HISTOLOGICAL STUDIES ON THE RELATION OF THE ADRENAL GLANDS AND OVARIES TO THE NEOPLASTIC DISEASES OF THE BREAST

by

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I. INTRODUCTION

The matter that the normal mammary glands are affected by sex hormones can be made clear from the changes of mammary glands in puberty, pregnancy and after menopause, and the opinion that these changes are controlled by hypophysis, ovaries and adrenal cortices, is now confirmed in general. Therefore, it is easily conceived that in case of pathological state of mammary glands, particularly in neoplastic diseases of the breast, these sex hormones would also play an important part.

The start of researches for the relation between neoplastic diseases of the breast and sex hormones was the idea of Prof. Dr. Y. Aoyagi who noticed that the cases with disturbances of the female reproductive system and with the imperfection of sexual life were comparatively numerous in his detail investigations of the patients with neoplastic diseases of the breast. In the treatment of mammary tumors, however, the ovariectomy of Beatson, Lett et al. at first, the Androgen treatment of Nathanson et al. and the Estrogen treatment of Huggins et al., had been performed. And of late, the adrenalectomy and hypophysectomy have been undertaken. But the treating results of neoplastic diseases of the breast by means of such a hormone therapy or of the extirpation of endocrine organs are not always perfect, and the functional mechanism is not yet distinctly explained.

Not only in European and American countries but in Japan, the number of patients with neoplastic diseases of the breast, especially chronic cystic mastitis (mastopathia) has recently the tendency to increase, and then the relation between mammary tumors and hormones has been noticed in the aspects of its genesis, diagnosis and treatment.

At our clinic, the endocrinological studies on neoplastic diseases of the breast has been systematically carried on, and the present author has made some researches in the histological field on the relation of the adrenal cortices and ovaries to the neoplastic diseases of the breast.

II. MATERIALS AND METHODS

In animal experiment of neoplastic diseases of the breast, mice have mainly

been used. It is known that some strains of mice have an extremely high percentage of mammary cancer and some have a low one.

The author applied, as the experimental materials, female mice of the mixed strain (Japanese Gifu strain), and he could experimentally grow mammary cancers or mastopathia-like changes in some animals, after repeated pregnancy and disorder of lactation, according to the method of Dr. T. KOSHI, one of his collaborators. We took out, as control, the adrenal glands and ovaries of the mice of which mammary glands had normal findings in histological observation and general conditions had no unusual matters, and we compared them with those of the mice in which mammary cancers or mastopathia-like changes were found. Then, the age of these mice was from about 100 to 749 days, and mostly 400～550 days. It can be said that they were relatively old aged.

We can observe some considerable differences of adrenal cortices according to the alimentary condition, strain, age and sex of animals; particularly it is well known that the intake of protein and of solution of various salts gives some differences of the weight of the adrenals and of reflex behavior of adrenal cortices to various kinds of stress.

On the above mentioned standpoint, the author applied female mice of the mixed strain (Japanese Gifu strain) in all cases and made their growing environment as constant as possible, giving the mixed feed of wheat, rice and fish powder, added with some vegetable and water. Just before slaughter, the body weight of mice was measured and whether the sexual cycle of each mouse was corresponding to oestrus, metooestrus, dioestrus or praeoestrus, was investigated, by smear test. After that, the mice were instantaneously decapitated and killed, for the purpose of avoiding any influence of stress : and immediately the paired adrenals and ovaries were taken out and after weighed by a torsion balance (1mg sensitive), fixed with 10% neutral formalin. After fixation the formalin was removed by washing in running tap water, and the adrenals and ovaries of one side respectively, after embedded in paraffin, were stained with BOEMEL'S hematoxylin and eosin (H. E.) and those of the other side, after sectioned with the freezing microtome at 10～20 microns, were stained with sudan Ⅲ GOLDMAN, some by oil red : and SCHULTZ reaction for cholesterol, SCHIFF'S reagents and acetone solubility were examined.

Ⅲ. NORMAL MORPHOLOGICAL FINDINGS OF ADRENAL CORTICES AND OVARIES OF CONTROL FEMALE MICE

1) Adrenal Cortices

The weight of adrenals is presented in Table 1.

Table 1. Weight of adrenals of control mice

(Means ± standard errors)

Number of mice examined	Mean body weight (g)	Mean weight of paired adrenals (mg)
35	27.8 ± 7.8	14.8 ± 4.1

Histological Findings

ARNOLD (1866) classified the mammalian adrenal cortex into 3 zones, namely the zona glomerulosa, the zona fasciculata and the zona reticularis, from the arrangement of cells (Fig. 1, 2). In mouse, this classification is distinct, and especially the zona reticularis of mouse is called X zone.

Capsule: The capsule consisted of thin connective tissue, and a plenty of spindle-shaped cells (fibroblast-like cells) with dark chromatin stained nuclei were found in it. There was a sharp distinction between these capsule cells and the cells of zona glomerulosa. In the capsule, mitosis was not observed.

Zona glomerulosa: It was a most exterior zone of cortex. The cells were small and poor in cytoplasma. The arrangement of cells was irregular, and their nuclei were relatively small and rich in chromatin.

Zona fasciculata : It was a greater part of cortex. The cells had a regular fascicular arrangement toward the medulla. The shape of cells was a large polygon, and their nuclei were larger than those of zona glomerulosa and poor in chromatin, being vesicular.

Zona reticularis : The size of cells was smaller than that in zona fasciculata. The cells were irregularly arranged, and their nuclei were also small, and chromatin was granular and dark stained. The cytoplasma was very acidophil and the nuclei were closely gathered. In this zone, a large number of shrunken cells and pyknose were seen and most of them had brown pigments.

Histochemical Findings

It was very easy to classify the three zones on the histochemical point of view, too. The zona fasciculata, however, could be more divided into two parts, i. e. (1) Outer Fasciculata: the outer zone of zona fasciculata and mostly rich in lipids, (2) Inner Fasciculata: the inner zone of zona fasciculata and markedly poor in lipids.

Sudan III stain

Capsule: Lipid granules were not observed.

Zona glomerulosa: Most parts had a small quantity of lipids which were fein droplets. In some cases, lipids were in moderate amount and in some cases, almost nonlipids were demonstrated.

Zona fasciculata: In the outer zone, lipids were in a large or moderate quantity, and in the inner zone they were in a moderate amount.

Zona reticularis: Lipids were in a small quantity or nothing, and moreover most of them were comparatively coarse and were irregularly sized. But it could be distinctly distinguished from the so called brown degeneration which will be latter mentioned.

In the medulla, no lipids were demonstrated (Fig. 3).

SCHIFF and SCHULTZ reactions

They almost coincided with sudan III findings, and sudanophilic droplets were most numerous in the outer fasciculata, markedly scanty in the inner fasciculata and were almost negative in the zona reticularis.

Acetone solubility

Some frozen sections were put into acetone, corked closely and placed at room temperature for an hour. And after washed in water, they were stained by sudan Ⅲ (Acetone Sudan Ⅲ). Then the above mentioned lipid droplets disappeared. That is to say, the acetone solubility was positive. After the acetone management, the positive materials of both SCHIFF and SCHULTZ reaction were not stained, and then the acetone solubility was positive.

Differentiating the quantity of lipids according to the sexual cycle, we could notice that the lipids, as a whole, were generally reduced in the oestrus more than in dioestrus, and that the decrease of lipids was more marked in the pregnancy than that in cases of control and the lipids existed, localized in the outer fasciculata. In the mice of childbed the quantity of lipids was, in general, more than in the ones of pregnancy. The lipid distribution in adrenals of the control female mice is showed in Table 2.

Table 2. Lipid distribution in adrenals of control mice

Mouse No.		Capsule	Zona glome.	Outer fasci.	Inner fasci.	Zona reticu.
Dioestrus	8	−	+	⫴	⫲	⫲
	9	−	⫲	⫴	⫲	+
	16	−	⫲	⫴	⫲	⫲
	26	−	+	⫲	⫲	−
	35	−	+	⫲	+	−
	40	−	÷	⫲	+	−
	67	−	÷	⫴	⫲	+
	68	−	+	⫴	⫲	+
	70	−	+	⫲	⫲	+
	72	−	−	⫲	+	−
	77	−	+	⫴	⫴	÷
Praeoestrus	10	−	+	⫲	+	−
	17	−	+	⫲	+	−
	41	−	+	⫲	+	−
	85	−	+	⫲	÷	−
Oestrus	38	−	+	⫲	⫲	÷
	69	−	÷	⫲	−	−
Metooestrus	15	−	+	⫲	+	÷
	24	−	÷	⫴	⫴	−
	25	−	÷	⫴	⫴	+
	39	−	+	⫲	⫶	+
	42	−	+	⫲	⫶	−
	80	−	+	⫲	⫲	⫶

Note : − lipid absence + small amount ⫲ moderate amount ⫴ large amount

2) Ovaries

The weight of ovaries is expressed in Table 3.

Table. 3. Weight of ovaries of control mice
(Means ± standard errors)

Number of mice examined	Mean body weight (g)	Mean weight of paired ovaries (mg)
35	27.8 ± 7.8	25.8 ± 9.9

Histological Findings

The surface of ovaries except hilum, was covered with flat or short cylindric germ epithelium. The most exterior zone was the tunica albuginea and its development was extremely poor. Next the ovarian cortex itself lay and in it the follicles and corpora lutea existed. The medulla occupied the central part of ovary and was characterized by a profusion of blood vessels with connective tissue.

Follicles: In ovarian cortex, a plenty of indefinitely sized and round follicles were found and, as the development of follicles, all the stages, from young to mature follicles, could be observed. The young follicles were small, the follicle epithelium consisted of flatt cells, and as its development progressed, the follicle epithelium became gradually several layers and irregular polygons, which were called stratum granulosum. Among them some cavities, in which liquor folliculi stayed, were produced, and in some parts, the comulus oophorus held ovulums. Around the stratum granulosum, the theca interna (theca cell), rich in blood vessels, existed and in its outside, the theca externa formed by connective tissue, lay. The follicles, by enlargement, reached the surface of ovaries. The mature follicles busted as a result of the increasing tension of the fluid filling it.

Corpora lutea: All around its circumference was covered by the connective tissues. The lutea cells were irregular polygons and their border was distinct. Their nucleus was seated nearly on the center and the lutea cells had some differences of stainability for eosin which was considered to be related to their functions. The central part of corpora lutea was a mass of connective tissue and was lacking in lutea cells. And the ovarian lutea cells, which resembled adrenal cortical cells, gradually began to atrophy and to shrink. The proliferation of connective tissue became marked and the corpus luteum was finally degenerated and absorbed completely (Fig. 4, 5, 6,).

Atretic follicles : The fact that when follicles gradually develop and does not carry out the ovulation, the ovum becomes extinct and changes into the atretic follicle, has been known since GROHE (1863) and SLAVJANSKI (1870). The stratum granulosum was absorbed, and the theca interna was thickened and the connective tissue entered from the theca externa. With the shrinking of atretic follicles, the thickening of theca interna became obvious and the ovum became narrow. As the changes advanced more, they were considered to turn into the interstitial cells of ovarian stroma.

Interstitial tissue: It existed sporadically in the environs and the central parts of ovaries, and as it contained a large quantity of lipids, it took the light color of eosin at H.E.staining and seemed light cells.

Histochemical Findings

The germ epithelium of ovary was lipid negative. And the cortical ovarian stroma existed in an extremely small quantity and was lipid negative.

In follicles, the stratum granulosum was always lipid negative and the theca interna was always lipid positive. And, moreover, as the follicles grew, the amount of lipids in the theca interna was disposed to be increased. Among them, the main substance was cholesterol, judged from SCHULTZ reaction.

The atretic follicle took intensively the color of lipid and the interstitial tissue was also lipid positive. However, they were both in a small number.

In the corpora lutea the sudanophilic droplets, which were also SCHIFF positive, were very small and evently distributed throughout the luteal bodies, but in the older sets of corpora lutea, the sudanophilia and SCHIFF positive materials were comparatively scant and were unevenly distributed as coarse globules, indicating coalescence and disappearance of lipid droplets. The above mentioned differences of stainability of corpora lutea to eosin at H. E. staining, is considered to be due to the difference of lipid quantity (Fig. 7).

The lipid distribution in ovaries of control female mice are presented in Table 4.

Table. 4. Lipid distribution in ovaries of control mice

s.g. : stratum granulosum th. int. : theca interna

	Mouse No.	Germ epithelium	Cortical cell in stroma	Young follicles		Nearly mature folicles		Mature follicles		Atretic follicles	Corpora lutea	Interstitial tissue
				s. g.	th. int.	s. g.	th. int.	s. g.	th. int.			
Dioestrus	8	−	−	−	−	−	+	−	##	##	###	
	9	−	−	−	−	−	+	−	+	##	##	
	16	−	−	−	−	−	+	−	+		##	
	26	−	−	−	−	−	+	−	##	##		
	35	−	−	−	−	−	+	−	##		##	
	40	−	−	−	−	−	+	−	+		##	
	67	−	−	−	−	−	+	−	+			##
	70	−	−	−	+	−	+	−	+	##		##
	72	−	−	−	−	−	+	−	+		##	##
	77	−	−	−	−	−	+	−	+		###	##
	78	−	−	−	−	−	+	−	##	###	###	
Praeoestrus	10	−	−	−	−	−	+	−	+	##	##	
	41	−	−	−	−	−	+	−	##			###
	82	−	−	−	−	−	+	−	+		###	
	85	−	−	−	+	−	+	−	+	##	##	##
Oestrus	69	−	−	−	−	−	+	−	+	##		##
	38	−	−	−	−	−	+	−	+			
Metoestrus	15	−	−	−	−	−	##	−	##	##		##
	24	−	−	−	−	−	+	−	##	##		
	25	−	−	−	−	−	+	−	+			
	39	−	−	−	−	−	+	−	##		##	
	42	−	−	−	−	−	+	−	##	##		###

Note : − lipid absence + small amount ## moderate amount ### large amount

From the above mentioned results, as NISHIZUKA said, it can be supposed that the theca cells have endocrinological function and the hormone producting power of stratum granulosum is to be negatived. And the interstitial tissue resembles the theca interna on the histochemical standpoint, and it seems to show that the interstitial tissue has also the endocrinological function. The sudanophility of atretic follicle was also pointed out by GREEP and JONES (1950) and is an interesting point.

Ⅳ. HISTOLOGICAL CHANGES ON THE ADRENAL CORTICES AND OVARIES IN MICE WITH NEOPLASTIC DISEASES OF THE BREAST

The close connection between the development of neoplastic diseases of the breast and ovaries was explained, as above mentioned, but the histological studies on changes of ovaries in the individum with neoplastic diseases of the breast are very few.

KIER et al. (1952) reported abnormal endometrial morphology, suggesting ovarian disfunction of a non-ovulatory type in 5 out of 15 patients with benign breast lesions.

SOMMERS et al. (1952) reported that the ovaries of 83 of 100 women with breast cancer examined after death showed the morphologic evidence of cortical stromal hyperplasia, and described that the alterations were considered morphologic stigmata of hyperestrogenism, most likely secondary to overstimulation of the anterior lobe of the pituitary.

RHODENBURG and BULLOCK (1915) said that in the ovaries of mice with spontaneous tumor something not functionating increased and in a part of the cases, hyaline, fatty and cystic changes were be demonstrated.

The adrenal cortex has indeed a close relation with sexual function, so that it is called the dritte gonad (BOTTELA-LLUSIĀ 1953). In females, the main producting organ of androgens is the adrenal cortex and it plays an important part, on this point of view.

With the popularization of the general adaptation syndrome by SELYE, the problem of adrenal glands increased its importance from this view. In practice, however, as it is difficult to obtain the materials of human being more than ovaries, there has nowadays been only few reports of its histological reports. The present author investigated the adrenal glands of 15 mice with spontaneous mammary cancer and of 18 with spontaneous mastopathia-like changes.

1. RESULTS OF MICE WITH SPONTANEOUS MAMMARY CARCINOMA

1) Adrenals

The weight of adrenals is shown in Table 5 and it had significant difference from the control data (Table 1).

Table 5. Weight of adrenals of mice with spontaneous mammary carcinoma

Number of mice examined	Mean body weight (g)	Mean weight of paired adrenals (mg)
15	31.2 ± 4.8	15.0 ± 2.8

Histological Findings

The capsule of adrenals in some cases was not different with that in the control, but in some cases the thickening was marked and the mitosis was seen in it (Fig. 8, 9).

The zona glomerulosa in a part of the cases had no difference from that in the control cases, but in 13 of 15 cases (87%) the considerable hyperplasia of basophilic cells was observed not only in the zona glomerulosa but in the zona fasciculata (Fig. 8, 9, 10). Those cells spread around the original cortical cells, and were wedge sharped or sometimes adenomatous. The changes of this kind were seen here and there in the adrenal cortex and the original cortical cells were mostly enlarged. The hyperplasia of basophilic cells gathered together and made a nodule, sometimes occupying a greater part of the adrenal cortex. These findings were same to those which were named the nodular hyperplasia by FEKETE, WOOLLEY and LITTLE (1941).

The hypertrophy of the cells of zona fasciculata was observed in 13 of 15 cases (87%) (Fig. 11).

The zona reticularis in 11 of 15 cases (73%) was large masses, impregnated with lipids, and was light stained with eosin, seen as homogenous and round parts (Fig. 13). These findings were same to the changes named as the brown degeneration by CRAMER and HORNING (1937). Besides the zona reticularis disappeared and the adrenal cortex consisted of the zona glomerulosa and fasciculata in 2 of 15 cases (14%), and on the other hand, the former became wide, owing to its hyperplasia, in 5 of 15 cases (Fig. 12).

Histochemical Findings

The thickened capsule was sudan negative, and was also negative in SCHULTZ and SCHIFF reaction.

The cells of zona glomerulosa and fasciculata with nodular hyperplasia were sudan negative and were also negative in both SCHIFF and SCHULTZ reaction.

The findings of the brown degeneration of zona reticularis, was sudan positive and SCHULTZ reaction positive, but SCHIFF reaction was almost negative and the acetone solubility was negative (Fig. 14).

The amount of lipid materials in adrenal cortices were lessened, as a whole, and remained strong in the outer fasciculata, becoming unusually small granules (Fig. 15, 16). Judged from the schema of DEANE et al. (1945, 1948), it was considered that the adreno-cortical function was activated in general.

These adrenal changes of mice with spontaneous mammary carcinoma are presented in Table 6.

2) Ovaries

The weight of ovaries is shown in Table 7, having no significant difference from the control data (Table 3).

Table 6. Adrenal changes of mice with spontaneous mammary carcinoma

Mouse No.	Nodular hyperplasia in z. glome. and z. fasci.	Hypertrophy of cortical cell in z. fasci.	Brown degeneration in z. reticularis	x zone	Lipid distribution
5	##	+	##	Enlarged	Decreased
19	##	+	##	Unchanged	〃
22	##	+	+	〃	〃
30	+	+	+	Enlarged	Unchanged
40	+	+	+	〃	Decreased
48	##	+	−	Disappeared	〃
59	##	+	−	Unchanged	〃
92	+	+	##	〃	〃
129	+	+	##	〃	Unchanged
152	+	+	##	Enlarged	〃
155	##	−	−	〃	〃
162	##	+	−	Disappeared	Decreased
175	##	±	##	Unchanged	Unchanged
186	##	+	+	〃	〃
187	−	+	##	〃	Decreased

Table. 7. Weight of ovaries of mice with spontaneous mammary carcinoma

Number of mice examined	Mean body weight (g)	Mean weight of paired ovaries (mg)
15	31.2 ± 4.8	23.7 ± 6.9

Histological Findings

The cortical cells just under germ epithelium proliferated swirlingly in 7 of 15 cases (47%) (Fig. 17). These cell masses resembled keenly the cells of nodular hyperplasia in adrenal cortex and were the findings, named as the cortical stromal hyperplasia, described by SOMMERS et al. (1952). In 8 of 15 cases (53%) the findings had no great difference with the control cases.

The number of follicles were generally few, or the progress of follicular development was indistinct and in some of comparatively developed follicles the degeneration was observed, or in others the mitosis (Fig. 18). And in most cases the disturbances of follicular development were supposed. In 10 of 15 cases (67%) the unusual findings were found, and 5 cases (33%) had no significant difference with the control.

The formation of corpora lutea was disturbed in most cases (Fig. 17). The cases with no corpora lutea, the ones with a small number of corpora lutea and the ones with a small number of imperfect corpora lutea were 10 of 15 cases (67 %), and 5 cases (33%) had no difference with the control mice.

The interstitial tissue increased in 9 of 15 cases and contrarily disappeared in 2 cases (13%).

The atretic follicles generally increased in number, in most cases.

And the cases with large cystic follicles were 5 of 15 cases (33%). Most of them had a large cyst, but in one case had 4 cysts (Fig. 20, 21).

Besides, there was a case with considerable bleeding in stroma and hyaline degeneration.

Histochemical Findings

The cells, proliferating swirlingly just under germ epithelium, were sudan negative and were also negative in both SCHULTZ and SCHIFF reaction.

The findings of sudan stain in follicles were same to the control cases.

The cells of stratum granulosa were sudan negative and only the theca cells were sudan positive (Fig. 19) and SCHULTZ reaction positive.

As above mentioned, the corpora lutea had generally disturbances of corpora lutea formation. In the cases with corpora lutea, however, they were sudan positive, but in same cases with imperfect corpora lutea, they were sudan negative.

As the cases with increased interstitial tissue and atretic follicles were comparatively numerous, the cases with increased sudanophilia as whole ovaries (Fig.19), in comparison with the control cases, were 7 of 15 cases (47%), and a small number of the cases, in which sudanophilia could be almost unobservable, existed. These ovarian changes of mice with spontaneous mammary carcinoma are presented in Table 8.

Table 8. Ovarian changes of mice with spontaneous mammary carcinoma

Mouse No.	Disturbance of follicular development	Disturbance of corpora lutea formation	Interstitial tissue	Ovarian stromal hyperplasia	Other notions
5	+	+ (2)	Increased	+	Hyaline degeneration, Bleeding
19	+	+ (0)	〃	−	
22	+	− (3)	〃	+	
30	+	+ (3)	〃	+	Follicular cyst
40	−	+ (3)	〃	−	
48	−	− (5)	Unchanged	−	
59	−	+ (0)	Increased	+	
92	+	+ (0)	Unchanged	+	
129	−	− (6)	〃	−	
152	+	+ (0)	〃	+	Follicular cyst
155	+	+ (2)	Increased	−	
162	+	+ (1)	Unchanged	+	Follicular cyst
175	−	+ (1)	Increased	−	
186	+	− (5)	Unchanged	−	Follicular cyst
187	+	− (4)	Increased	−	Follicular cyst

Note : In brackets shows the number of corpora lutea

2. RESULTS OF MICE WITH SPONTANEOUS MASTOPATHIA

1) Adrenals

The weight of adrenals is shown in Table 9, which had no significant difference from the control data (Table 1).

Table 9. Weight of adrenals of mice with spontaneous mastopathia

Number of mice examined	Mean body Weight (g)	Mean weight of paired adrenals (mg)
18	27.0 ± 2.2	12.3 ± 1.7

Histological Findings

The capsule of adrenals had no difference from the control cases, and any marked thickening was not observed, as seen in the cases of mammary carcinoma.

The zona glomerulosa in some cases had no difference with the control mice. In 11 of 17 cases (65%), however, the considerable hyperplasia of basophilic cells, turning not only toward the zona glomerulosa but to the zona fasciculata, i.e. the nodular hyperplasia was seen, and especially in one case, making a large group, it pressed the adrenal medulla (Fig. 22). But the mitosis was found in only one case.

The cells of zona fasciculata were enlarged in 13 of 17 cases (76%), and it was mainly the hypertrophy of cytoplasma. On the other hand, in no case the zona fasciculata was shrunken.

As for the zona reticularis the hyperplasia existed and the X zone became wide in 5 cases (29%). In the extreme cases the zone occupied one half of adrenal cortex. And in no case the X zone was shrunken or disappeared. The proliferated X zone accompanied hyperemia, but the enlargement of sinusoid was not observed in almost all cases. In only two cases the enlargement of sinusoid was found. The brown degeneration was seen in 7 of 17 cases (41%) (Fig. 23). In one case there was the brown degeneration of zona glomerulosa. In the other one case the accessory adrenal gland existed (Fig. 24).

Histochemical Findings

The capsule had no lipids, as in the control mice, and was negative in both SCHIFF and SCHULTZ reaction.

The cells of nodular hyperplasia in zona glomerulosa and fasciculata were same to those of the cases with mammary carcinoma, and they were sudan negative, had no lipids and were negative in both SCHIFF and SCHULTZ reactions.

The brown degeneration of zona reticularis was same to that of the cases with mammary carcinoma, and the zone was positive in sudan staining (Fig. 25) and SCHULTZ reaction (Fig. 26) but almost negative in SCHIFF reaction and negative in actone solubility.

The lipid depletion of all the adrenal cortices was slight, compared with the cases with mammary carcinoma, but, in comparison with the control cases, the depletion could be also observed. It was localized mainly in the outer fasciculata and the lipid droplets were unusually small.

Judged from the schema of DEANE et al. (1947, 1948), it was generally conceived that the moderate activation of functions of adrenal cortices existed. These adrenal changes of mice with spontaneous mastopathia are presented in Table 10.

2) Ovaries

The weight of ovaries is shown in Table 11 and it had no significant difference from the control data.

Histological Findings

In 11 of 18 cases (61%) the follicles had no difference with those of the control cases (Fig. 27, 28), and the cases with a small number of young follicles or those

Table. 10. Adrenal changes of mice with spontaneous mastopathia

Mouse No.	Nodular hyperplasia in z. glome. and z. fasci.	Hypertrophy of cortical cell in z. fasci.	Brown degeneration in z. reticularis	X zone	Lipid distribution
1	+	+	−	Enlarged	Decreased
25	++	+	−	〃	〃
35	++ mitose	+	++	〃	Unchanged
60	++	+	−	〃	Decreased
83	++	+	++	Unchanged	Unchanged
99	−	−	−	Enlarged	〃
101	−	+	+	〃	Decreased
116	−	+	+	〃	〃
120	−	+	+	Unchanged	〃
140	++	+	−	Enlarged	〃
173	−	+	−	〃	Unchanged
212	+	−	++	〃	〃
251	−	−	−	Unchanged	〃
255	++	+	−	Enlarged	Decreased
257	++	−	+	Unchanged	Unchanged
286	+	+	−	〃	〃
288	+	+	−	Enlarged	〃

Table 11. Weight of ovaries of mice with spontaneous mastopathia

Number of mice examined	Mean body weight (g)	Mean weight of paired ovaries (mg)
18	27.0 ± 2.2	26.7 ± 6.8

with few follicles on the whole were 7 (39%). But no case had the considerable disturbances of follicular development, as seen in the cases with mammary carcinoma.

The corpora lutea were mostly good in formation, namely in 15 of 18 cases (83%) (Fig. 27, 28), and there was no corpora lutea in only 3 cases (17%).

The interstitial tissue and atretic follicles tends to increase in 9 cases (50%), and in 9 cases (50%) there was no difference to those of the control mice.

Four cases (22%) had a large follicular cysts and in 2 cases of them the bleeding follicular cysts were observed. And in one case the ovary was filled with large or small cysts, and its parenchyma part was narrow (Fig. 29). Some of them were bleeding follicular cysts and in others the cyst wall was luteinized. In two cases the bleeding luteal cysts were demonstrated (Fig. 30). And the proliferation of granulosa cells was extremely strong and it spread whole ovary and there was no corpora lutea in one case (Fig. 31).

The proliferation of cortical cells just under germ epithelium was found in 2 cases (11%), but it was not so strong as that in the cases with mammary carcinoma.

And the hyaline degeneration in stroma was observed in one case.

Histochemical Findings

The sudanophilic findings of ovary were same to the control cases; the stratum

granulosum was sudan negative and only the theca interna was sudan positive and SCHULTZ positive.

The behavior of sudan staining and SCHULTZ reaction in corpora lutea, interstitial tissue and atretic follicles were same to the control data. These ovarian changes of mice with spontaneous mastopathia are presented in Table 12.

Table. 12. Ovarian changes of mice with spontaneous mastopathia

Mouse No.	Disturbance of follicular development	Disturbance of corpora lutea formation	Interstitial tissue	Ovarian stromal hyperplasia	Other notions
1	+	− (4)	Unchanged	−	
25	−	− (4)	Increased	−	
35	−	− (5)	〃	+	Cyst of corpora lutea
60	+	− (5)	〃	−	
83	+	+ (0)	Unchanged	−	Follicular cyst
99	−	− (1)	Increased	−	
101	−	− (4)	Unchanged	−	
116	−	− (5)	Increased	−	
120	−	− (4)	〃	−	
140	+	− (4)	Unchanged	−	
173	−	− (1)	〃	−	Follicular cyst, Hyaline degeneration
212	−	− (7)	Increased	−	
240	+	+ (0)	〃	−	Follicular cyst
251	+	− (1)	〃	−	
255	−	− (4)	Unchanged	−	
257	+	+ (0)	〃	−	Proliferation of granulosa cell
286	−	− (2)	〃	−	Follicular cyst
288	−	− (4)	〃	+	

Note : In brackets shows the number of corpora lutea

3. DIFFERENCES BETWEEN CANCER OF THE BREAST AND MASTOPATHIA

As shown in Table 13, in adrenal cortices the nodular hyperplasia, hypertrophy of zona fasciculata and brown degeneration in X zone had some differences of frequency but had no difference in quality, and the lipid depletion in cortices, however, were generally strong in cases of cancer of the breast, and then the adrenocortical function was considered to be generally activated in cases of cancer of the breast more than that in cases of mastopathia.

As to the ovaries, both the disturbance of follicular development and of corpora lutea were markedly severe in frequency and in quality, in cases of cancer of the breast, and especially it was characteristic that the corpora lutea formation was good in cases of mastopathia.

In comparison of cases with cancer of the breast and ones with chronic cystic mastitis, it was characteristically true that the cases with follicular cyst were numerous in the latter and the developing ratio was thrice much, as shown in Table 14. There was no difference between the developing ratios of follicular cyst

in cases with cancer of the breast and ones with mastopathia.

Table 13. Histological changes in the adrenal cortices and ovaries of mice with cancer or cystic diseases of the breast

Organs	Histologic changes	Cancer (15 cases)	Cystic diseases (18 cases)
Adrenal cortices	Nodular hyperplasia in zona glomerulosa and zona fasciculata	87%	65%
	Hypertrophy of zona fasciculata	87%	76%
	Brown degeneration in x zone	73%	41%
	Decreased of lipid distribution	60%	47%
Ovaries	Disturbance of corpora lutea formation	67%	17%
	Disturbance of follicular development	67%	39%

Table. 14. Difference between cancer of the breast without chronic cystic mastitis and cancer of the breast with chronic cystic mastitis

	Follicular cyst	Ratio
Cancer of the breast without chronic cystic mastitis (9 cases)	2 (22%)	1
Cancer of the breast with chronic cystic mastitis (6 cases)	4 (67%)	3
Chronic cystic mastitis (18 cases)	4 (22%)	1
Controls (35 cases)	0 (0%)	0

4. HISTOLOGICAL OBSERVATION IN A CERTAIN FEMALE CASE WITH CANCER OF THE BREAST OF WOMAN

A 32-year-old female. Diagnosis: Cancer of the breast. Pathological diagnosis: Carcinoma simplex. She had no observable effects of treatment, but the bilateral ovariectomy and adrenalectomy were carried out. The changes of her adrenal cortices were as follows.

The capsule was found to be increased in thickness and the cell groups with hyperplasia of basophilic cells were observed. The cells were small, and their nuclei were spindle shaped and sudan negative (Fig. 32).

The development of capsular adenoma was extremely good, the hyperplasia of subcapsular cells were marked, the fibroblast-like cells entered toward the central part from the region just under capsule and they seemed to be tumor-like cells, but the mitosis was not found (Fig. 33).

And the light cells and the dark ones of adrenal cortices were mixed with each other, the cortical cells were enlarged, the lipids existed spottedly and the lipid depletion was seen, as a whole (Fig. 32). The proliferation was strong and the findings of activation was demonstrated.

In the ovaries, compared with those of a 32-year-old drowned woman (Fig. 34), the young follicles were very few and the degeneration was seen (Fig. 35). As the bleeding of corpora lutea was found (Fig. 36) and the corpus fibrosum and corpus albicans (Fig. 37) existed, it was considered that the corpora lutea formation

was normal. And the cortical stromal hyperplasia was observed (Fig. 35). It is interesting that the changes of same tendency to the cancers of the breast in mice were found.

V. THE INFLUENCE OF STEROID HORMONES ON THE ADRENAL CORTICES AND OVARIES

The adreno-cortical and ovarian functions were greatly modified by the various hormone environments, and especially some of the steroid hormones exerted special effects on the adrenal and ovarian functions.

As it was an obvious fact that there was a close connection between steroid hormones and cancer of the breast, the author performed the following experiments for the purpose of comparing the changes after simple medication of steroid hormone with the above mentioned pathological morphology of neoplastic diseases of the breast in mice.

MATERIALS AND METHODS

Applying female mice of the mixed strain (Japanese Gifu strain) of 30-day-old from birth, Estradiol pellet, as Estrogen, 1.25 mg was planted into their inguinal region for three times every 50 days and Testosterone pellet, Androgen, 6.25mg was planted for three times every 50 days.

RESULTS

1. Androgen-Treated Mice

1) Adrenals

Within one month after the first Testosterone plantation (6.25 mg), after the second plantation (12.5mg) and after the third plantation (18.75mg) the atrophic images were seen. The cells of zona glomerulosa and fasciculata were small, the cortices were narrow and the X zone was shrunken or disappeared (Fig. 38). Histochemically, the lipid droplets were depleted, localized in the outer fasciculata in a small number, and in the inner fasciculata the lipid droplets in scattered cells were clumping (Fig. 39). Schultz and Schiff reactions were negative in almost all the cases. In some cases the spheroid complex or fatty metaplasia, which was characteristic at the use of androgen, appeared. These vacuolated changes were seen in the cells of zona fasciculata and not found in those of zona glomerulosa.

2) Ovaries

The follicular development had no difference with that in the control mice and the growth of mature follicles was rather large, compared with that in the control cases.

The corpora lutea were absent in all the cases and the interstitial tissue and atretic follicle was not observed (Fig. 40). Therefore, histochemically the sudanophilia of ovaries was decreased.

In the cases after one year since thrice plantation of Testosterone pellet, very interesting findings were obtained. According to Dr. Koshi, one of the collaborators, the ducts of mammary glands were dilatated, and the duct junctions were found

more than those in the control mice. In the adrenal cortices, the hypertrophy of cells of zona fasciculata was observed. And the nodular hyperplasia turned from the zona glomerulosa to the zona fasciculata and the brown degeneration of X zone was considerably seen (Fig. 41). These findings of adrenal cortices resembled the above mentioned changes in the mice with mammary cancer and mastopathia, and moreover they also resembled the later mentioned changes in estrogen treated mice.

In the ovaries, the corpora lutea formation was sufficient, the follicular development had no difference with the control mice and the interstitial tissue and atretic follicle also had tends to increase (Fig. 42, 43), resembling the findings of ovaries in the mice with spontaneous mastopathia or the latter mentioned changes after a short while since estrogen treatment.

2. Estrogen-Treated Mice

1) Adrenals

In the cases after one month respectively since the first plantation of Estradiol pellet (1.25mg), since the second plantation (2 5mg) and since the third plantation (3.75mg), the X zone showed hyperplasia and was widened, and there was hyperemia and enlargement of sinusoid. The cells of zona fasciculata, as a whole, had tends to hyperplasia, and in some cases the zona fasciculata became adenomatous and the mitosis was observed. In 3 of 34 cases the zona fasciculata was pressed and shrunken by the hyperplasia of X zone, and a blood lake was found in one case (Fig. 44). The cells of zona glomerulosa had no abnormal findings, but the nodular hyperplasia turning from the zona glomerulosa to the zona fasciculata was observed in 11 of 34 cases (32%), especially more in the cases after 3 times of plantation. It is not intensive, however, compared with the cases of above mentioned spontaneous mammary cancer (Fig. 45). Histochemically, the cortical lipids were markedly decreased, localized in the outer fasciculata in a small quantity and the droplets were unusually small. The brown degeneration of X zone was demonstrated in 14 of 34 cases (41%) (Fig. 46).

The cancer of adrenal cortex caused by estrogen treatment was found in one case (Fig. 47, 48).

2) Ovaries

In the cases after only one time of the pellet plantation, the ovaries had almost no difference with those of the control mice, but in the ones after two or three times the ovaries were mostly shrunken, and contrarily in the cases killed after more than 40 days from the plantation the ovaries had no changes with those of the control mice. Then it was considered, that after the plantation of Estrogen pellet the follicular development was promoted by the estrogen function and the mature follicles became numerous, but a large quantity of estrogen rather brought the atrophy of the whole ovary, and that after 40 days the effect of estrogen diminished and the ovary gradually recovered to the normal condition. In one of 4 cases after one time of plantation the corpora lutea was in the complete condition, but after two or three times the corpora lutea was absent in all the cases (Fig. 50). The interstitial tissue and atretic follicles had tends to increase. The cortical

stromal hyperplasia was found in 9 of 34 cases and the medullary vascular hyperplasia was in 4 cases (Fig. 51). And the follicular cyst, which developed three or four times as mature follicles, were seen in 3 cases (Fig. 49).

The changes of adrenal cortices and ovaries in the cases of mammary cancer grown by estrogen treatment were same to the above mentioned changes in the mice with spontaneous mammary cancer (Fig. 52).

DISCUSSION

According to SELYE (1941), the effect of androgen to the adrenal cortex is generally considered to induce cortical atrophy, through the pituitary ACTH depression.

GREEP and JONES (1950) reported that androgen had a tendency to deplete cells of cholesterol and thereby lessened the activity of steroid hormone producting cells. The cells atrophy, but it is specific. It is not considered the hyperfunction of adrenal cortex, but the judment of cortical function is difficult in the findings, they said. The androgen is rather considered to hinder the producing mechanism of lipid droplets, from early period.

The characteristic functions of androgen in histology are fatty metaplasia. It is the phenomenon that the cortical cells had metaplasia to the cyclic fat cells, and SELYE (1950) considered it the specific reaction of androgen.

It is well known that in mice with X zone, whether male or female, the androgen injection can make the zone disappear, but the activity of androgen to adrenal cortex changes its expression according to the kinds of animals, the quantity of androgen and so on.

The activity of androgen to ovaries is also different, according to the kinds of animals, the quantity of androgen, the period of treatment and so on, and the large amount of androgen in a short period was used brings about stimulation to the ovaries. And it is considered that the prolonged treatment, in any quantity, causes the gonadotrophin secretion of hypophysis and the restraining effect of ovaries.

GREEP and JONES (1950) reported that the large amount of androgen promoted the formation of mature follicles and the sudanophilia of stroma was decreased and the number of corpora lutea decreased or disappeared.

SELYE (1950) emphasized that the function of estrogen to adrenal cortex was to promote the secretion of ACTH. It is interpreted, as its results, that estrogen causes the hypertrophy of adrenal cortex, but this effect is due to the anterior pituitary ACTH secretion. In some points, however, the explanation is not enough. He said that the hyperemia in adrenal cortex and the dilatation of sinusoid were specific.

GREEP and JONES (1950) pointed out that estrogen, contrary to androgen, had tendency to promote the hormone production and brought about the hyperplasia of the inner fasciculata and zona reticularis in rat.

JONES (1949) emphasized that the X zone was dependent on a gonadotrophin possibly LH in nature, not on ACTH.

Although the function of estrogen to ovary is different, according to the kind, age and sexual cycle of animal, and the amount and period of treatment and so on, it is understood that when a large dose in a short period was used the existing follicles were generally luteinized and when used in a long period the ovary atrophied and stopped its function owing to the decrease of gonadotrophin secretion.

The data of the present author, as above mentioned, are agreed with the reports of many scholars. In the cases, however, which after three times of androgen plantation (18.75mg), were left for about one year, as they were, the changes of adrenal cortices and ovaries were same to those in mice with spontaneous mastopathia-like changes. It became afterward clear that the mammary glands of this group had mastopathia-like changes and the hypothesis of the present author was satisfied. It is considered that these changes were brought about by the atrophy of androgen producting tissue, owing to the androgen function, and the later relative hyperestrogenistic condition.

From the experiments, the author was impressed by the matter that the morphology of mammary glands could be possibly presumed by the changes of adrenal cortex and ovary.

It has been made clear that the changes of adrenal cortex and ovary caused by the artificial hormone imbalance after androgen or estrogen taking were much slighter in the grade than those in the pathological neoplastic diseases of the breast. On this point, it is considered that the mammary cancer and mastopathia are not grown only by the mere stimulation of hormone imbalance, but can be generated by the addition of the other factors.

VI. HISTOLOGICAL CHANGES OF THE ADRENAL CORTICES AND OVARIES IN MICE WITH EHRLICH'S TUMOR AND BASHFORD CANCER

The author has already explained the changes of adrenal cortices and ovaries in mice with cancer of the breast. For the purpose of studying whether results or causes of neoplastic diseases are these changes, the author carried out the following experiments, comparing the changes of adrenal cortices and ovaries, with the cancer of the other region than the mammary glands. As the cancers grown in mice, EHRLICH's tumor and BASHFORD cancer were well known. The cases of neoplastic disease, developing from the transplantation of these two kinds of cancers, were investigated.

MATERIALS AND METHODS

1) EHRLICH's Tumor

The author infused the ascites of mice of EHRLICH's ascites tumor, divided by the courtesy of the Bacteriological Division, Kyoto Prefectural Medical College, into the abdominal cavity of adult mice and took out the ascites (Fig. 53) after about 10～14 days when it reached the maximum value (named EHRLICH's tumor, ascites type). And we injected subcutaneously the ascites into the back in adult

female mice of the mixed strain (Japanese Gifu strain). In about one week after the injection, a little-finger-tip-sized tumor grew, and it gradually developed and became, in 50 days after the injection, the sparrow egg or walnut growth. When left as it was, the central part of the tumor became necrosis and sometimes the animals died. Then, the mice were slaughtered respectively after 7, 21, 40and 51 days from the injection (named EHRLICH's tumor, subcutaneous type) (Fig. 54, 55, 56). Then the author examined the subcutaneous type of cancer in 14 of 21 mice.

2) BASHFORD Cancer

The author received a mouse of BASHFORD cancer (transplanted in 17 generation) from the 1st Pathological Division, Osaka University Medical School, and transplanted it into the female mice of the mixed strain (Japanese Gifu strain) of 2-month-old from birth. We resected a fore-finger-tip-sized tumor in the subcutaneous region of back skin and made a number of pieces of it in penicillin solution. And we put respectively one of the pieces into the subcutaneous tissue of back skin of mice, and sutured the skin, injecting penicillin solution for the purpose of protecting infection. In all the successful cases of transplantation, the tumor reached the little-finger-tip or walnut growth (Fig. 57). In 1～2 months after the transplantation, the animals were slaughtered and examined. The author researched into 9 cases of mice with successful transplantation.

RESULTS

1) EHRLICH's Tumor

The weight of adrenals in 14 mice of EHRLICH's tumor (subcutaneous type), is shown in Table 15, and it was markedly lighter than that of the control mice and of the ones with neoplastic diseases of the breast.

The zona glomerulosa of adrenal cortices had almost no abnormal findings. The zona fasciculata was narrow, and the cells were small and atrophic. The zona reticularis was widened and the hyperplasia was observed (Fig. 58) in 10 of 13 cases (76.9%). The hyperemia and enlargement of sinusoid were found in some cases, but in some cases the zone was normal.

Table 15. Weight of adrenals of mice with EHRLICH's Tumor (subcutaneous type)

Number of mice examined	Mean body weight (g)	Mean weight of paired adrenals (mg)
14	26.0 ± 4.5	9.6 ± 1.2

Histochemically, the lipid depletion was markedly observed and almost disappeared in some cases (Fig. 59). The brown degeneration of X zone was not seen. And also there was no formation of nodular hyperplasia.

The weight of ovaries in mice with EHRLICH's tumor (subcutaneous type), is presented in Table 16 and it was markedly light.

Table 16. Weight of ovaries of mice with EHRLICH's Tumor (subcutaneous type)

Number of mice examined	Mean body weight (g)	Mean weight of paired ovaries (mg)
14	26.0 ± 4.5	13.7 ± 3.9

The ovaries were generally small and atrophic. The follicular development was normal (Fig. 60) in most cases, and in one of 11 cases the bleeding follicular cyst was found. The corpora lutea existed in most cases, but in 3 of 11 cases (27.2%) the corpora lutea were absent. In 8 cases (72.8%) the corpora lutea existed, but the number of them were generally few, compared with the control mice (Fig.61). The interstitial tissue and atretic follicles were not found. And in 4 of 11 cases (36.3%) the proliferation of theca cells was seen (Fig. 62).

In 4 mice with EHRLICH's tumor (ascites type), the zona glomerulosa of adrenal cortices took fascicular arrangement and in some cases it displayed the figure of activation. The zona fasciculata was atrophic and the zona reticularis had no abnormal findings.

The changes of ovaries in mice with EHRLICH's tumor (ascites type) were not different from those in ones with subcutaneous type.

2) BASHFORD Cancer

In the zona glomerulosa of adrenal cortices there was no abnormal findings. The zona fasciculata had no difference with that of the control mice, or was generally atrophic, and the zona reticularis had no difference with that of the control mice. The hyperplasia of X zone, as seen in the subcutaneous type of EHRLICH's tumor, was not observed. And there was neither nodular hyperplasia, nor brown degeneration (Fig. 63). Histochemically, the lipid findings were not different with those of EHRLICH's tumor.

In ovaries, the atrophy was generally slight, compared with that in the cases of EHRLICH's tumor. There was neither disturbance of follicular development nor of corpora lutea formation, but the number of corpora lutea were generally numerous more than that in EHRLICH's tumor (Fig. 64). The interstitial tissue and atretic follicles were not observed.

The above mentioned findings are distinctly different from those in the cases of mammary cancer and mastopathia-like changes. Therefore, at least, it is apparent the findings in mice with neoplastic diseases of the breast are not the associated secondary changes after cancer, namely the results of cancer development. Perhaps it can be suggested that they play a causal part.

VII. HISTOLOGICAL CHANGES OF ADRENALS AND OVARIES OF MICE INJECTED EMULSION OF MAMMARY CANCER TISSUES

The author performed the following experiments, for the purpose of investigating whether or not the changes of adrenal cortices and ovaries in mice with mammary cancer were generated by the histotoxin of mammary cancer.

MATERIALS AND METHODS

The author extirpated a tumor of mice with spontaneous mammary cancer, and made emulsion from it with a homogenizer. The emulsion was diluted into decuple physiological salt-solution and after centrifuged enough, was divided into the supernatant clear fluid and sediment. The upper fluid 0.5 cc or 1.0 cc was injected subcutaneously in back skin of adult female mice of the mixed strain (Japanese Gifu strain). During 7 days and one month after, the animals were slaughtered, and their adrenal cortices and ovaries examined.

RESULTS

The zona glomerulosa of adrenal cortices had no difference with that of the control mice. The zona fasciculata in some cases had no difference with that of the control mice, but the tendency of hypertrophy was noticed. In no case it was shrunken. The zona reticularis had no difference with that of the control mice. The brown degeneration and nodular hyperplasia were not found at all (Fig. 65). Histochemically, the lipid depletion was observed, and the lipids existed, localized in the outer fasciculata.

The ovaries had no difference with those of the control mice (Fig. 66).

Except the matter that the adrenal cortices showed the figure of activation due to stress, the changes, as seen in mice with mammary cancer, were not observed. Judging from these facts, the author thinks the changes in mice with mammary cancer are not caused by the histotoxin of mammary cancer.

VIII. DISCUSSION ABOUT ALL THE FINDINGS

Fekete, Woolley and Little (1941) noticed that the adrenal cortices showed the characteristic changes which progressively lead to the formation of nodular hyperplasia, after the experiment of imbalance of sex glands pituitary system, i. e. the ovariectomy in mice, and in 1943 they reported that the nodular hyperplasia was the changes caused by hormone imbalance. The same matter was recognized by Flux (1954).

Furth and Sobel (1947) emphasized that the nodular hyperplasia, same to that in the report of Fekete et al., in the adrenal cortices of the mice in which the sex glands pituitary imbalance was made by transplantation in graft of normal ovaries in spleen.

This matter was recognized by Lipschutz, and furthermore from his comprehensive experiments, he insisted that the appearance of follicular and luteal cyst and of bleeding luteal and follicular cyst of rare occurrence was one of the circumstantial evidence that they were caused by the disfunction of sex glands pituitary system.

The author thinks it can be considered that the nodular hyperplasia of adrenal cortices found in mice with mammary cancer and mastopathia, and furthermore the findings of bleeding follicular and luteal cysts are the findings caused by the hormone imbalance originated from ovaries and adrenal cortices, i. e. the sex glands

in an extensive sense, at case of neoplastic diseases of the breast, judging from the reports of many scholars.

Then, in these cases what kind of condition is the hormone imbalance?

Is it the hyperandrogenism? No, it is generally the relative hyperestrogenic condition.

KIER et al. (1952) reported that in 15 patients with benign breast lesions, they extracted the bensenoid which belonged to estrogen in the tissue of mammary glands and the 3 keto-steroid which belonged to progesterone and androgen, and measured their quantity with ultraviolet ray, and performing the examination of endometrial morphology, they observed the ovarian disfunction of a non-ovulatory type in 5 of the 15 patients. And they said, they thought that the benign breast lesions were generated by the hyperestrogenism or the shortage of antagonistic hormone, and especially that the latter was caused by the disturbance of corpora lutea formation of a non-ovulatory type. But practically, they did not carry out the examination of ovaries.

The similar findings are seen in the mammary cancer. SOMMERS and TELOH (1952) reported that they found the cortical stromal hyperplasia of ovaries in 83 of 100 human cases (83%) and they stressed that the described alterations were considered the morphological stigmata of hyperestrogenism, most likely secondary to the overstimulation of the anterior lobe of pituitary. But they said that the similar changes were also seen in 50 of 133 control cases (37.6%).

The author found these changes in 7 of 15 mice (47%) with mammary cancer and in 2 of 18 cases (11%) with mastopathia. And the same findings were seen in 9 of 34 mice (26.5%) treated with Estradiol pellet.

Judged from the experiments of SELYE (1941), GREEP and JONES (1950), ANDO (1955) and OHI (1955), and from the results of the present author after the steroid homone treatment, the described findings adrenal cortices and ovaries in neoplastic diseases of the breast, can not always be said to be the hyperestrogenism, and it is considered that the hormone imbalance, caused by the relative hyperestrogenism due to the keto-steroid, e. g. androgen, progesterone and so on, existed in a pretty high ratio. In this point, the hypoandrogenism can be supposed from the latter mentioned findings in X zone. And judged from the fact that in cases of mastopathia, the corpora lutea formation is mostly good, the secretion of progesterone is not considered to be reduced, and then the secondary hypoandrogenism can be conceived.

The reports of chemical measurement of estrogen, androgen and progesterone are numerous, and Dr. KYOZO MASUDA, the lecturer of our clinic, emphasized that the ovaries and adrenal cortices in mastopathia cases cannot be called to be in the conditions of hyperfunction or hypofunction, but in the disfunctional condition, judging from the results of sex hormone measurement in urine. The present author thinks that he himself could prove it histologically.

As to the brown degeneration in X zone of adrenal cortices in mice, it has be noticed in a view point of the connection between steroid and tumor development,

since BURROWS (1936) and CRAMER and HORNING (1937) found it in mice with mammary cancer. It has now became clear, however, that the brown degeneration can be also observed before the growth of mammary cancer.

On the other hand, BLAISDELL, GARDNER and STRONG (1941) reported that there was no definite relation between the brown degeneration and mammary cancer.

The author found the brown degeneration in 73% of mice with spontaneous mammary cancer and in 41% of mice with spontaneous mastopathia, but in the control mice such a change was never seen. Then the author wishes to affirm the emphasis of CRAMER et al. Moreover the author consideres that this change has an important connection with mastopathia.

While there are three zones, i. e. the zona glomerulosa, fasciculata and reticularis, what meaning have echo of them in the mechanism of adrenal cortex? Nowadays it is not completely explained.

The explanation was classified into the escalator theory or cell-migration theory advocated by GOTTSCHAU (1883) and the zonal theory by DEANE and GREEP (1946). Especially, the latter has recently been a subject of controversy, and at least functionally the zonal theory is generally supported by a number of scholars. It is considered that the zona glomerulosa secretes the mineral corticoid, and the zona fasciculata is completely dependent upon ACTH and secretes the glycocorticoid. The zona reticularis is the zone which secretes a sexual hormone, and especially JONES (1949) reported that the X zone of mice was the androgenic zone and was dependent on a gonadotrophin, possibly LH in nature.

The above mentioned brown degeneration of X zone is negative in acetone solubility and seems a marked clumping of lipid droplets, and it is considered the inactive secretory state of hormone function. Then the X zone which is called the androgenic zone, is in the hypofunctional state. The author interpreted it as the relative hyperestrogenism, owing to the hypoandrogenism.

When a living body is exposed to the outside stimulus, the demand for adrenocortical hormone is increased and the adrenal cortex is enlarged and various kinds of morphological and histochemical changes of it appear. Then, from these findings, it is possible to guess the adrenocortical activity. In the risen secretion of ACTH the adrenal cortex shows the findings of hyperfunction and at the reduced secretion of ACTH the adrenal cortex shows the findings of hypofunction. However, about the hypertrophy or atrophy observed practically in adrenal cortex, a plenty of various kinds of appearing mechanism can be conceivable. Of course, the intensity and continuing period of stress and the bodily conditions may give differences of it, but the other hormones than ACTH, which have influences to adrenal cortex, and the humoral factor should be taken into consideration.

In the adrenocortical findings of mice with mammary cancer in case of author, gonadotrophin has certainly some considerable influences, mixed with ACTH.

Generally, at case of adrenocortical hyperfunction, the hypertrophy accompanied with the decrease or disappearance of lipid droplets, is observed, and especially the cell hypertrophy of zona fasciculata is found and the weight of adrenal gland is

increased.

At case of adrenocortical hypofunction, the atrophy of cells is observed and the lipid droplets became coarse.

The schema, with which we can judge, like this, the size of adrenal cortex, the decrease of lipid droplets and the adrenocortical activity, has been described by DEANE and GREEP (1947), DEANE, SHAW and GREEP (1948), OHI (1956) and so on.

The data in mice with neoplastic diseases of the breast in case of author, can be considered, from the idea of stress, a kind of resistant conditions. Not only mammary cancer, but mastopathia is one of stressors, and moreover when the disturbances are intensive in a certain degree, the nodular hyperplasia or hypertrophy appears and the findings of hyperfunction is may be accompanied with it.

SUMMARY

From the morphological and histochemical findings of ovaries and adrenal cortices in mice with neoplastic diseases of the breast, especially mammary cancer and mastopathia (chronic cystic mastitis), the following results were made clear.

1) In case of neoplastic diseases of the breast, the condition of hormone imbalance originated in sexual glands, was proved. The hormone imbalance was the cause of unusual findings in adrenal cortices and ovaries.

2) It has been conceived that the imbalance was caused not only by the hyperestrogenism, but more by hypoandrogenism.

3) It has been re-examined that the brown degeneration of X zone of adrenal cortices as CRAMER and HORNING reported, had a close connection with mammary cancer. And moreover, its relation with mastopathia has also been proved. Furthermore the brown degeneration is considered a index of the imbalance of sex hormone due to the hypoandrogenism.

4) From the idea of stress, the adrenal cortex is considered the resistant condition. As both the mammary cancer and mastopathia were respectively a kind of stressors, it showed the hyperfunctional condition.

5) In comparison of mammary cancer and mastopathia, the findings of ovaries in the former had an extremely intensive organic changes and in case of the latter the changes were slight.

The findings of adrenal cortices in mammary cancer had more hyperfunctional changes.

6) The findings of transplantable cancer and of neoplastic diseases of the breast in mice were different to each other at all. The findings of ovaries and adrenal cortices in neoplastic diseases of the breast were not the associated secondary changes caused by the cancer, namely the ones generated by the result of development of neoplastic diseases, but it was considered that the abnormality of ovaries and adrenal cortices played a causal part.

7) It was ascertained that, from the experiments of tissue emulsion of mammary cancer, the changes of ovaries and adrenal cortices in neoplastic diseases of

the breast were not generated by the histotoxin of mammary cancer.

8) The author reported the changes of adrenal cortices and ovaries, in a case of cancer of the breast of woman, and these findings were similar to those in mice with mammary cancer.

In conclusion, the author wishes to thank Dr. KYOZO MASUDA, the lecturer of our clinic and Assist. Prof. Dr. Y. NISHIZUKA, Pathological Division, Kyoto University for their guidance throughout the period of this study. The author wishes to thank Dr. T. KOSHI, for his kindness to receive the mice with mammary tumor.

An abstract of this study has been reported by Dr. K. MASUDA, at the General Meeting of the Japanese Surgical Society, Apr. 30, 1956, and at the Symposium of Tumor of the Breast of the Japanese Surgical Society, Apr. 2, 1957, and by the author at the General Meeting of the Japanese Assoiation for Endocrinology, Oct. 30, 1955, Apr. 2, 1956 and March 31, 1957.

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EXPLANATION OF PLATES

Fig. 1. Adrenal of intact control female mouse consists of an outer connective tissue capsule, zona glomerulosa, zona fasciculata, x zone and medulla. (Hematoxylin Eosin stain, ×100.)

Fig. 2. The magnification of Fig. I. (H.E. stain, ×200.)

Fig. 3. Adrenal of intact control female mouse. Sudanophilic material in zona glomerulosa, unusually strong reaction in outer fasciculata and weak to absent in more central region. (Sudan Ⅲ. stain, ×100.)

Fig. 4. Ovary of intact mouse. (Dioestrus) Corpora lutea and many follicles in all stage of development are seen. Note good follicular development. (H.E. stain, ×40.)

Fig. 5. Ovary of control mouse. (Praeoestrus) Seven corpora lutea and few healthy follicles are seen. (H.E. stain, ×40.)

Fig. 6. Ovary of control mouse. (Oestrus) No corpora lutea and many follicles in all stage of development are seen. (H. E. stain, ×40.)

Fig. 7. Ovary of control mouse. Heavy sudanophlia in corpora lutea lighter in theca interna and interstitial cells. The stratum granulosum of the mature follicles has no sudanophilia. (Sudan Ⅲ. stain, ×100.)

Fig. 8. Adrenal of female mouse with spontaneous mammary cancer. The outer connective tissue capsule was found to be increased in thickness, formation of nodular hyperplasia of basophilic cells in zona glomerulosa and zona fasciculata. (H.E. stain, ×100.)

Fig. 9. The magnification of Fig. 8. (H.E. stain, ×400.)

Fig. 10. Adrenal of mouse with spontaneous mammary cancer. Formation of nodular hyperplasia extending from zona glomerulosa to zona fasciculata, hypertrophy of zona fasciculata cells. (H. E. stain, ×400.)

Fig. 11. Adrenal of mouse with spontaneous mammary cancer. Considerable hypertrophy of zona fasciculata cells. (H.E.stain, ×100.)

Fig. 12. Adrenal of mouse with spontaneous mammary cancer. Hyperplasia of x zone and there is a tendency towards hyperemia and enlargement of sinusoid. (H.E. stain, ×100.)

Fig. 13. Adrenal of mouse with spontaneous mammary cancer. Shows enlarged cells in zona reticularis, filled with large masses of lipid material. This is very advanced stage of the brown degeneration. H.E. stain, ×100.)

Fig. 14. Adrenal of mouse with spontaneous mammary cancer. A ring of isolated masses of sudan stained brown degeneration lies around the medulla. (Acetone sudan Ⅲ. H. stain, ×100.)

Fig. 15. Adrenal of mice with spontaneous mammary cancer. The amount of lipid material in the adrenal cortex is lessened, remained strong and unusually small in outer fasciculata. (Hematoxylin sudan Ⅲ. stain, ×100.)

Fig. 16. Same as Fig. 15. Adjacent sections treated by Schiff reagent have very similar appearance. ×100.)

Fig. 17. Ovary of mouse with spontaneous mammry cancer. No corpola lutea, disturbance of follicular development are seen, and there is considerable hyperplasia of a group of subcapsular region and numerous interstitial cells. (Hematoxylin sudan Ⅲ. stain, ×40.)

Fig. 18. Ovary of mouse with spontaneous mammary cancer. Comparatively developed follicles the degeneration was observed, or in others the mitosis. (H.E. stain, 400.)

Fig. 19. Ovary of mouse with spontaneous mammary cancer. Interstitial mass intensely calored and increased in number of them. (Sudan Ⅲ. stain, ×100.)

Fig. 20. Ovary of mouse with spontaneous mammary cancer. Follicular cyst. (Hematoxylin sudan Ⅲ. stain, ×100.)

Fig. 21. Ovary of mouse with spontaneous mammary cancer. A large follicular cyst and numerous small ones. (H. E. stain, ×100.)

Fig. 22. Adrenal of mouse with spontaneous mastopathia. Considerable formation of nodular hyperplasia. (H. E. stain, ×100.)

Fig. 23. Adrenal of mouse with spontaneous mastopathia. Brown degeneration of the x zone. (H. E. stain, ×100.)

Fig. 24. Adrenal of mouse with spontaneous mastopathia. A : Original adrenal gland, B :Accessory adrenal gland. (H. E. stain, ×100.)

Fig. 25. Same as Fig. 23. Frozen section treated with Sudan Ⅲ. (×100.)

Fig. 26. Same as Fig. 23. Frozen section treated with Schultz reaction for cholesterol have very similar appearance as Fig. 25. (×100.)

Fig. 27. Ovary of mouse with spontaneous mastopathia. Corpora lutea and many follicles in all stage of development are seen. (H. E. stain, ×40.)

Fig. 28. The magnification of Fig. 27. Two corpora lutea and four follicles are seen. Note good corpora lutea formation and follicular development. (×100.)

Fig. 29. Ovary of mouse with spontaneous mastopathia. Many follicular cysts are seen, some parts are bleeding follicular cysts, some parts luteinized. (H. E. stain, ×40.)

Fig. 30. Ovary of mouse with spontaneous mastopathia. The large space is a bleeding luteal cyst. (H.E. stain, ×100.)

Fig. 31. Ovary of mouse with spontaneous mastopathia. In this case no corpora lutea and marked proliferation of the stratum granulosum. Young follicles and immature follicles are seen here and there. (H.E. stain, ×100.)

Fig. 32. Adreal cortex of woman with mammary cancer. The cell groups with hyperplasia of basophilic cells were observed. The cells were small, and their nuclei were spindle shaped and sudan negative. And the light cells and dark cells of adrenal cortices were mixed with each other, the cortical cells were enlarged, the lipids existed spottedly and the lipid depletion was seen, as a whole. (Hematoxylin sudan Ⅲ. stain, ×100)

Fig. 33. Same case as Fig. 32. Capsular adenoma. (Hematoxylin sudan Ⅲ. stain, ×100.)

Fig. 34. Narmal ovary of 32-year-old woman. (H.E. stain, ×100.)

Fig .35. Ovary of woman with mammary cancer (same case as Fig. 32.) Young follicles are lessened and the ovarian cortex was found to be increased in thickness and cellular density in cortical stromal hyperplasia. (H.E. stain, ×100.)

Fig. 36. Same case as Fig. 35. Bleeding from corpus luteum is presented. (left uppper part) (Hematoxylin sudan Ⅲ. stain, ×100.)

Fig. 37. Same case as Fig. 35. Corpus albicans are presented (Hematoxylin sudan Ⅲ. stain, ×100.)

Fig. 38. Adrenal of intact female mouse after treatment with androgen. (18.75mg.) Adrenal cortex is narrow and atrophic, x zone has disappeared. (H.E. stain, ×100.)

Fig. 39. Adrenal of intact female mouse after treatment with androgen. Inner fasciculata and zona reticularis present a picture of marked lipid depletion. (Hematoxylin sudan Ⅲ. stain, ×100.)

Fig. 40. Ovary of mouse after treatment with androgen. (18.75mg) Note good follicular development, corpora lutea and interstitial tissues are absent. (H. E. stain, ×40.)

Fig. 41. Adrenal of intact female mouse after treatment with androgen (18.75mg.) and killed 300 days later. Hypertrophy of zona fasciculata cells and brown degeneration of zona reticularis, there is a tendency towards formation of nodular hyperplasia extending from zona glomerulosa to zona fasciculata. (H.E. stain, ×100.)

Fig. 42. Ovary of mouse after treatment with androgen (18.75mg.) and killed 300 days later. Corpora lutea and many follicles in all stage of development are seen. There is a tendency to increase the number of interstitial tissue and atretic follicle. (H.E. stain, ×40.)

Fig. 43. The magnification of Fig. 42. Two corpora lutea and interstitial cells are seen and clear areas which contain lipid. (H. E. stain, ×400.)

Fig. 44. Adrenal of intact female mouse after treatment with estrogen (2.5mg.) showing typical blood lake and zona fasciculata is degenerating and atrophic. (H. E. stain, ×100.)

Fig. 45. Adrenal of intact female mouse after treament with estrogen (3.75mg). Hypertrophy of zona fasciculata cells and proliferation extending from capsule to zona fasciculata. (H. E. stain, ×400.)

Fig. 46. Adrenal of intact female mouse after treatment with estrogen. Heavy sudanophilia in outer fasciculata, which is unusually small droplet and brown degeneration in x zone. (Sudan Ⅲ. stain, ×200.)

Fig. 47. Cancer of adrenal cortex produced by estrogen (3.75mg.). (H.E. stain, ×100.)

Fig. 48. The magnification of Fig. 47. Giant cells in zona fasciculata and zona reticularis. Note the mitotic figure. (H. E. stain. ×800.)

Fig. 49. Ovary of mouse after treatment with estrogen (2.5mg.) Follicular cyst is seen, but no corpora lutea. (H.E. stain, ×40.)

Fig. 50. Ovary of mouse after treatment with estrogen (3.75mg.) Many mature follicles and numerous interstitial cells are seen, but no corpora lutea. (H.E. stain, ×100.)

Fig. 51. Ovary of mouse after treatment with estrogen (3.75mg.). Medullary vascular hyperplasia. (H.E. stain, ×100.)

Fig. 52 Ovary of mouse with mammary cancer produced by estrogen (3.75mg). Bleeding from ovarian stroma and hyaline degeneration is seen. No corpora lutea. (H.E. stain, ×100.)

Fig. 53. Tumor cell in ascites of mouse with EHRLICH's tumor. (Fixed with methanol, stained with GIEMSA reagent, oil immersion ×1000.)

Fig. 54. Tumor cell of EHRLICH's tumor (subcutaneous type). (After embedded in paraffin, stained with H.E. ×100.)

Fig. 55. Same as Fig. 54. Necrosis of central region, colloid degenerations and tumor cells are seen. (H.E. stain, ×100.)

Fig. 56. Tumor cell of EHRLICH's tumor (subcutaneous type). Note the mitotic figure. (Fixed with methanol, stained with GIEMSA reagent, oil immersion ×1000.)

Fig. 57. Cancer cell of mouse with BASHFORD's cancer. (After embedded in paraffin, stained with (H.E. ×100.)

Fig. 58. Adrenal of female mouse with EHRLICH's tumor (subcutaneous type). Zona glomerulosa is normal in appearance, zona fasciculata is degenerating and narrow, x zone is maintained with the nuclei normal in appearance and widened. (H.E. stain, ×100.)

Fig. 59. Adrenal of female mouse with EHRLICH's tumor (subcutaneous type). Adrenal cortex present a picture of marked lipid depletion. (Sudan Ⅲ. stain, ×100.)

Fig. 60. Ovary of mouse with EHRLICH's tumor (subcutaneous type). Good follicular development, but tend to atrophy in the ovary. (H.E. stain, ×40.)

Fig. 61. Ovary of mouse with EHRLICH's tumor (subcutaneous type). Two corpora lutea. Number of corpora lutea less than control mouse. (H. E. stain, ×40.)

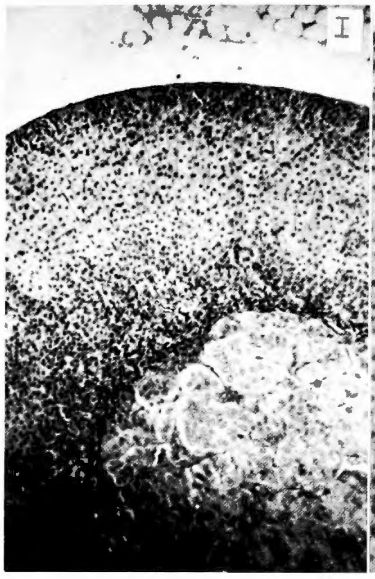
Fig. 62. Ovary of mouse with EHRLICH's tumor (sbcutaneous type). There is considerable Proliferation of theca cells. (H.E. stain ,×100.)

Fig. 63. Adrenal of female mouse with BASHFORD's cancer. Atrophy of adrenal cortex. (H. E. stain, ×100.)

Fig. 64. Ovary of mouse with BASHFORD's cancer. Note good follicular development and corpora lutea formation. (H.E. stain. ×40.)

Fig. 65. Adrenal of intact female mouse treated by emulsion. No significant difference between the control adrenal, except tend to enlarge the cell of zona fasciculata. (H.E. stain ×100.)

Fig. 66. Ovary of intact mouse treated by emulsion. No significant difference between the control ovary. (H.E. stain, ×40.)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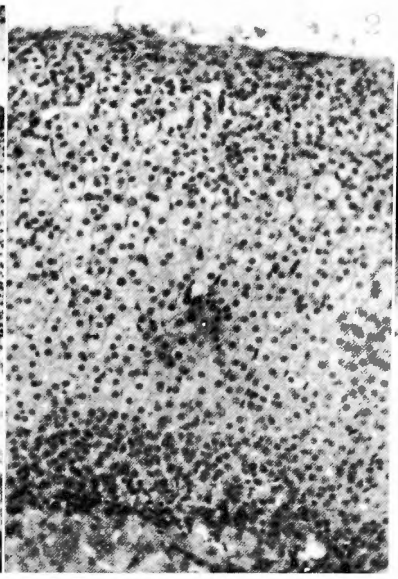
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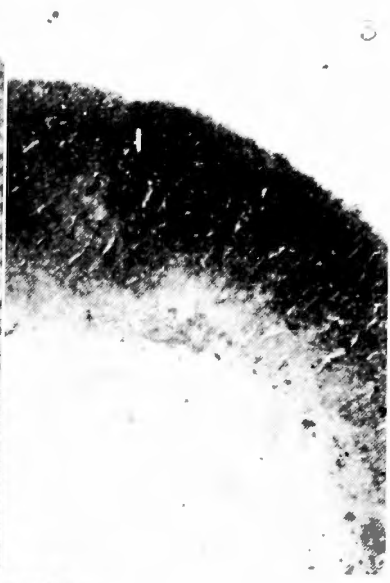
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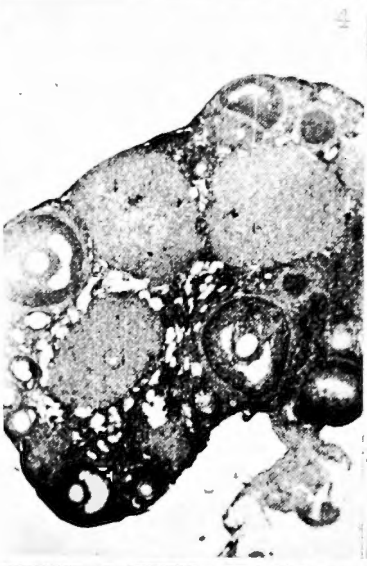
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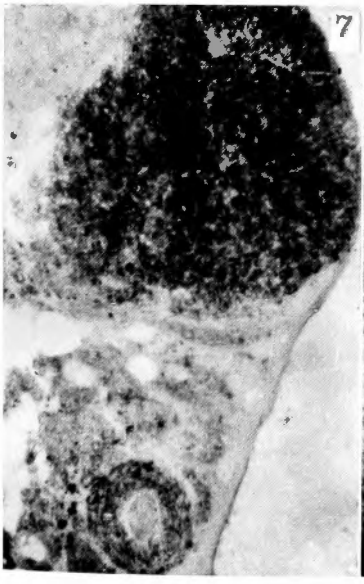
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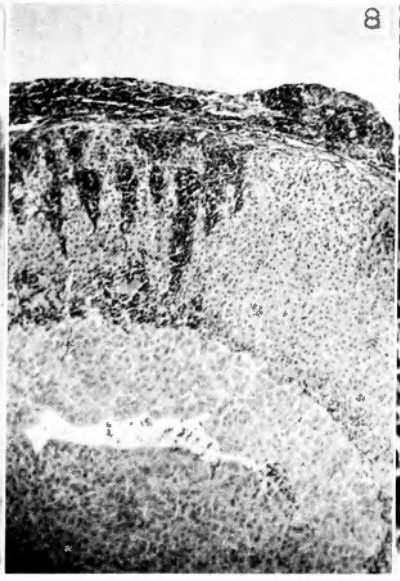
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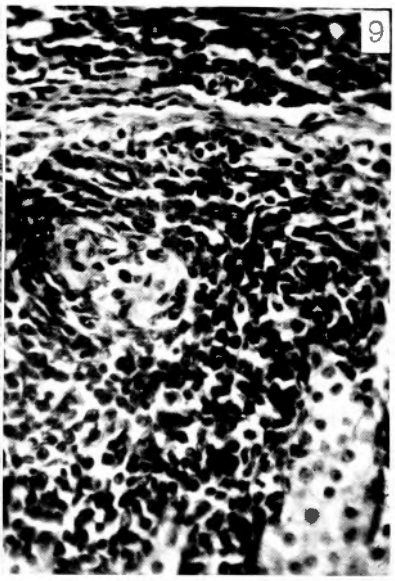
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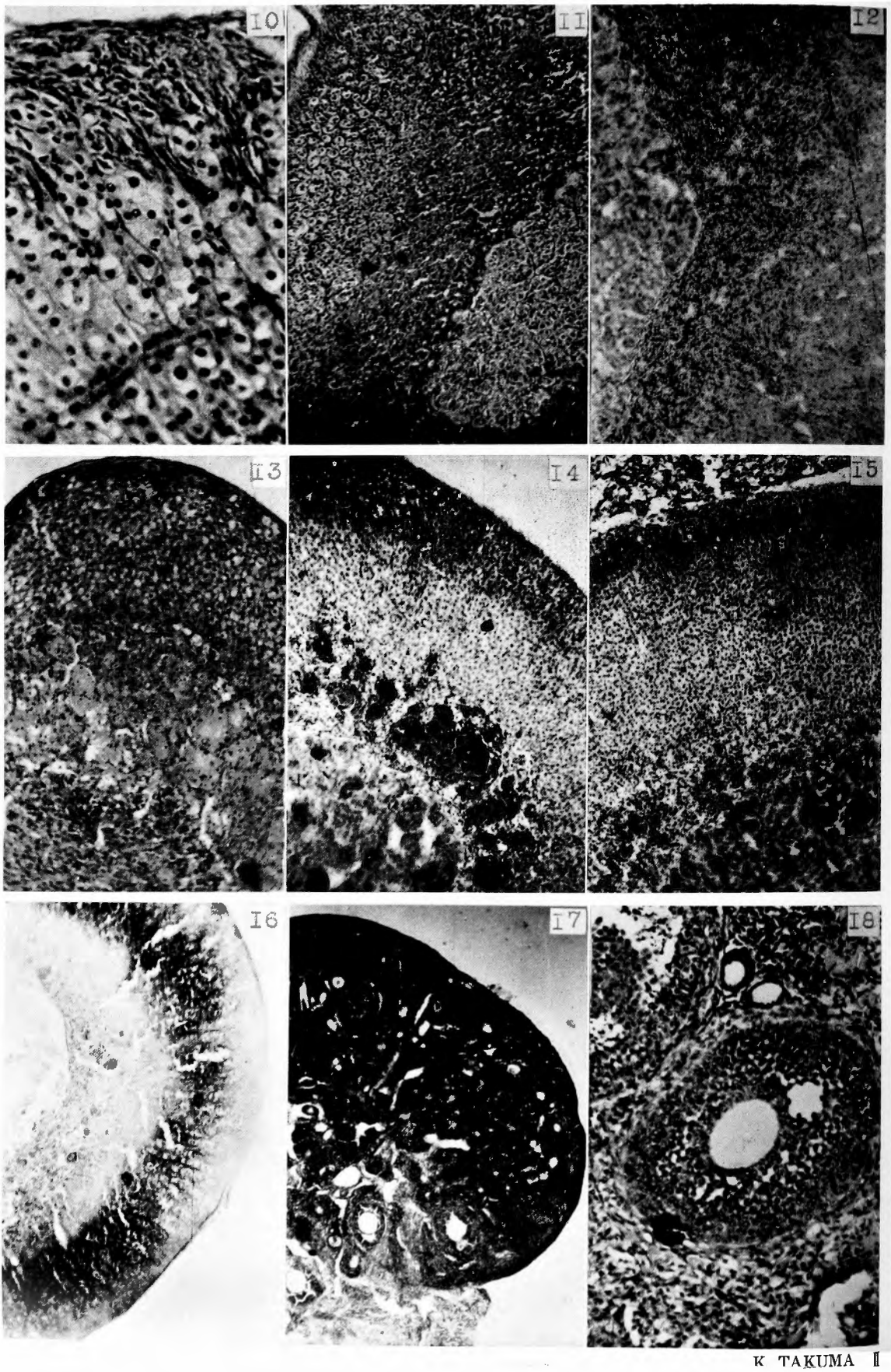

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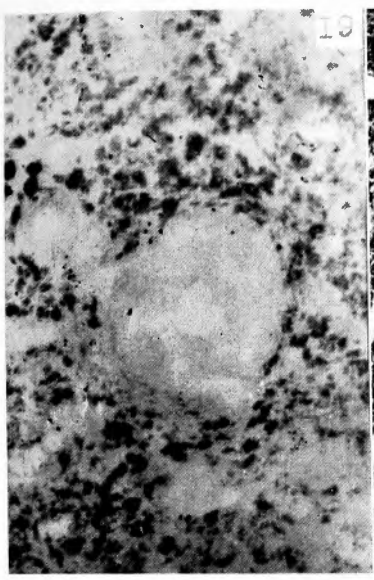
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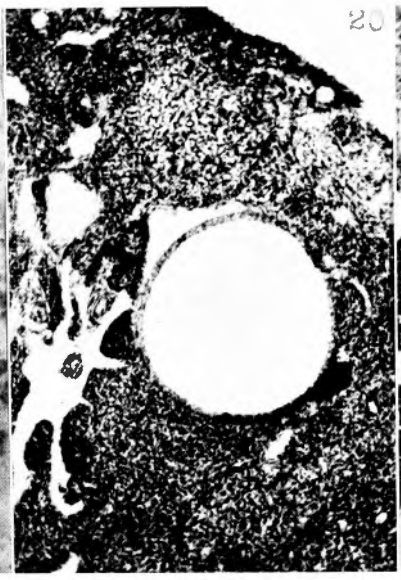
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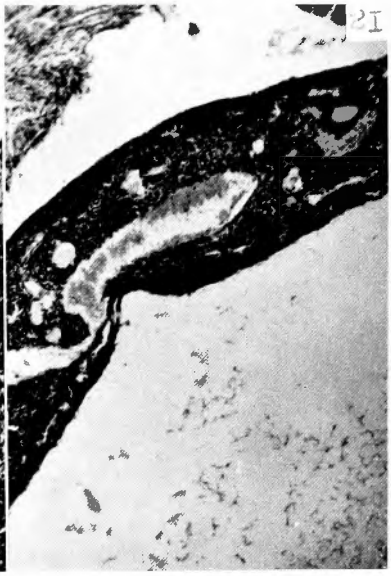
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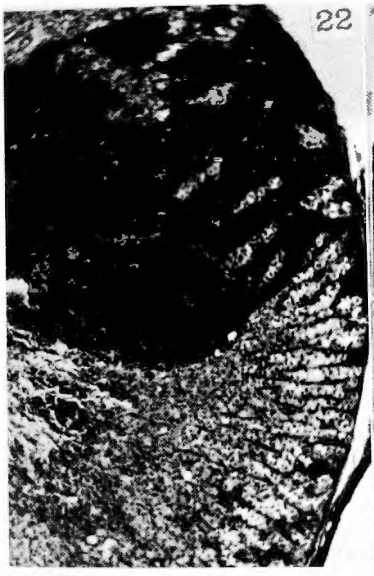
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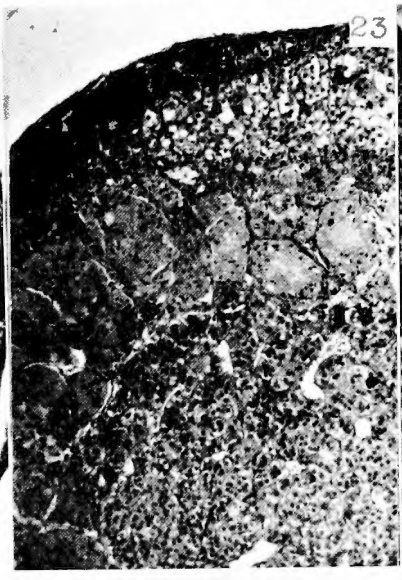
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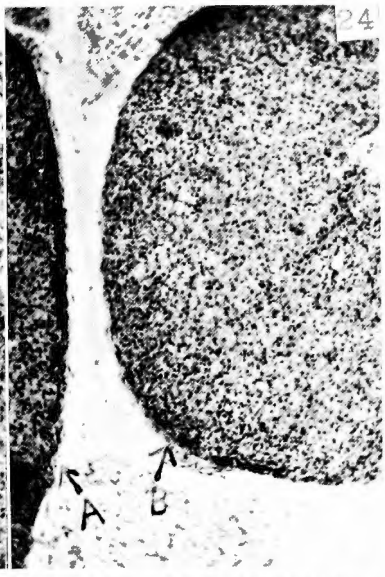
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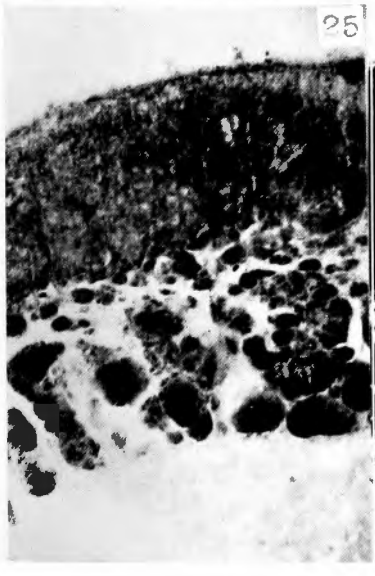
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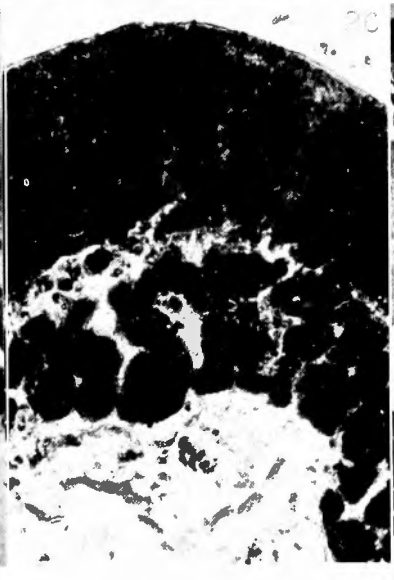
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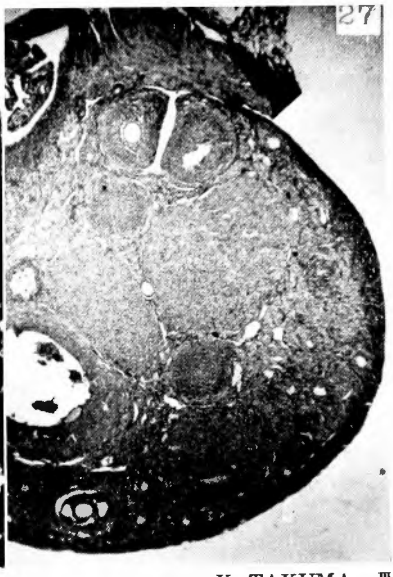
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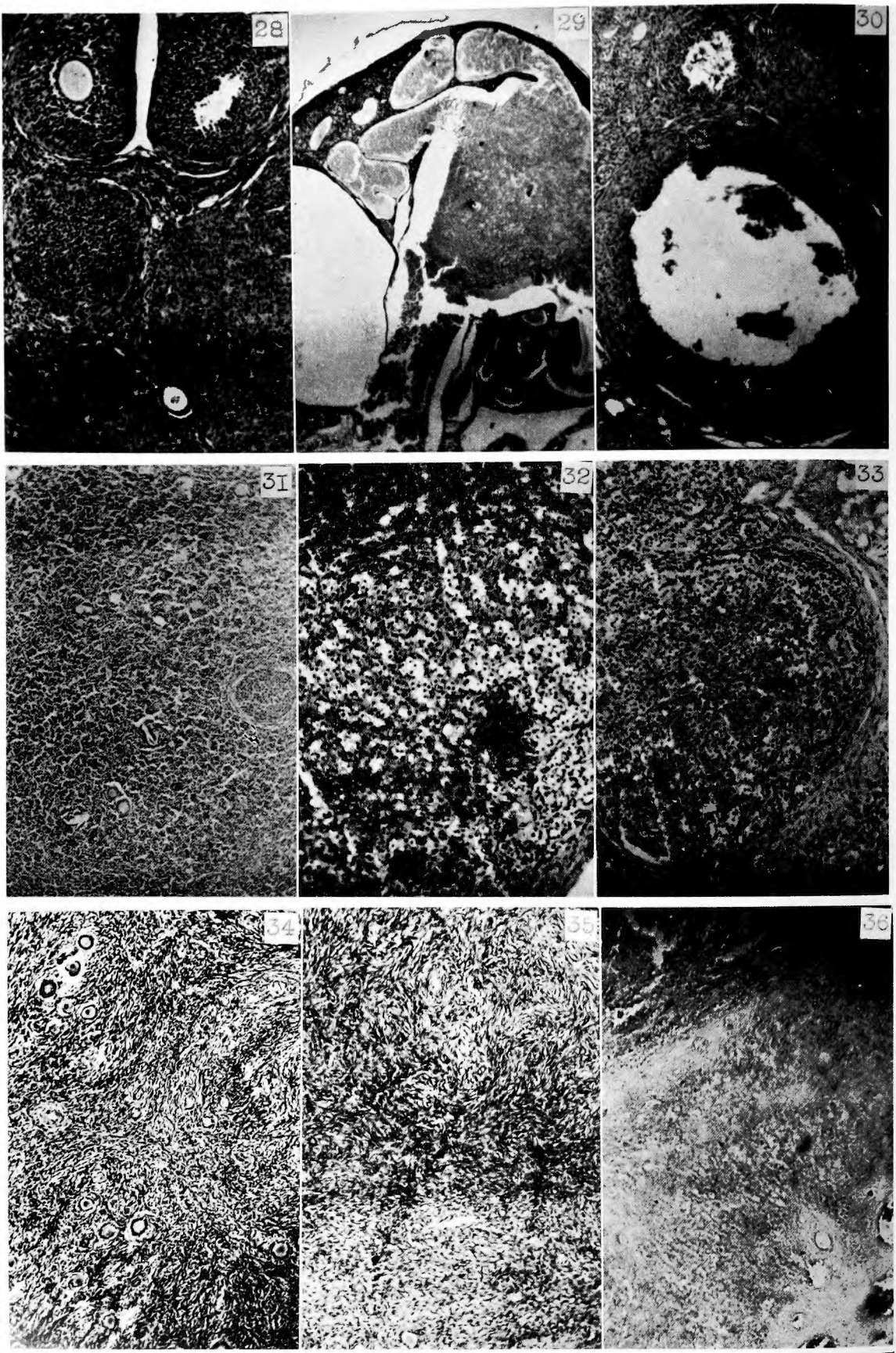
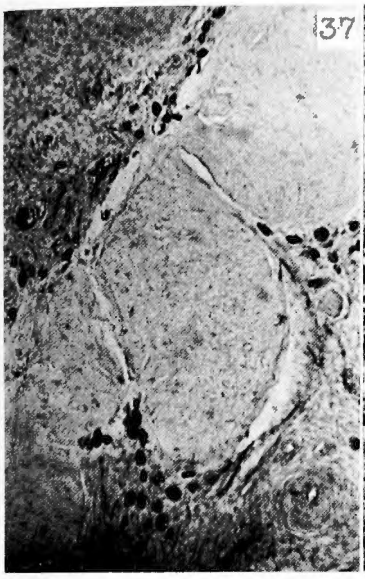


K. TAKUMA Ⅳ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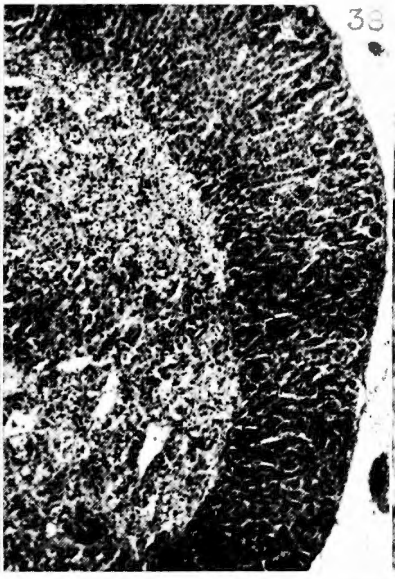
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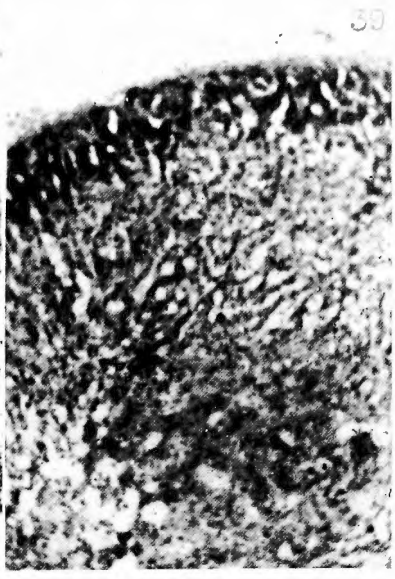
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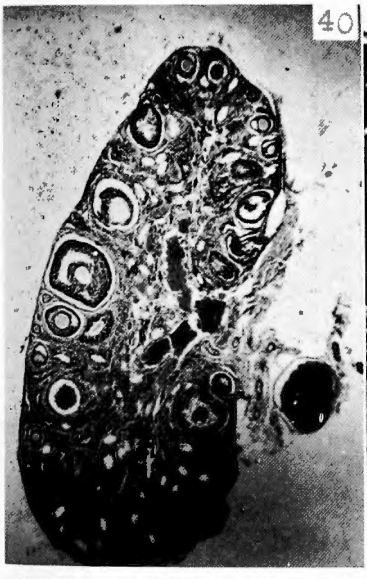
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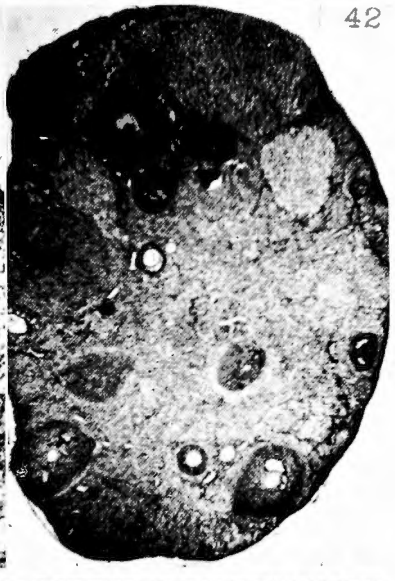
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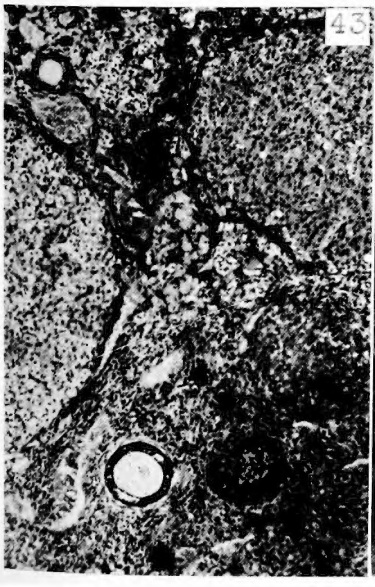
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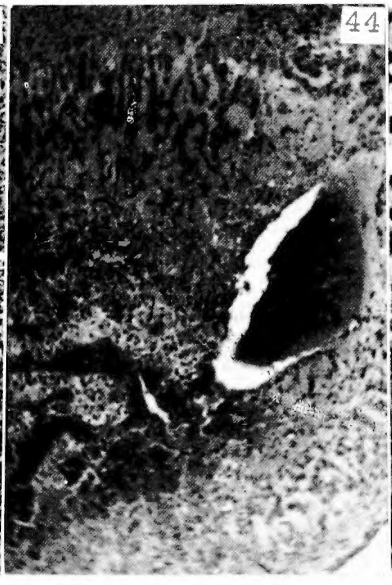
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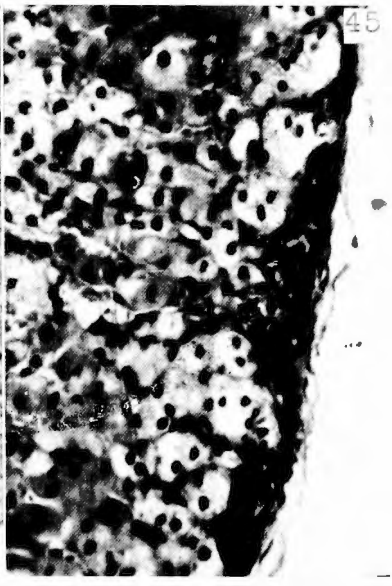
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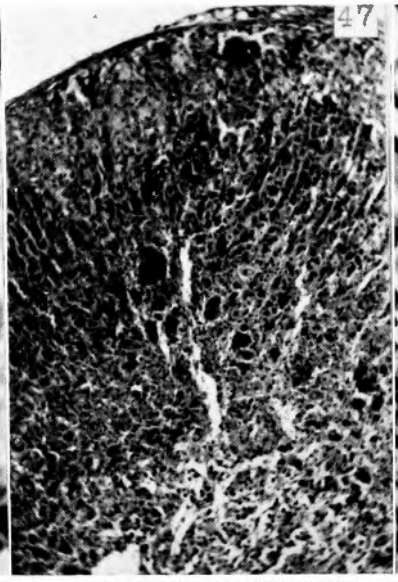
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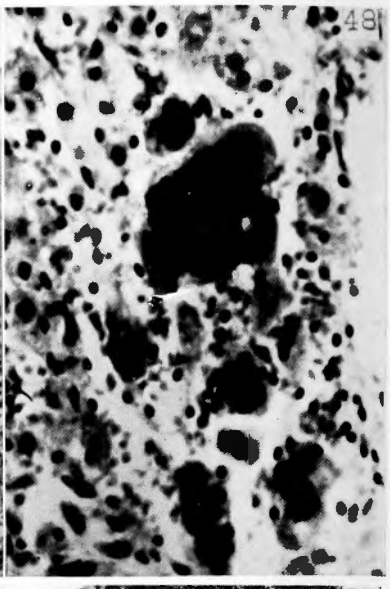
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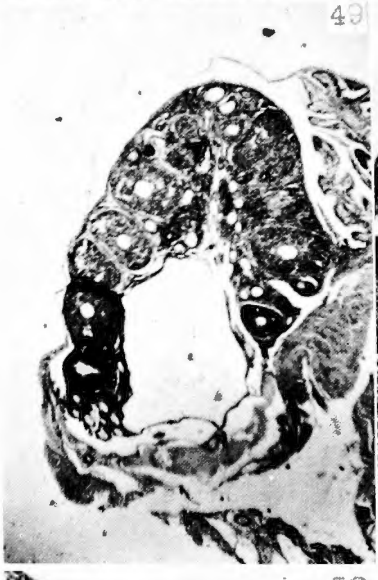
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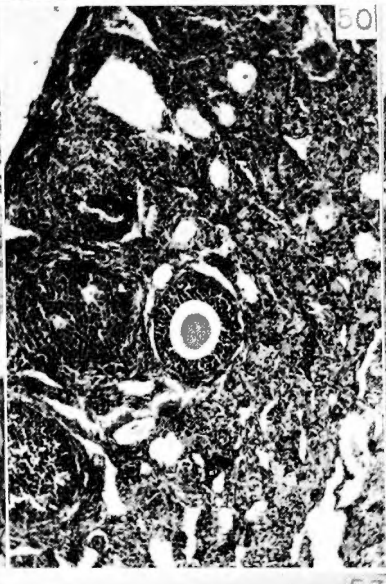
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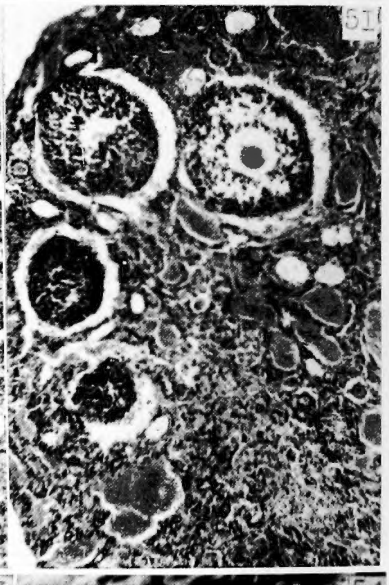
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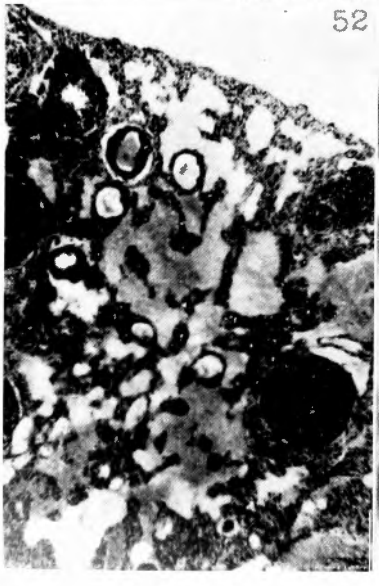
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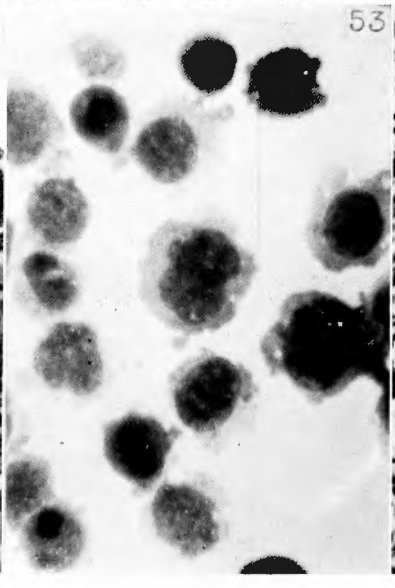
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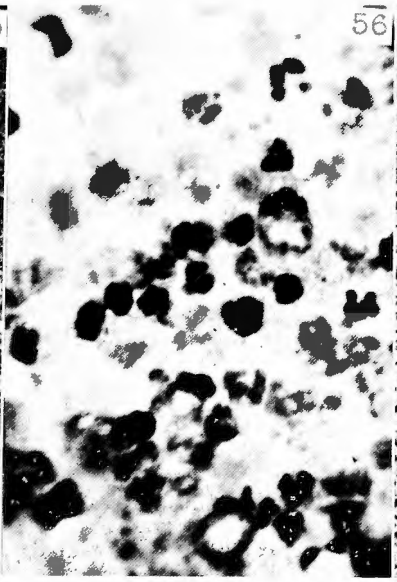
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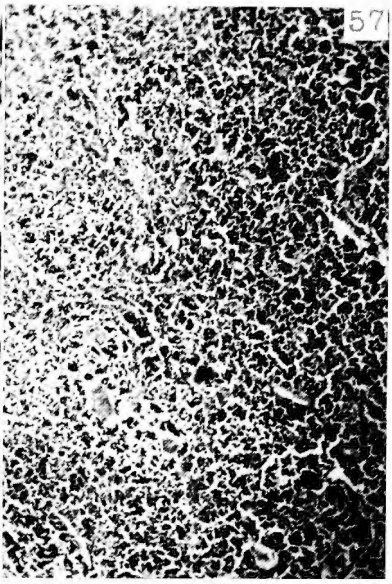
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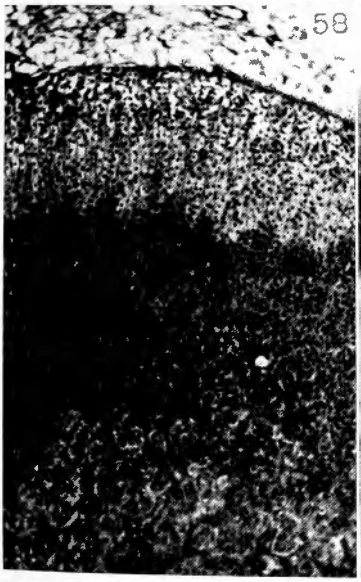
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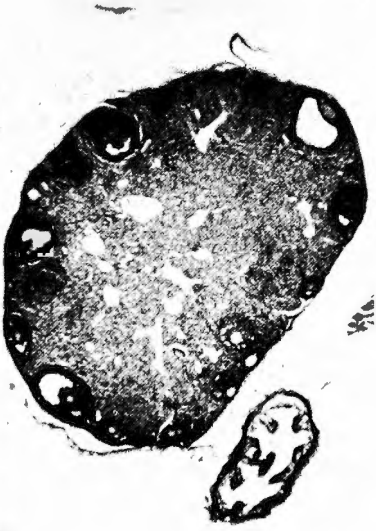
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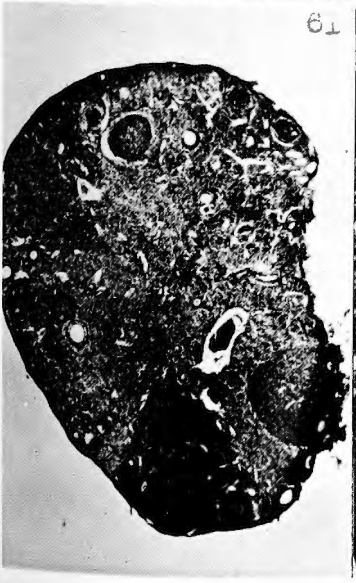
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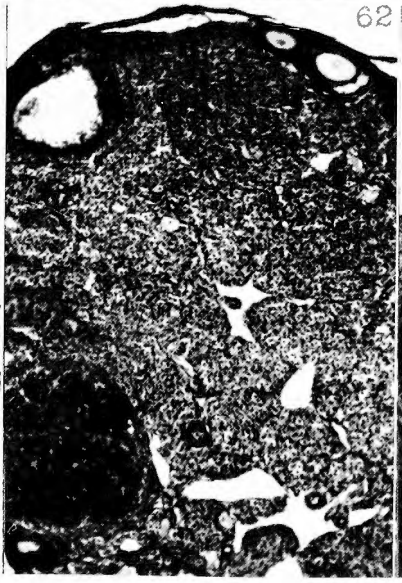
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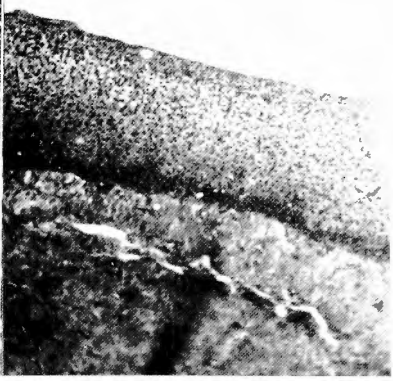

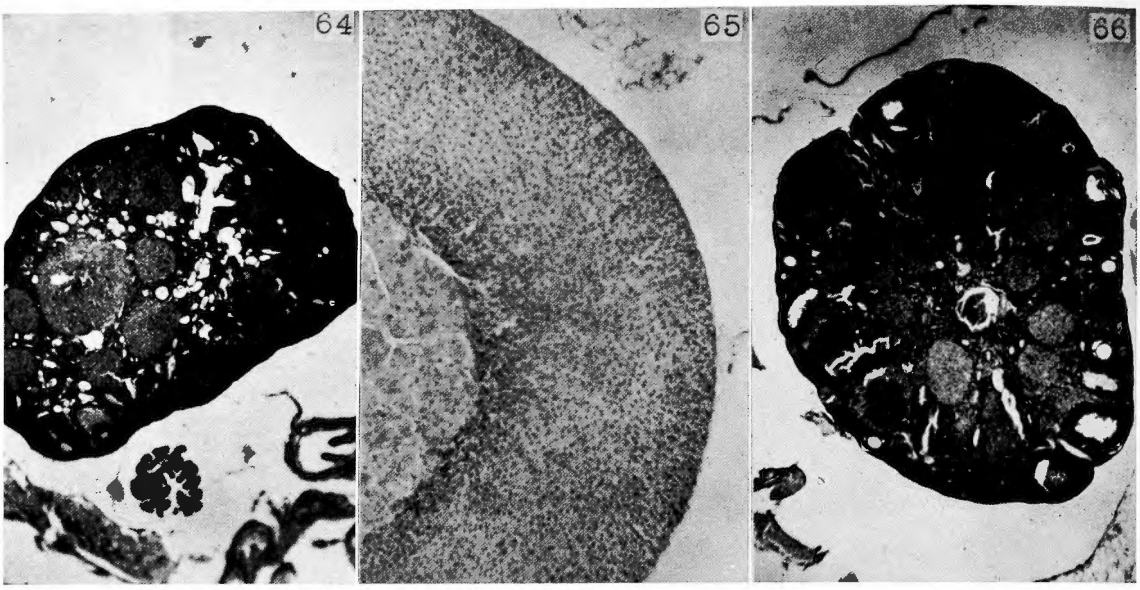
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乳腺腫瘍と副腎皮質卵巣との関係に関する組織学的研究

京都大学医学部外科学教室第2講座（指導：青柳安誠教授）
大学院学生 宅間皓

乳腺腫瘍殊に乳癌或いはマストパチー様変化を来したマウスの副腎皮質，卵巣の組織学的及び組織化学的な変化について研究し，これとSteroidhormone投与による影響，Ehrlich腫瘍，Bashford癌マウスの副腎皮質，卵巣の変化，マウスの乳癌組織のエマルジョン注射による副腎皮質，卵巣の変化とを比較して，次の結論を得た．

1. 乳腺腫瘍の場合には，性腺に起源をもつたホルモンのアンバランスの状態にあることを立証した．このホルモンアンバランスは副腎皮質，卵巣の異常が原因であると考える．

2. 更にアンバランスの状態がEstrogen過剰によるとばかり云えないのであつて，Androgen低下による要素が大なることを推定した．

3. 副腎皮質のX層の褐色変性はCramer & Horning（1937）が述べた如く，乳癌と密接な関係にあることを追試したが，更にマストパチーの場合にも大なる関係があることを証明した．而も褐色変性の像はAndrogen低下による性ホルモン系のアンバランスの一つの指標になるものと考える．

4. Stressの概念から云えば，副腎皮質は抵抗期の状態と考えられ，乳癌及びマストパチー共に一つのStressorであり，機能亢進の像を呈していると考えられる．

5. 乳癌とマストパチーとを比較すると，卵巣では乳癌の場合にはるかに機質的変化が高度であり，マストパチーの場合は軽度であつた．殊にマストパチーでは黄体の形成は良好であつた．副腎皮質の変化は乳癌の場合がより機能亢進の像を示していた．

6. 移殖腫瘍例（Ehrlich腫瘍，Bashford癌）と乳腺腫瘍例の変化とは全く異つており，乳腺腫瘍例の副腎皮質，卵巣の変化は癌による二次的変化即ち乳腺腫瘍発生の結果起つた変化ではなくて，副腎皮質，卵巣の異常が原因的役割を演じているものと考える．

7. 乳癌組織のEmulsionの実験より，乳腺腫瘍例の副腎皮質，卵巣の変化は乳癌組織毒によつて起つた変化ではないことを確めた．

8. 乳癌人間例の1例について，その副腎皮質，卵巣の変化を報告したが，それらの変化がマウス乳癌例の変化と同じ傾向であつた．