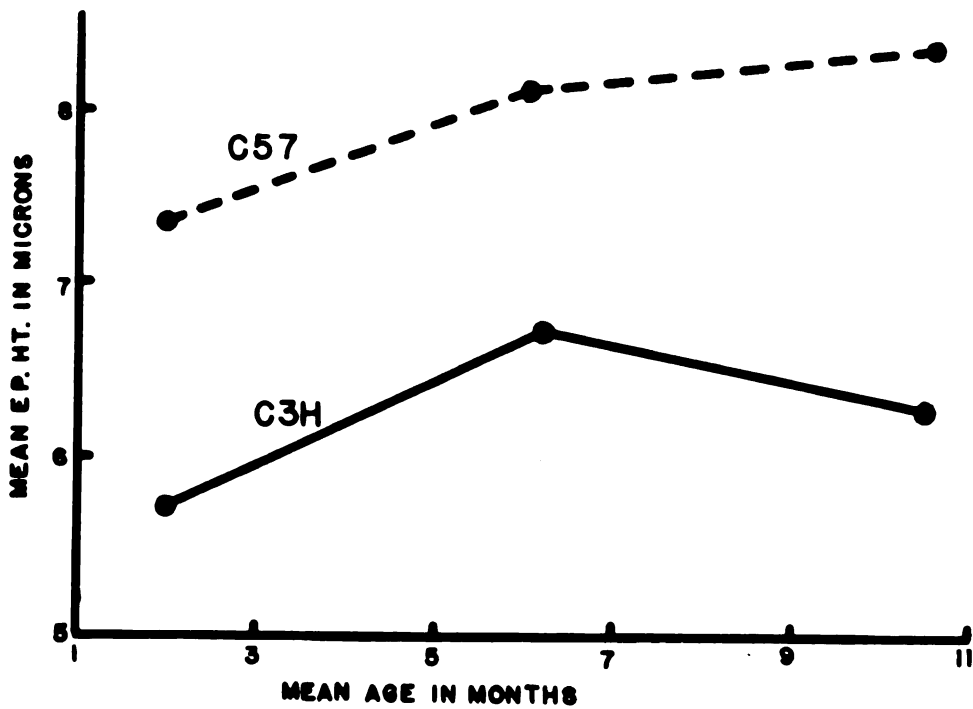


FIG. 9. EPITHELIAL HEIGHT OF THYROID FOLLICLES IN THREE AGE GROUPS OF C3H AND C57 MICE.

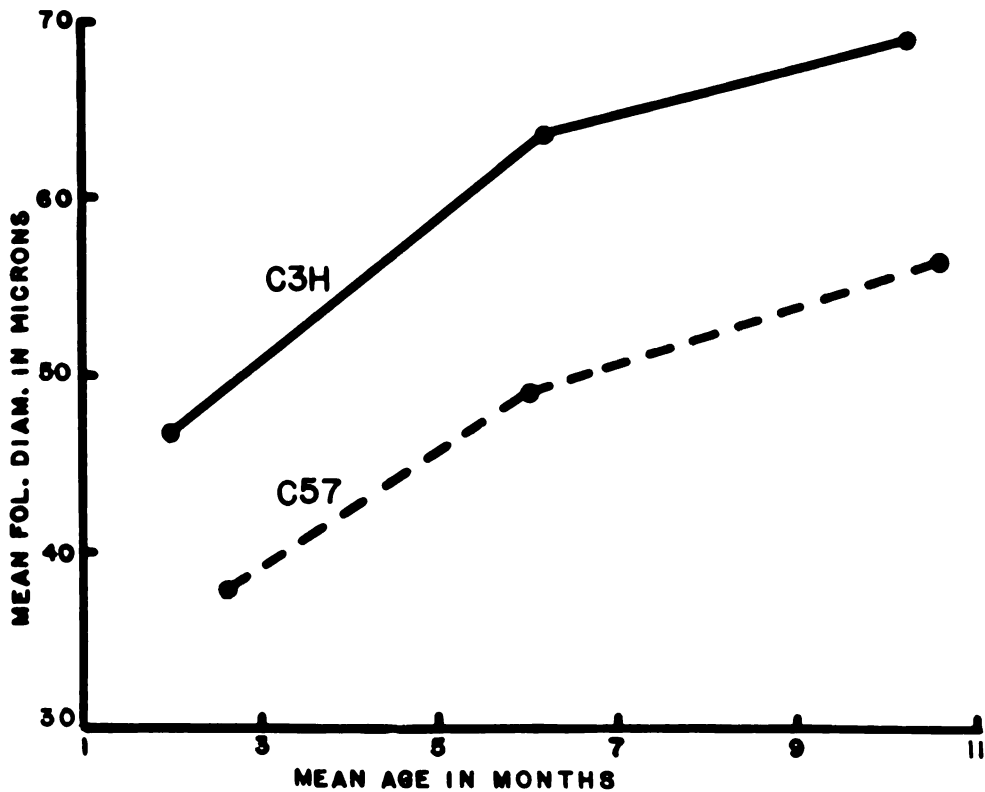


FIG. 10. DIAMETER OF THYROID FOLLICLES IN THREE AGE GROUPS OF C3H AND C57 MICE.

I and II is significantly higher than in the corresponding age groups of C3H mice (t value 3.24 and 4.03 respectively) and that a t value of 2.05 suggests but does not conclusively demonstrate a higher epithelium in the C57 mice of group II. The diameters measurements in C57 age groups I, II, and III are significantly higher than the corresponding measurements in C3H mice (t values, 2.99, 2.66, and 5.21, respectively).

IV. DISCUSSION

It was shown in this study that there was no significant difference between the height of the epithelium or diameter of the thyroid follicles in males and females from the C3H line of mice. Essentially the same relationship was observed in males and females of the C57 strain. The results show that differences in epithelial height and follicle diameter are independent of sex when animals of the same age are compared. The *t* values presented in Tables I, II, and III show that the height of the thyroid epithelium is significantly higher and that the follicle diameter is significantly lower in C57 than in C3H mice. This view supports the observations of Gross and Schwartz (1951). They maintained that C3H mice have a slower thyroxine turnover than C57 mice as indicated by their studies with thyroxine labeled with I^{131} . The results reported in the present paper may be interpreted on the basis of their observations, since a delayed thyroxine turnover in C3H mice would cause this hormone to be retained in the body and thus retard further secretion of the thyroid glands in the animals.

It has been noted in the preceding review of the literature that both thyroid-stimulating and thyroid-inhibiting drugs may decrease mammary tumor incidence. As Husely and Bittner (1946) pointed out, there must be an adequate hormonal balance for mammary tumor proliferation. This would explain why antagonistically acting drugs might produce the same effect, i.e., decrease the rate of tumor development by upsetting the thyroxine balance in these mice.

V. SUMMARY AND CONCLUSIONS

1. The histological appearance of one hundred C3H and C57 mice was studied.

2. No essential difference was observed between males and females in the C3H or C57 lines of mice.

3. Age differences appeared to be independent of strain or sex.

4. It was noted that C3H mice had a lower epithelial height and a larger thyroid follicle diameter than was present in mice of corresponding ages in the C57 strain.

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1. The first step is to identify the problem or question that needs to be answered.

2. The second step is to gather relevant information.

3. The third step is to analyze the information and identify the key factors.

4. The fourth step is to develop a plan of action.

5. The fifth step is to implement the plan and monitor the results.

6. The sixth step is to evaluate the results and make adjustments as needed.

7. The seventh step is to document the process.

8. The eighth step is to communicate the results to the relevant stakeholders.

9. The ninth step is to review the process and make improvements.

10. The tenth step is to repeat the process as needed.

11. The eleventh step is to ensure that the process is sustainable.

12. The twelfth step is to ensure that the process is scalable.

13. The thirteenth step is to ensure that the process is adaptable.

14. The fourteenth step is to ensure that the process is effective.

15. The fifteenth step is to ensure that the process is efficient.

16. The sixteenth step is to ensure that the process is cost-effective.

17. The seventeenth step is to ensure that the process is transparent.

18. The eighteenth step is to ensure that the process is accountable.

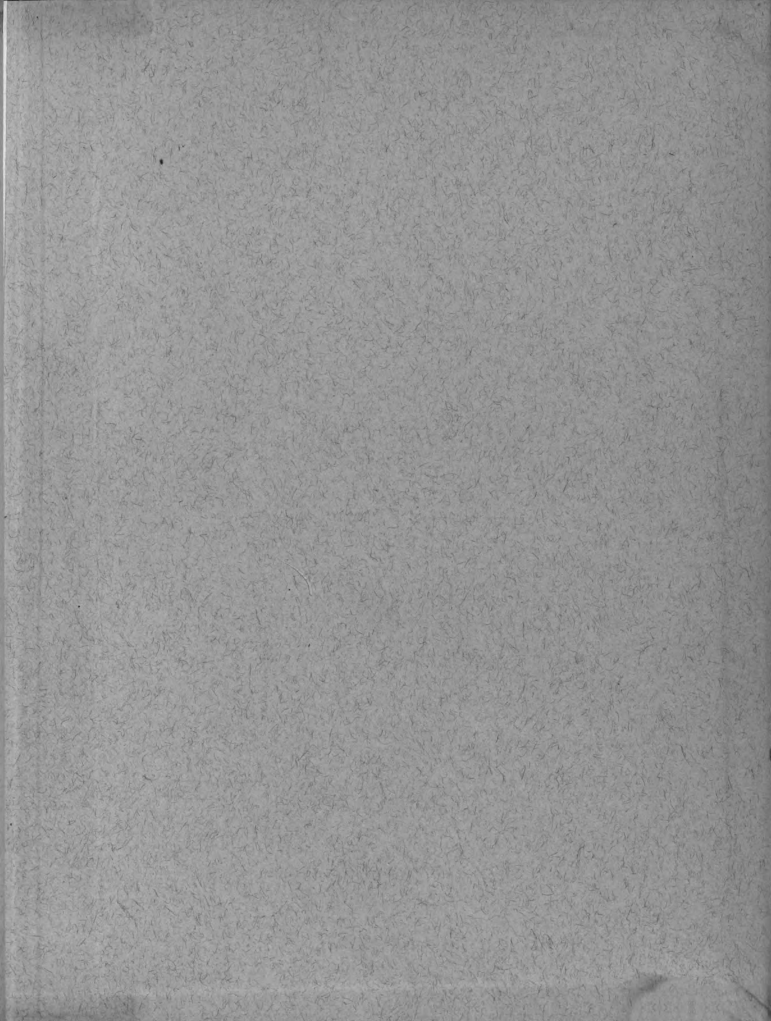
19. The nineteenth step is to ensure that the process is ethical.

20. The twentieth step is to ensure that the process is legal.

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