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HISTOLOGICAL STUDIES ON ADRENAL GLANDS REMOVED SURGICALLY FROM PATIENTS WITH ADVANCED CANCER OF THE BREAST

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Histological and histochemical examinations were made on adrenal glands removed from 35 cases of patients with advanced cancer of the breast, receiving surgical endocrine therapy.

Adrenal weight and width of Fasciculata-Reticularis (F-R) were increased temporarily after menopause. Adrenal weight, width of F-R and histological findings were correlated with excreted amounts of 17-hydroxycorticosteroids, 17-ketosteroids and estrogens, and more striking correlations were noted between F-R weight and these hormones.

According to the histological judgement of adrenal cortical function, these patients revealed 42.9% of hyperfunction, 42.9% of normal and 14.2% of hypofunction, including a case of adrenal cortical adenoma and of adrenal cortical hyperplasia among the cases of hyperfunction. In the effective cases of adrenalectomy, adrenal weight, F-R width and particularly F-R weight showed a significant increase as compared with the ineffective cases. Histologically, the greater part of effective cases were regarded as the hyperfunction, while almost normal findings were seen in the greater part of ineffective cases, and a marked improvement was observed in the case with adrenal cortical tumor. Many of cases with a longer cancer-bearing period revealed hyperfunctional findings.

Adrenal metastasis of breast cancer was noted in 26%, bilateral metastasis constituting two thirds of them, and the metastasis seemed to arise all in the medulla.

In ovariectomized cases, adrenal weight and cortical width showed a tendency to decrease and most of them indicated histologically a tendency of hypofunction.

The cancer of the breast is a hormone-dependent tumor which can be expected to have remission by removing a source of estrogen. Although Schinzinger[62], Beatson[5], Boyd[8] and Thomson[71] conducted effectively the ovariectomy for the patients having cancer of the breast, later on the surgical therapy has been taken up concerning the adrenal gland, an extraovarian source of estrogen.

As for the adrenalectomy, as a surgical endocrine therapy of the advanced metastatic carcinoma of the breast there have been many reports by Huggins and his co-workers[26~42], West[76][77], Strode[64] and Roe[56], improvements being

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said to be observed in about 50 per cent of the treated patients. On the effectiveness of adrenalectomy in advanced cancer of the breast, Huggins stated that it was observed in those having adenocarcinoma and papillary carcinoma, those administered effectively with androgen before operation or with successful castration, those excreting much estrogens, and those in older age.

It appears that no definite relationship has yet been found in the histological findings between cancer of the breast and the adrenal cortex. Cramer[11] has pointed out "brown degeneration" in cancer of the breast of mice, while Fekete[20] and Flux[23] have considered that the nodular hyperplasia in the adrenal cortex may be a source of estrogen, when cancer of the breast appears in about a half of mice of JAX-dba strain after the ovariectomy. In the case of human cancer of the breast, Huggins[41] measured weight, content of lipid and ascorbic acid in the removed adrenal gland of the patients with the disease, not noting any difference from the normal adrenal gland. According to Sirtori[63], zona fasciculata was hypertrophic in 53 per cent of the adrenal glands in the patients with advanced cancer of the breast, a correlation being seen between the width of zona reticularis and sex-steroids, and in the effective case an increase was noted in the amount of estrogens contained in adrenal homogenate and urine.

Although the effectiveness of the surgical endocrine therapy in advanced cancer of the breast has already been widely recognized, many subjects to be elucidated remain untouched concerning the endocrinological background of the therapy, above all its indication, effectiveness and the postoperative relapse. Particularly in human cancer of the breast, histological endorsement to the behavior of the adrenal cortex is extremely incomplete. The author made histological and histochemical examinations on the adrenal glands removed from the patients having advanced cancer of the breast and at the same time attempted to clarify a relationship between adrenal cortical function and morphological findings.

MATERIALS AND METHODS

Materials

Examinations were made on the adrenal glands removed from 35 women with advanced cancer of the breast who had received the surgical endocrine therapy at the second Department of Surgery, Nagoya University, during the period from May 1957 to July 1961 (Table 1). The patients ranging in age from 32 to 70 years old included 19 cases with primary cancer of the breast and 16 cases showing relapes. The cancer bearing period from appearance of the symptoms to adrenalectomy varied from 15 days at the shortest to 10 years at the longest, being within one year in 7 cases, 1 to 3 years in 16 cases and over 3 years in 12 cases. The amounts of excreted 17-ketosteroids, 17-hydro xycorticosteroids and estrogens in 24 hour urine were as shown in Table 1.

TABLE 1. Materials

Patient No.	Years of age	Diagnosis (mammary cancer)	Cancer-bearing period	Operations	Side of adrenal glands	Disturbance of liver function	Steroids excretion per 24 hours		
							17-Keto-steroids (mg)	17-Hydroxy-cortico-steroids (mg)	Estrogens (μg)
1	32	Relapsed	1 Y. 1 M.	1) Ovariectomy 2) Shunt-operation	Right	++			
2	34	Relapsed	1 Y. 6 M.	1) Ovariectomy 2) Shunt-operation	Right	++			
3	34	Advanced metastatic	5 M.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	+++	4.2		19.5
4	34	Advanced metastatic	3 Y.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	−			
5	35	Advanced metastatic	3 M.	1) Ovariectomy 2) l-Adrenalectomy 3) r-Adrenalectomy	Left and Right	−	1.9	4.5	
6	35	Relapsed	3 Y.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	++		5.4	26.1
7	36	Advanced metastatic	8 M.	1) Ovariectomy 2) Adrenosplenal shunt 3) r-Adrenalectomy	Right	−			14.4
8	37	Advanced metastatic	4 M.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	−	10.2	3.5	18.0
9	38	Advanced metastatic	2 Y. 1 M.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	−	9.7		31.4
10	38	Advanced metastatic	1 Y. 2 M.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	−			15.0
11	39	Relapsed	3 Y. 8 M.	1) Ovariectomy 2) Shunt-operation	Right	+	3.8	1.2	18.2
12	40	Relapsed	4 Y.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	+			23.3
13	40	Relapsed	3 Y.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	−			7.7
14	40	Relapsed	8 Y. 9 M.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	+			9.3
15	42	Advanced metastatic	11 M.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	++			11.1
16	43	Advanced metastatic	2 Y.	1) Ovariectomy 2) Shunt-operation	Right	−	4.3	6.6	
17	43	Relapsed	3 Y.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	+	7.1	8.2	
18	43	Advanced metastatic	2 M.	1) Ovariectomy 2) Shunt-operation	Right	−			

TABLE 1. (*Continued*)

Patient No.	Years of age	Diagnosis (mammary cancer)	Cancer-bearing period	Operations	Side of adrenal glands	Disturbance of liver function	Steroids excretion per 24 hours		
							17-Keto-steroids (mg)	17-Hydroxy-cortico-steroids (mg)	Estrogens (μg)
19	44	Advanced metastatic	7 M.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	−			
20	44	Relapsed	1 Y. 1 M.	1) Ovariectomy 2) Shunt-operation	Right	−	4.9	8.4	20.7
21	47	Relapsed	8 Y.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	−	5.1	4.8	
22	48	Relapsed	1 Y. 9 M.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	−			10.6
23	49	Relapsed	4 Y.	1) Ovariectomy 2) Shunt-operation	Right	++			
24	49	Advanced metastatic	2 Y.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	−		7.5	68.1
25	52	Relapsed	3 Y. 5 M.	1) Ovariectomy 2) Bilateral adrenalectomy	Both		1.8	4.6	18.7
26	54	Relapsed	9 Y. 7 M.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	−	10.4		51.5
27	55	Relapsed	4 Y. 1 M.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	+		12.4	
28	56	Advanced metastatic	15 D.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	+	11.0	9.2	39.1
29	57	Advanced metastatic	4 M.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	−			
30	61	Advanced metastatic	3 Y.	1) Ovariectomy 2) Bilateral adrenalectomy	Both	−	7.2	7 4	
31	62	Advanced metastatic	10 Y.	1) Ovariectomy 2) Shunt-operation	Right	+	1.9	1.8	
32	63	Advanced metastatic	1 Y. 1 M.	1) Ovariectomy 2) Shunt-opertaion	Right	−	4.7	4.6	17.1
33	68	Advanced metastatic	1 Y.	1) Ovariectomy 2) Shunt-operation	Right	+	1.3	1.7	12.7
34	69	Advanced metastatic	1 Y.	1) Ovariectomy 2) Shunt-operation	Right	−	5.0	7.3	
35	70	Advanced metastatic	2 Y.	1) Ovariectomy 2) Shunt-operation	Right	++	10.0	8.5	

The operation was conducted under the endothracheal anesthesia using ether ordinarily, fluothane or cyclopropane in a few cases. As a rule, both ovariectomy and adrenalectomy were carried out in one stage (Table 2). Consequently, there were 1) bilateral ovariectomy and bilateral adrenalectomy: 20 cases, and 2) bilateral ovariectomy, left-adrenosplenic venous shunt and right adrenalectomy: 10 cases. However, in other few cases the operations were made in two stages. Namely, there were 3) 3 cases receiving bilateral ovariectomy as the first stage and bilateral adrenalectomy as the second stage, 4) one case having bilateral ovariectomy as the first stage, left adrenosplenic venous shunt and right adrenalectomy as the second stage, and 5) one case being operated by bilateral ovariectomy and left adrenosplenic venous shunt as the first stage and right adrenalectomy as the second stage.

TABLE 2. Operations

a) One stage operation	30 cases
1) Bilateral ovariectomy and bilateral adrenalectomy	20 cases
2) Bilateral ovariectomy, left adrenosplenic venous shunt and right adrenalectomy	10 cases
b) Two stage operation	5 cases
1) Bilateral ovariectomy ⟶ Bilateral adrenalectomy	2 cases
2) Bilateral ovariectomy ⟶ left adrenosplenic venous shunt and right adrenalectomy	1 case
3) Bilateral ovariectomy and left adrenosplenic venous shunt ⟶ Right adrenalectomy	1 case
4) Bilateral ovariectomy and left adrenalectomy ⟶ Right adrenalectomy	1 case

Treatment of the excised adrenal gland

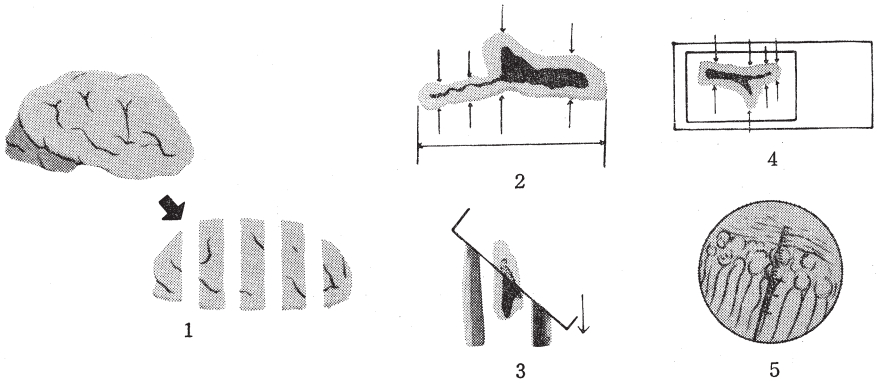
Examinations of the removed adrenal gland were placed in the order shown in Table 3. Immediately after the extirpation the adrenal gland was weighed after the surrounding fat was removed, a portion of the fresh tissue then being set aside for the staining of ascorbic acid. After a large part of the remaining tissue was fixed for 10 days in 10 per cent neutral formalin solution, macroscopical measurement was conducted. In order to measure grossly, the adrenal gland was divided into several thin sections, then each thin section was cut in two pieces, one for making paraffine section and the other for lipid staining. The paraffine sections were employed for the observation of histological findings and microscopical measurements.

Measurement of the adrenal cortical width

The adrenal gland fixed for 10 days in 10% neutral formalin solution was cut perpendicularly to its long axis and bottom surface, to make several thin sections of 5 to 6 mm in thickness (Fig. 1, Fig. 2). The gross measurement was conducted on a surface of the definite side of each thin section, the length

TABLE 3. Treatment of the Removed Adrenal Gland

Fresh adrenal glands just removed
↓
Weighing
↙ ↘
Fixing for 10 days in 10% neutral formalin solution → Gross measurement, dividing into several thin sections (about 6 mm thickness)
Staining of ascorbic acid using fresh materials
Staining of lipid
↘ ↗
Each thin section being cut in two (about 3 mm thikness)
↓
Making paraffine sections
↙ ↘
Staining by hematoxylin and eosin → Histological observaions
Staining by Zinsser's method → Microscopical measurements



1) Fixing for 10 days in 10% neutral formalin solution, the adrenal gland was divided into several thin sections. (*ca.* 6 mm thickness)
2) Gross measurement, the length and width being measured at several spots.
3) Making paraffine sections according to the usual method. Cut along the long axis.
4) Making hematoxylin-eosin samples. These samples were reduced in a definite proportion (*ca.* 3/4).
5) Microscopical measurement. One hematoxylin-eosin sample was examined at over 10 places. One adrenal gland was measured at several tens places. Microscopical values were lastly corrected according to reduced proportion.

FIG. 1. Measurement of each zone of the adrenal cortex.

and width being measured and recorded at several spots. After measured and recorded, the thin sections were paraffine embedded by usual method, being cut 7 μmm in thickness along the long axis to make hematoxylin-eosin stained samples. In the microscopical measurement using hematoxylin-eosin stained specimens, one specimen was examined at more than 10 places, while one adrenal gland was measured at more than several tens places by the use of objectmicrometer. Thus the thickness of capsule, zona glomerulosa and zona

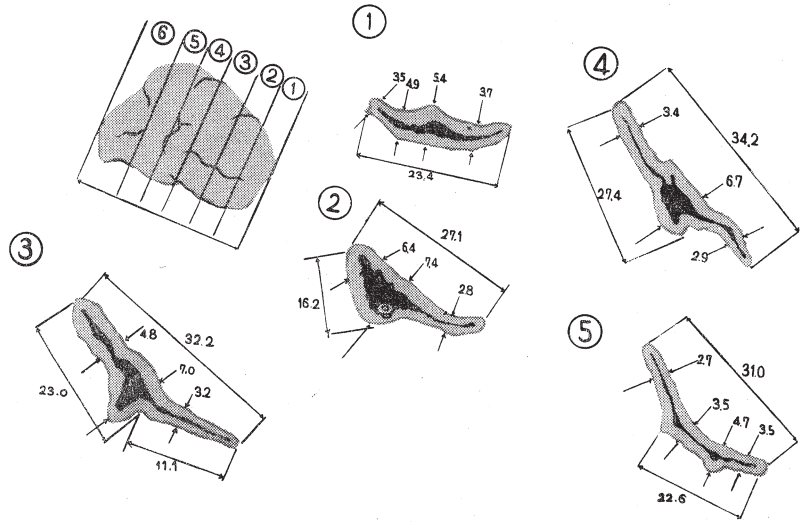


FIG. 2. A case of gross measurement, patient No. 17, Chizuko Yamane, 43 yrs of age, light adrenal gland, weight 4.7 g.

fasciculata-reticularis were measured respectively. All operations were conducted under a definite condition. As the microscopical values were reduced in a definite proportion as compared with the macroscopical values, they were lastly corrected.

Observation of histological findings

Observation of histological findings was chiefly made by using the hematoxylin-eosin stained specimen of about 5 μmm in thickness. Besides, Zinsser's staining was used for ketosteroid-protein complex. According to Zinsser[85], ketosteroid probably gets fuchsinophilia because of its affinity to polysulfonic acid pigment. In order to stain ascorbic acid, fresh material was used according to Girroud and Leblond's method modified by Sosa[49]. Ascorbic acid was noted as black granular sediments of silver corresponding to the Golgi's apparatus in particular within cytoplasm[17)72)7]. To make observation of lipid, the formalin-fixed specimen was cut into frozen sections of about 15 μmm in thickness, stained with Sudan III for 60 min., hematoxylin for 15 min. and sealed with glycerin.

Urinary 17-hydroxycorticosteroids were determined by the method of Reddy, Jenkins and Thorn, urinary 17-ketosteroids by the method of Drekter and urinary total estrogens by the modified method of Engel, Napp and Kersten.

RESULT

Adrenal weight

Being 3.2 to 5.4 g (mean: 4.0±0.11 g) at the right side and 3.7 to 5.3 g (mean: 4.4±0.12 g) at the left side (Table 4), the adrenal weight had a tendency to increase temporarily at the age of about 55, somewhat behind the menopause, but is markedly decreased after the age of 60 (Fig. 3). A positive correlation was noted between the adrenal weight and the amount of 17-ketosteroids, 17-hydroxycorticosteroids and estrogens excreted into the 24 hour urine (Fig. 4-a, b, c). The adrenal weight was 3.5 to 5.4 g (mean: 4.3±0.12 g) in the cases with effective adrenalectomy and 3.2 to 4.4 g (mean: 3.7±0.08 g) in the in-

TABLE 4. Adrenal weight and width of each adrenal cortical zone

Paient No.	Years of age	Side of adrenal glands	Adrenal weight (g)	Width of each cortical zone (mm)				F-R weight (g)	Effect of adrenalectomy	Menopause
				Capsule	Glomerulosa	Fasciculata-reticularis	Total cortical zone			
1	32	R	3.4	0.13	0.15	0.80	1.08	2.52	−	pre-
3	34	R	3.6	0.16	0.13	1.03	1.32	2.81	+	pre-
4	34	R	3.8	0.16	0.20	1.12	1.48	2.88	−	pre-
5	35	R L	3.4 3.7	0.09 0.15	0.15 0.17	0.65 0.87	1.19 0.89	2.48 2.71	−	pre-
6	35	R L	3.9 4.3	0.16 0.14	0.17 0.18	1.46 1.34	1.79 1.66	3.18 3.47	−	pre-
7	36	R	3.3	0.18	0.10	1.02	1.30	2.59	−	pre-
8	37	R	3.9	0.15	0.13	1.20	1.45	3.23	+	pre-
9	38	R L	4.4 4.2	0.14 0.13	0.18 0.24	1.36 1.30	1.68 1.67	3.56 3.27	+	pre-
11	39	R	3.5						+	pre-
12	40	R L	5.4 5.1	0.13 0.15	0.11 0.12	1.02 0.94	1.26 1.21	4.37 3.96	+	pre-
13	40	L	3.7	0.13	0.17	0.94	1.24	2.80	−	pre-
14	40	R	3.8	0.12	0.16	0.89	1.17	2.89	+	pre-
15	42	R	3.9	0.09	0.13	1.02	1.24	3.21	+	pre-
16	43	R	3.8	0.12	0.18	0.90	1.20	2.85	+	pre-
17	43	R L	4.7 4.2	0.11 0.10	0.23 0.19	1.06 0.99	1.40 1.28	3.56 3.25	+	pre-
18	43	R	3.9	0.11	0.20	1.37	1.68	3.18	−	pre-

TABLE 4. (*Continued*)

Patient No.	Years of Age	Side of adrenal glands	Adrenal weight (g)	Width of each cortitical zone (mm)				F-R weight (g)	Effect of adrenalectomy	Menopause
				Capsule	Glomerulosa	Fasciculata-reticularis	Total cortical zone			
19	44	R L	3.8 4.7						+	pre-
20	44	R	3.2	0.13	0.07	1.00	1.20	2.67	−	pre-
21	47	R L	3.6 4.1	0.12 0.11	0.17 0.22	0.88 1.05	1.17 1.38	2.71 3.12	−	pre-
22	48	L	4.0	0.13	0.17	0.96	1.26	3.05	−	post-
23	49	R	(5.7)						+	pre-
24	49	R L	3.9 4.2	0.16 0.12	0.11 0.17	0.96 1.04	1.23 1.33	3.04 3.28	+	pre-
25	52	R L	3.9 4.4	0.14 0.16	0.18 0.17	0.87 1.19	1.19 1.52	2.85 3.45	−	post-
26	54	R L	4.5 4.7	0.12 0.09	0.19 0.18	1.34 1.42	1.65 1.69	3.66 3.95	+	post-
27	55	R L	5.2 5.3	0.10 0.12	0.13 0.15	0.97 0.69	1.20 1.26	4.20 4.16	+	post-
28	56	R L	5.4 4.6	0.21 0.12	0.21 0.17	1.43 1.38	1.85 1.67	4.17 3.80	+	post-
29	57	R L	4.8 4.9	0.17 0.16	0.13 0.16	1.34 1.41	1.64 1.73	3.92 3.99	prevent.	post-
30	61	R	3.3	0.12	0.19	1.19	1.50	2.68	+	post-
31	62	R	3.7	0.16	0.15	0.84	1.15	2.70	−	post-
32	63	R	3.6	0.11	0.04	1.08	1.23	3.16	+	post-
33	68	R L	3.6 3.9	0.18	0.15	1.13	1.46	2.78	+	post-
34	69	R	3.7	0.15	0.09	0.95	1.19	2.95	+	post-

effective cases, a very significant increase in the weight being observed in the effective cases (Fig. 5).

Width of adrenal cortex

As shown in Table 4, the adrenal cortex at the right side had zona glomerulosa of 0.04 to 0.23 mm in width (mean: 0.15±0.009 mm), and zona fasciculata-reticularis of 0.65 to 1.46 mm in width (mean: 1.07±0.037 mm) and the one at the left side had zona glomerulosa of 0.12 to 0.24 mm in width (mean: 0.18±

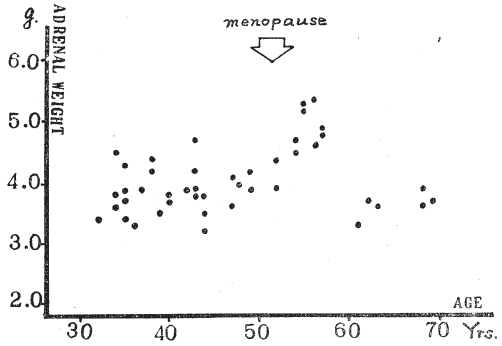


FIG. 3. Relationship between adrenal weight and age

0.008 mm) and zona fasciculata-reticularis of 0.87 to 1.42 mm in width (mean: 1.13 ± 0.053 mm).

Zona fasciculata-reticularis particularly showed a temporary increase in the width after the menopause, while zona gromerulosa did not have such a change

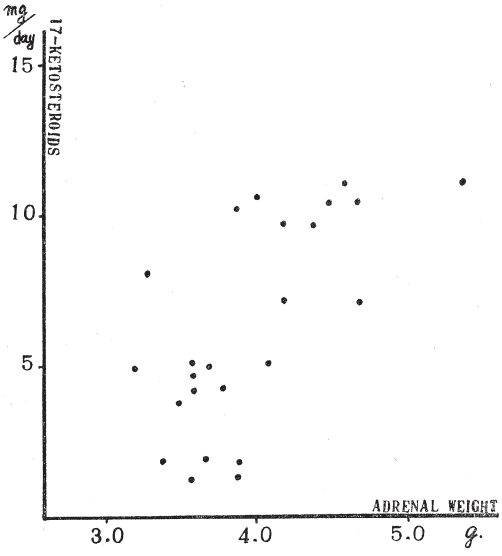


FIG. 4.—a) Adrenal weight and excretion of 17-ketosteroids

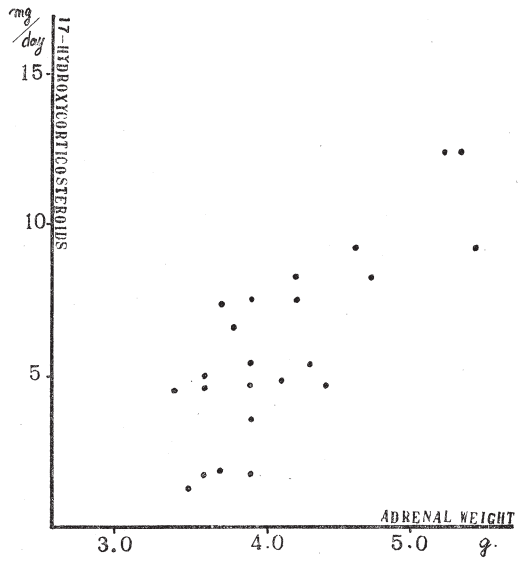


FIG. 4.—b) Adrenal weight and excretion of 17-hydroxycorticosteroids

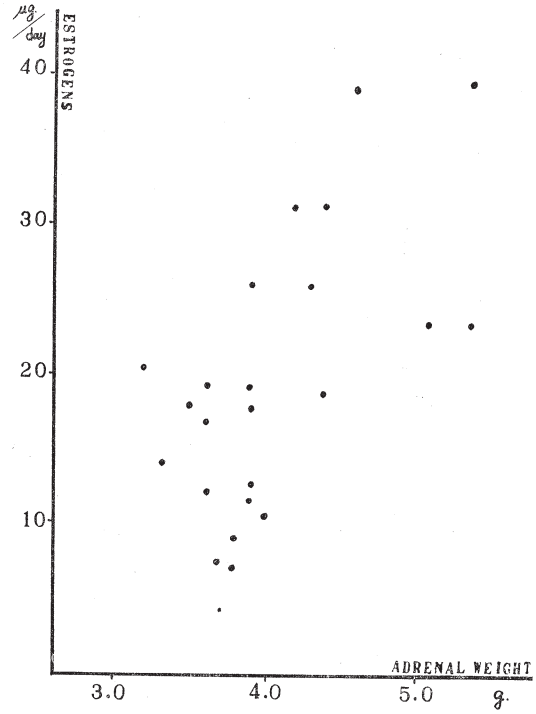


FIG. 4.—c) Adrenal weight and excretion of estrogens

FIG. 4. Relationship between adrenal weight and adrenal cortical function

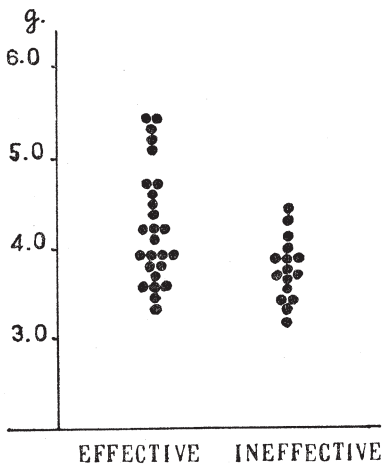


FIG. 5. Adrenal weight and effect of adrenalectomy

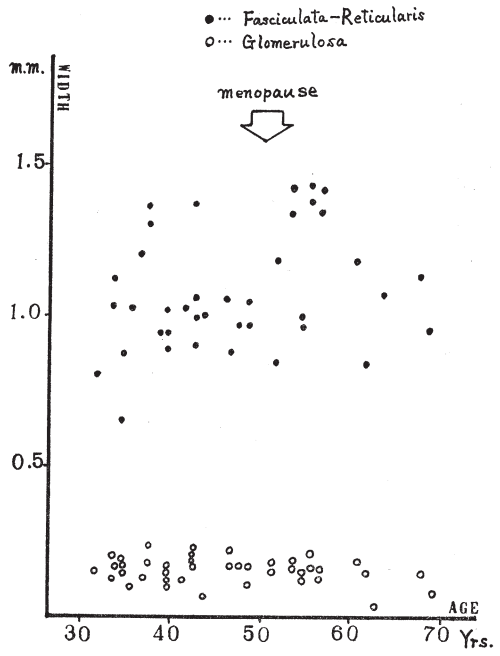


FIG. 6. Relationship between width of each adrenal cortical zone and age

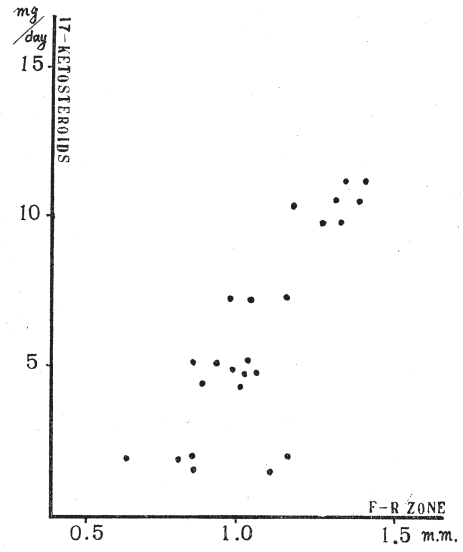


FIG. 7.—a) Width of F-R and excretion of 17-ketosteroids

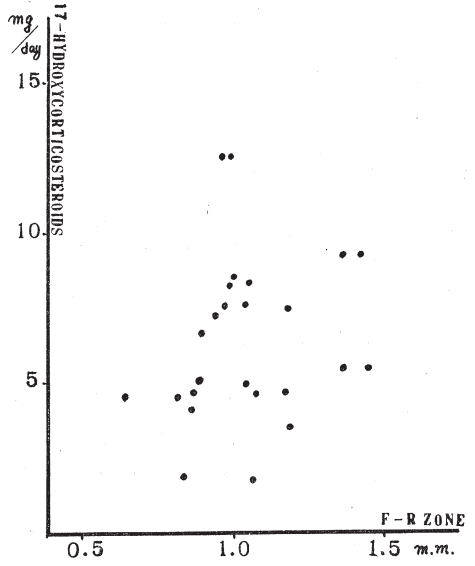


FIG. 7.—b) Width of F-R and excretion of 17-hydroxycorticosteroids

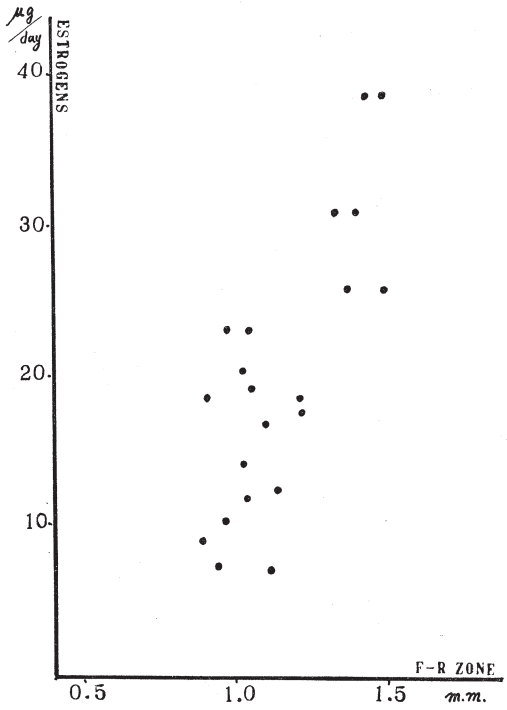


FIG. 7. c) Width of F-R and excretion of estrogens

FIG. 7. Relationship between width of F-R zone and adrnal cortical function

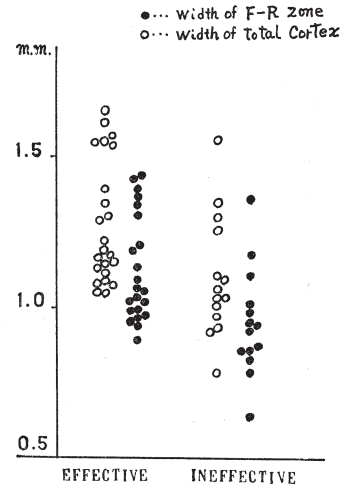


FIG. 8. Width of adrenal cortex and effect of adrenalectomy

(Fig. 6). A correlation could be seen between the zona fasciculata-reticularis, which had been considered to be a source of glucocorticoids and sex-steroids, and the excretion of 17-ketosteroids, 17-hydroxycorticosteroids and estrogens (Fig. 7—a, b, c). Zona fasciculata-reticularis was 0.94 to 1.43 mm in width (mean: 1.13±0.037 mm) in the cases of effective adrenalectomy and was 0.68 to 1.37 mm in width (mean: 0.98±0.052 mm) in the ineffective cases, the formers having significantly a hypertrophic tendency in zona fasciculata-reticularis in comparison with the latters (Fig. 8).

Weight of zona fasciculata-reticularis

A positive correlation was observed between adrenal weight and width of zona fasciculata-reticularis (Fig. 9) with some occasional exceptions against the above tendency. For example, in the adrenal cortex with well-developed giri-like structure, the cortex was also well-developed in spite of its narrowness, even excreting much steroids. Therefore it might be more rational to take up both of weight and width as a single unit which represents the adreno-

cortical function than selecting either of the two.

Zona fasciculata-reticularis weight

$$= \frac{\text{adrenal weight} \times \text{zona fasciculata-reticularis width}}{\text{adrenal cortical width}}$$

Although the above value does not show the correct weight of zona fasciculata-reticularis, it has a close correlation with the adrenal cortical function.

Relationships between the weight of zona fasciculata-reticularis and excretion of 17-ketosteroids, 17-hydroxycorticosteroids and estrogens were shown in Fig. 10 and Fig. 11-a, b, c. The weight was 2.78 to 4.37 g (mean: 3.49±0.11 g) in the cases having received effective adrenalectomy and 2.52 to 3.47 g (mean: 2.84±0.07 g) in the ineffective cases (Fig. 12), and a very significant difference was recognized between them. Therefore, it could be concluded that as compared with ineffective cases the effective cases showed a good development in zona fasciculata-reticularis.

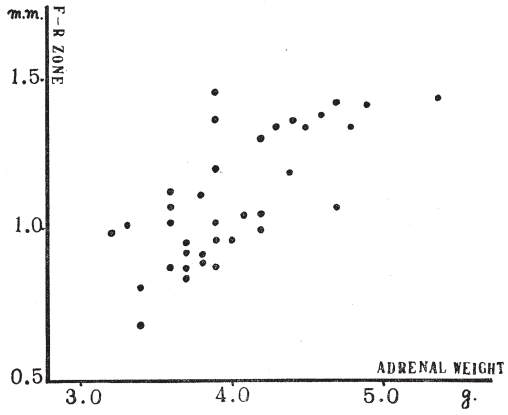


FIG. 9. Relationship between width of F-R zone and adrenal weight

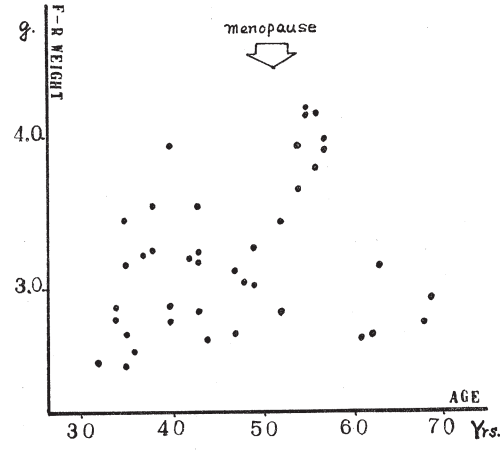


FIG. 10. Relationship between F-R weight and age

Histological expression of adrenocortical function

The most remarkable change observed in the organism exposed to a nonspecific stimulus is hypertrophy and multiplication of adrenal cortical cells and increase in weight of the adrenal gland[43)19)58)70)]. Consequently acceleration and lowering of adrenal cortical function can be discussed by using these changes as an indicator. In this case it has been known that various further histological changes take place in association.

Since Gottshaü[28)29)] the so-called escalator theory has been generally proposed on the form of multiplication of adrenal cortical cells. So it is generally considered that the cortical cells multiplied in the peripheral region of the adrenal cortex gradually move to the inner side and are degenerated and

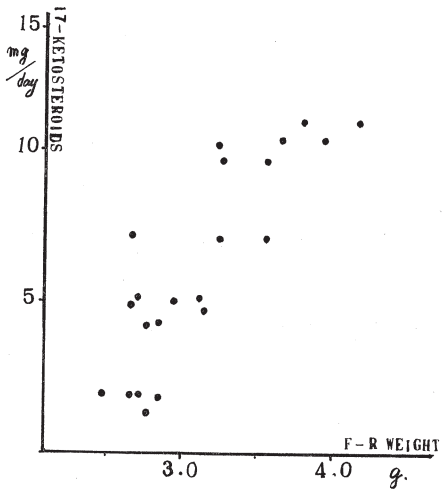


FIG. 11.—a) F-R weight and excretion of 17-ketosteroids

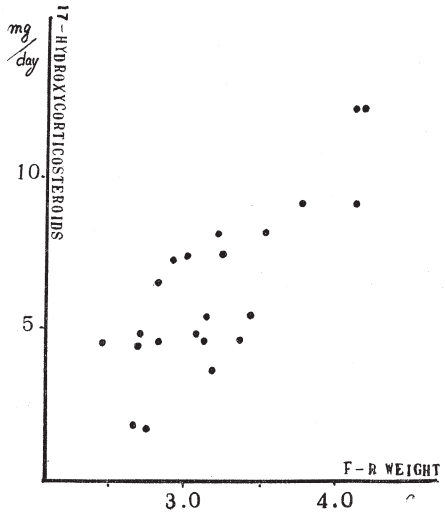


FIG. 11.—b) F-R weight and excretion of 17-hydroxycorticosteroids

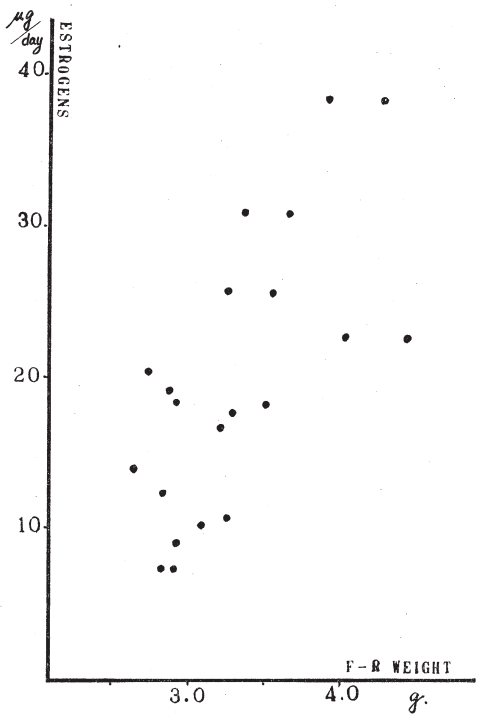


FIG. 11.—c) F-R weight and excretion of estrogens

FIG. 11. Relationship between F-R weight and adrenal cortical function

disposed in zona reticularis after replaced with the cells of inner layer[30)47)]. In addition it is also generally accepted that the capsule is a germinal layer resulting in multiplication of the cortical cells. Zwemer[86)87)] stated that glomerulosa cells generated from intracapsular non-differentiated fibroblasts gradually took a form of cortical cells and spongy cells having lipid granules. As it has been regarded as extremely difficult to find out the cell division in the human adrenal cortex, the author judged new generation and multiplication of the cortical cells mainly by the state of appearance of young cells probably identified as a transforming type of small capsular cells rich in chromatin at the subcapsular zone (Photo. 1).

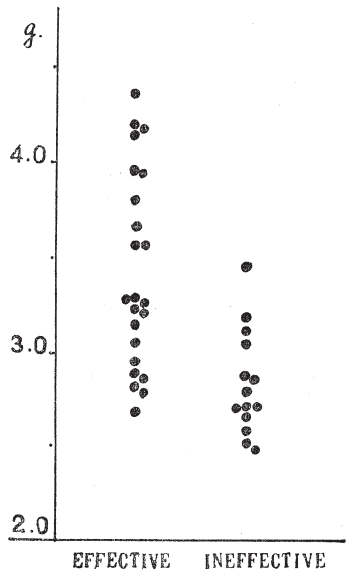


FIG. 12. F-R weight and effect of adrenalectomy

Nodular hyperplasias or cortical nodules can often be seen in the adrenal cortex. According to Selye[104)105)], and Baker[7)] a form of capsular adenoma is noted in the case of hypertrophy and proliferation of the adrenal cortex, while Wooley[80)81)] and Fekete[20)21)] have observed that in mice of JAX-dba strain a number of mitoses and nodular hypertrophy appear in the subcapsular region after ovariectomy, showing estrogenic activity. At any rate the nodular hyperplasia indicates vigorously multiplying mechanism of the cortical cells, thus being regarded as a finding associated with adrenal cortical hyperfunction. A large number of cortical nodules are spherical and circumscribed, presenting a tissue enveloped with relatively thin capsule and not completely different from the normal adrenal gland. In contrast with the true adenoma they usually appear bilaterally, being relatively small in size without autonomy but with a tendency to appear in the multi-number. Among them in various sizes smaller ones consist of a cell group showing irregular arrangement like glomerulosa cells, having a structure similar to zona fasciculata and zona reticularis with growing larger. Being scanty of interstitial tissues and blood vessels in general, these nodules appear in intracapsular (Photos. 2, 3), extracapsular (Photo. 4) and intracortical (Photo. 5) regions. Those in intracapsular region are called the capsular adenoma, while those in extracapsular region are named the accessory adrenal cortical tissue. In addition, in some cases the capsular trabeculae invades the inside of the cortex where the cortical cells are newly generated (Photo. 6) or a group of hypertrophic large foamy cells shows not a normal fascicular arrangement but a network-like or a mosaic structure (Photo. 7). These are sometimes re-

garded as a modified type of the cortical nodules. Cellular characteristics in the cortical nodules, such as proportion occupied by compact cells, amount, nature and state of distribution of lipofuscin granules, lipid granules and ascorbic acid, and the finding of Zinsser's ketosteroid-protein, are very similar to those of the cells of the adrenal gland to which the nodules belong (Photos. 8, 9). Therefore it is presumed that the cortical nodules have a hormonal activity quite similar to that of the adrenal cortex to which those belong in usual. In 3 cases having a strong tendency of hyperplasia and with markedly increased function of the adrenal cortex, the adrenal cortical tissue which consisted of relatively large cells having eosinophilic, compact protoplasm was appeared in fatty tissue surrounding the adrenal gland. In contrast to the ordinary accessory adrenal tissue this has no capsule, transferring directly to the fatty tissue. The fatty cells being adjacent to the above tissue are changed to hypertrophic and compact in nuclei and protoplasm; this finding suggests metaplasia from fatty cells surrounding the adrenal gland to cortical cells (Photo. 10).

Hyperemia is observed in sinusoids and capillaries of the animals with accelerated function of the cortex or exposed to stress, sometimes being seen even hemorrhage within the cortex[52] (Photo. 11). Lipofuscin granules regarded as the pigment indicating degenerative or aging manifestations appear usually around the deep zone of Reticularis in the adult adrenal gland, being increased in the amount and size in the case of cortical hyperplasia and cortical tumor. Accordingly, an increase in the amount of this pigment sometimes points out the finding associated with accelerated function or hyperplasia of the adrenal cortex. The findings stated above were shown in Table 5.

The morphology concerning hormone-production in the adrenal cortex has not yet been fully clarified. It has long been postulated that an abundance of lipid granules contained in the cells of the adrenal cortex would be hormone-bearing agents. Recently with the progress in the histochemical examination of ketosteroid, it has been made clear that the lipid granules are containing cortical hormones. However, in despite of many assumptions concerning relationship between adrenal cortical function and lipid granules, there has been no agreement among them. Some state that the lipid is increased at the time of accelerated function of the cortex and is decreased when the function is lowered[18)22)], others describe the reverse observation[57)84)]. According to Deane and his co-workers[14~17)] and Selye[60)], an increase in the amount of lipid takes place in the case of both hyper- and hypo-function of the adrenal cortex and also a decrease in lipid content is noted in the same manner. Consequently the width of the cortex, size of the cells and characteristics of lipid granules should be comparatively examined for the judgement of the cortical function. Generally speaking, the lipid granules are fine at the hyperfunction, while being rough at the hypofunction. It is concluded that as the lipid granules

TABLE 5. Histological Findings

Patient No.	Years of age	Side of adrenals	Nodular hyperplasia: Intra-cortical	Nodular hyperplasia: Intra-capsular	Nodular hyperplasia: Accessory adrenals	New generation of cortical cells	Mosaic structure	Hyperemia of sinusoids	Lipofascin gr.	Lipid pattern	Ascorbic acid	Adrenal metastasis	Histological judgement	Effect of adrenalectomy	Primary or relapsed
1	32	R	+	−	−	+	+	−	+	+1		−	Hypo.	−	Relap.
2	34	R	−	+	−	+	+	−	+	+1		−	Hypo.	+	Relap.
3	34	R	−	++	+	++	++	+	++	+2	++	−	Hyper.	+	Prim.
		L	−	+	+	++	+	+	++	+2	++	−	Norm.		
4	34	R	+	+	+	++	++	++	++	+2	+	+	Hyper.	−	Relap.
		L	+	++	−	+++	+++	+	+	+2	+	+	Hyper.		
5	35	R	+	−	+	++	++	−	+	+1		−	Norm.	−	Prim.
		L	−	+	−	+	+	−	+	0		−	Hypo.		
6	35	R	++	++	+	+++	+	+	+	+4	++	−	Hyper.	−	Relap.
		L	−	++	+++	++	+	−	+	+4	++	−	Hyper.		
7	36	R	−	+	+	++	+	+++	+	+1	+	−	Norm.	−	Prim.
8	37	R	+	+++	+	+++	−	+	+	+3	++	+	Hyper.	+	Prim.
		L	+	++	+++	++	++	−	+	+3	++	+	Hyper.		
9	38	R	+++	+	+	++	++	+	++	+1		−	Hyper.	+	Prim.
		L	++	+	+	+++	+	++	++	+1		−	Hyper.		
10	38	R	−	−	−	++	+	++	+	+3	++	−	Norm.	Pre-ventive	Prim.
		L	−	−	−	++	+	+	+	+3	++	−	Norm.		
11	39	R	+	++	−	++	++	+	+	+3	++	−	Hyper.	+	Relap.
12	40	R	+	+++	+	++	++	+	+++	+3	+++	−	Hyper.	+	Relap.
		L	+	++	++	++	++	+	+++	+2	++	−	Hyper.		
13	40	R	−	+	−	++	+	+	++	+2	+	+	Norm.	−	Relap.
		L	−	+	+	++	++	−	+	+2	+	+	Norm.		
14	40	R	+	+	−	++	+	−	+	+2	+	−	Norm.	+	Relap.
		L	−	+	−	+++	−	+	+	+2	+	−	Norm.		
15	42	R	+	+	+	+	++	−	+	+2	+	+	Norm.	+	Prim.
		L	−	++	+	++	+	−	+	+2	+	+	Norm.		
16	43	R	−	+	+	+++	++	−	+	+2		−	Norm.	+	Prim.
17	43	R	+	+++	+	++	++	+++	++	+4		−	Hyper.	+	Prim.
		L	+	+++	−	++	++	+++	++	+4		−	Hyper.		
18	43	R	±	+	−	+	+	−	+	+2	+	−	Norm.	−	Relap.
19	44	R	+	+	−	+	+	−	+	0		−	Norm.	+	Prim.
		L	+	+	+	++	++	+	+	0		−	Norm.		
20	44	R	−	++	+	+	++	−	+	+1	+	+	Norm.	−	Prim.

TABLE 5. (*Continued*)

Patient No.	Years of age	Side of adrenal	Nodular hyperplasia: Intra-cortical	Nodular hyperplasia: Intra-capsular	Nodular hyperplasia: Accessory adrenals	New generation of cortical cells	Mosaic structure	Hyperemia of sinusoids	Lipofuscin gr.	Lipid pattern	Ascorbic acid	Adrenal metastasis	Histological judgement	Effect of adrenalectomy	Primary or relapsed
21	47	R L	+ +	+ +	+ −	+ +	+ +	+ +	++ ++	+1 +2		− −	Norm. Norm.	−	Relap.
22	48	R L	+ +	+ ++	− −	++ ++	+ +	− −	+ +	+1 +1	+ +	− −	Norm. Norm.	−	Relap.
23	49	R	−	−	−	+	−	−	+	0		+	Hypo.	+	Relap.
24	49	R L	± ++	+ ++	− +	++ ++	++ ++	+ +	++ ++	+1 +2		− −	Norm. Hyper.	+	Prim.
25	52	R L	− +	− +	− −	++ ++	+ −	+ +	+ ++	0 +1	± +	− +	Hypo. Norm.	−	Relap.
26	54	R L	+ −	+ ++	+ −	+++ ++	+ −	+ +	+ ++	+3 +3	++ ++	− −	Hyper. Hyper.	+	Relap.
27	55	R L	++ ++	+++ +++	+ +	+++ +++	+++ ++	+ +	+ +	+2 +1	+ +	− −	Hyper. Hyper.	+	Relap.
28	56	R L	++ ++	++ ++	++ ++	+++ +++	+++ +++	+++ +++	++ ++	+3 +3		− −	Hyper. Hyper.	+	Prim.
29	57	R L	++ −	+ −	++ −	++ ++	+ +++	− −	++ ++	+2 +2	++ ++	− −	Hyper. Norm.	Pre-ventive	Prim.
30	61	R L	+ +	++ +	+ +	++ ++	+ ++	+ +	++ ++	+3 +3	++ ++	− −	Hyper. Hyper.	+	Prim.
31	62	R	+	−	+	++	+	++	+	+1		+	Norm.	−	Prim.
32	63	L	−	−	−	+	+++	−	+	+1	+	−	Norm.	+	Prim.
33	68	R L	− ++	+ −	+ +	++ ++	+++ +++	++ ++	+++ ++	+2 +2	++ +++	+ −	Hyper. Hyper.	+	Prim.
34	69	R	+	++	−	++	++	−	+	0		−	Norm.	+	Prim.
35	70	R	−	+	−	+	++	−	++	0		−	Norm.	+	Prim.

contained in the cortical cells become more fine and abundant, the cortical function is much accelerated. Yoshimura[84] presumes that lipid granules are usually decreased in number or almost disappear when exposed to acute or chronic stress, while stainable granules being increased instead and that a small type of lipid granules, namely those produced just from the stainable granules contain a much quantity of hormone, thus probably forming the most effective hormone-bearing agents. As stated above, characteristics and distribution of lipid in the adrenal cortical cells can be a powerful indicator for the

supposition of their function. Concerning the distribution of adrenal cortical lipid, the author was in accordance with the judgement by Currie[12] and Symington[16] referring to the characteristics of the lipid granules (Table 6, Photos. 12, 13 and 14). As the behavior of ascorbic acid was similar to that of lipid granules, it was made a subsidiary method for the judgement of the cortical function.

TABLE 6. Assessment of Adrenal Patrerns (Currie)

Adrenal pattern	Assessment
"Normal" lipid-laden adrenal	0
Focal lipid depletion of 1~25 per cent of the cortex	+1
Focal lipid depletion of 25~50 per cent of the cortex	+2
Focal lipid depletion of 50~95 per cent of the cortex	+3
Almost complete or complete diffuse depletion	+4

Histological and histochemical findings

Chiefly from the histological standpoint the judgement of the adrenal cortical function was made synthetically in reference to the state of generation of the cortical cells, increase and decrease in the number of cortical nodules, mosaic structure of cortex, hyperemia and enlargement of sinusoids, lipofuscin granules, size of the cortical cells, characteristics and distribution of lipid granules, width of the adrenal cortex and weight of the adrenal gland (Table 5). Due to this histological judgement histological findings of the adrenal glands of 35 cases of the patients having cancer of the breast disclosed 5 cases (14.3%) with hypofunction, 15 normal cases (42.9%) and 15 cases (42.9%) with hyperfunction. The hyperplasia (Photo. 16) of the bilateral adrenal cortex was observed in one of the cases with hyperfunction and the adrenal cortical adenoma about 4 mm in diameter (Photo. 17) was found in the left adrenal gland of another case.

A certain correlation was observed between the histological finding and excreted amount of 17-ketosteroids, 17-hydroxycorticosteroids and estrogens (Fig. 13). Of 35 adrenalectomized cases both subjective and objective findings were improved in 21 cases, no improvement was noted in 12 cases, and 2 cases received preventive adrenalectomy for the suppression of the relapse. The histological findings obtained from 21 effective cases indicated 2 cases with hypofunction (9.5%), 7 normal cases (33.3%) and 12 cases with hyperfunction (57.1 %). On the other hand, the histological findings of 12 ineffective cases disclosed 3 cases with hypofunction (25.0%), 7 normal cases (58.3%) and 2 cases with hyperfunction (16.7%) as shown in Table 7. That is, in the effective cases a majority of them showed the histological finding indicating hyperfunction, while in the ineffective cases normal histological findings were much more. In the

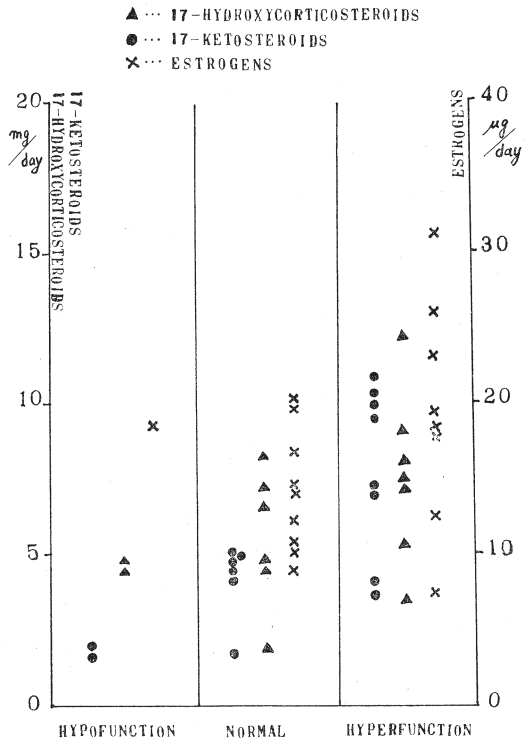


FIG. 13. Relationship between histological finding and urinary steroids

TABLE 7. Relationship between Effect of Adrenalectomy and Histological Finding

	Assessment by lipid pattern					Histological judgement		
	0	+1	+2	+3	+4	Hypo-function	Normal	Hyper-function
Effective	5	6	12	10	2	2 (2)	11 (7)	21 (adrenals) (12) (cases)
Ineffective	2	9	6	0	2	3 (3)	12 (7)	4 (2)

cases in which the interval between appearance of cancer of the breast and adrenalectomy was less than 3 years there were 3 cases with hypofunction, 11 normal cases and 6 cases with hyperfunction, while in the cases with the interval of over 3 years there were 2 cases with hypofunction, 4 normal cases and 9 cases with hyperfunction. From above results, it could be concluded that those having a longer period of interval between the appearance of breast cancer and adrenalectomy showed much more findings of hyperfunction.

Adrenal metastasis of breast cancer

Patients having adrenal metastasis of breast cancer were 6 (26%) of 23 cases examined for their bilateral adrenal glands, of 6 cases bilateral metastasis being noted in 4 cases, unilateral metastasis being seen in 2 cases. Moreover, those having a longer cancer-bearing period showed much more frequency of the adrenal metastasis. Patients with the metastasis of cancer in the remote organs usually showed higher occurrence of adrenal metastasis than those without metastasis. It appeared that the adrenal metastasis of cancer primarily arised chiefly in the medulla (Photo. 18). The number of cases (6 cases) with nodular metastatic lesions clearly divided from the adrenal tissue is more than that of cases (3 cases) having diffuse infiltrative metastatic lesions.

Ovariectomized cases

As shown in Table 8, 5 patients before menopause received adrenalectomy at a definite interval after the ovariectomy. The adrenal weight was 3.3 to 4.7 g (mean: 3.7±0.21 g), being somewhat decreased in weight as compared with that of 3.2 to 5.4 g (mean: 4.2±0.11 g) in one stage operation group. As for the width of the adrenal cortex, zona gromelurosa is 0.10 to 0.17 mm in width (mean: 0.14±0.015 mm), and zona fasciculata-reticularis was 0.65 to 1.02 mm

TABLE 8. Ovariectomized Cases

No. 13.	40 years	Premenopausal	Ovariectomy	⟶ 100 days	Bilateral adrenalectomy
No. 19.	44 years	Premenopausal	Ovariectomy with Mastectomy	⟶ 1 month	Bilateral adrenalectomy
No. 1.	32 years	Premenopausal	Ovariectomy	⟶ 7 months	Left adrenosplenal shunt with right adrenalectomy
No. 7.	36 years	Premenopausal	Ovariectomy with left adrenosplenal shunt	⟶ 2 months	Right adrenalectomy
No. 5.	35 years	Premenopausal	Ovariectomy with left adrenalectomy	⟶ 1 month	Right adrenalectomy

Patient No.	Side of adrenal	Adrenal weight (g)	Width of the cortex (mm)			F-R weight (g)	Nodular hyperplasia			New generation of the cortical cell	Mosaic structure	Hyperemia of sinusoids	Lipofuscin gr.	Lipid pattern	Ascorbic acid	Histological findings
			G.	F-R	Total		Intra-cortical	Intra-capsular	Accessory adrenals							
13	R	3.7	0.17	0.94	1.24	2.80	−	+	−	++	+	+	++	+2	+	Normal
	L						−	+	+	++	++	−	++	+2	+	Normal
19	R	3.8					+	+	−	+	+	−	+	0		Normal
	L	4·7					+	+	+	++	++	+	+	0		Normal
1	R	3.4	0.15	0.80	1.08	2.52	+	−	−	+	+	−	+	+1		Hypo-function
7	R	3.3	0.10	1.02	1.30	2.59	−	+	+	++	+	++	+	+1	+	Normal
5	L	3.7	0.17	0.87	1.04	2,71	+	−	+	++	++	−	+	+1		Normal
	R	3.4	0.15	0.65	0.87	2.48	−	+	−	+	+	−	+	0		Hypo-function

in width (mean: 0.85±0.068 mm), both showing a tendency to be reduced in width in comparison with zona fasciculata-reticularis of 0.84 to 1.46 mm in width (mean: 1.12±0.032 mm) in one stage group. Histologically, there were none of hyperfunction, 3 cases of normal and 2 cases of hypofunction. However most of these cases were not effective on adrenal surgery.

DISCUSSION

According to Engel[19] and Tepperman[70] increase and decrease in the weight of adrenal glands are most correct indicator for examining the state of adrenal cortical function. Hartman[35] states that these are due to the degree of hyperplasia and multiplication of the cortical cells and increase in the amount of blood and water. The increase in weight is not significant by stimuli given during a short period of time, becoming remarkable after the continuous stimulation for a definite period of time[58]. In this series, examination of surgically removed adrenal glands of 35 cases of women bearing breast cancer conducted from a viewpoint of the age disclosed that an increase in adrenal weight was observed at the age of about 55, several years behind the menopause. Simultaneously, width of the adrenal cortex, particularly fasciculata-reticularis zone showed almost the same tendency. In general, in spite of the ovarian hypofunction in post menopausal women the excretion of estrogens was not always decreased as compared with those in premenopausal[9,31,37,65]. Hadfield[33] stated that the decreased excretion of estrogens from ovaries after menopause or ovariectomy promoted excretion of pituitary gonadtrophin, then stimulating excretion of estrogens in fasciculata-reticularis zone of the adrenal cortex. In connection with this, there has been many reports about hypertrophy of adrenal cortex caused by gonadtrophic hormone[1,9,73,74]. These evidences appear to explain a temporary hypertrophic tendency and histological finding of hyperfunction in fasciculata-reticularis zone during the postmenopausal period. It is generally said that nodular hyperplasia is increased after menopause at which ovarian function is decreased. Fekete[20] and Flux[23] stated that in the ovariectomized mice nodular hyperplasia appeared in the multinumber, the structure of which was similar to that of ovarian lutein cells of mice, forming a source of estrogen. In this series increase in number of cortical nodules after menopause of ovariectomy is not always remarkable. However, in the cases where examinations showed cortical hyperfunction, it was observed that nodular hyperplasia tended to increase.

As it has often been stated that in animals under various stress the hyperplasia of adrenal cortex, increase in adrenal weight and accelerated excretion of glucocorticoids are noted, it is interesting to find a relationship between morphological finding and function in the human adrenal glands and further to know a possibility of the functional dualism[6,14,16] as stated by Deane. Ex-

amination of the relationship among the amount of 17-ketosteroids, 17-hydroxy-corticosteroids and estrogens excreted into the urine, weight of excised adrenal glands and cortical width revealed that correlations were found out between excreted amount of the steroids and adrenal weight, between the former and width of fasciculata-reticularis zone respectively. Consequently, it was clearly noted in the human adrenal glands that increase and decrease in excretion of corticosteroids were closely related to those in width of fasciculata-reticularis zone. Although the result was obtained which indicated that a correlation between excreted amount of estrogens and width of fasciculata-reticularis zone was not so clear as in the case of glucocorticoids, it must be considered that as for the source of estrogens before menopause the ovary had a primary significance, that cortical nodules or zona reticularis were significantly considered as sources of estrogens and additionally the entero-hepatic circulation of estrogens in relation to the liver function. Observation of the relationship between histological findings and cortical function disclosed that those with more advanced hyperfunction of the cortex evidenced histologically and histochemically showed much amount of excreted steroids. As described by Currie and Symington, much more cases with decreased lipid granules were seen in those of the cortical hyperfunction, with not always distinct correlation between them. When adrenal cortical function is discussed in the human adrenal glands from a histological viewpoint, the indicator seems to be as follows: Fasciculata-Reticularis weight, increase and decrease in cortical nodules, characteristics of lipid granules, other histochemical subsidiary methods and other microscopical findings. As the cortical nodules are considered to conduct excreting activity similar to that of adrenal cortical cells to which they belong because of their various staining behaviors, it is considered with difficulty that they produce somewhat specific steroids only.

As for the adrenal cortical function, it is interesting to examine whether there is a noticeable difference between normal and breast cancer patients, or what difference can be found between effective and ineffective cases of the surgical endocrine therapy. Examining 27 cases of postmenopausal patients having breast cancer, Brown[9] pointed out that the patients excreted much more estrogens than the normal. Fujimori[24] stated that estrogens in the blood were increased at the early period of breast cancer, being normal in those with advanced breast cancer. On the other hand, according to Nathanson[53] and Masuda[50][51], there was no significant difference between normal and breast cancer patients.

Huggins[41] examined histologically using 51 of adrenal glands removed from breast cancer patients the weight, solid substances, lipid, ascorbic acid, Cl^-, Na^+ and K^+, not noting any difference with adrenal glands considered normal, except for an increase in water. Observing 88 cases of adrenal glands excised from patients with advanced breast cancer, Sirtori[63] reported

43% of hyperplasia and 43% of normal in the zona gromelurosa, 55% of hyperplasia and 35% of normal in the zona fasciculata and 43% of hyperplasia and 43% of normal in the zona reticularis, a correlation being observed between width of the zona reticularis and sex-steroid. Experimentally, Cramer[11] stated that "brown degeneration" was noted in the high percentage in the adrenal cortical X-zone when breast cancer appeared in mice of DZ strain administered with estrogens or grew spontaneously, thus suggesting a possible correlation between breast cancer and brown degeneration. Fekete[21] and Flux[23] attempted to find out causal relation between unodular hyperplasia and appearance of breast cancer in mice of dba strain. The author did not find any characteristic change in the adrenal glands which appeared to have a close relation to breast cancer in human breast cancer. The histological judgement showed 14.3% of cortical hypofunction, 42.9% of normal, and 42.9% of hyperfunction, the result being considerably similar to that obtained by Sirtori. Of 35 cases of patients having breast cancer, adrenal cortical hyperplasia was seen in one case at age 61 and adrenal cortical adenoma was noted in one case at age 68 and a dramatic remission was seen by adrenalectomy in these cases. Further examination will be needed to clarify whether adrenal cortical tumor appears more frequently in breast cancer patients.

On the effectiveness of the surgical endocrine therapy for the breast cancer Huggins[42] stated that the therapy was effective in relatively older patients ranging in age from 40 to 65 years old, patients with a longer interval between operation of breast cancer and its relapse, and patients excreting more estrogens. Dao[13], Galante[26] and Hadfield[33] noted that estrogens were excreted in abundance in the effective cases. Sirtori recognized an increase in amount of estrogens in the adrenal homogenate. In this study the effective ones showed a tendency to increase in both adrenal weight and width of fasciculata-reticularis zone as compared with that in ineffective cases, the above result being in accordance with the consideration that with better function of Fasciculata and Reticularis, namely with more amount of excreted corticosteroid in general, more effectiveness could be expected by the surgical endocrine therapy. Judging from histological finding cortical hyperfunction was observed in more than a half (57.1%) followed by normal function (33.3%) in the effective cases, but in the ineffective cases normal cortical function was seen in over a half (58.3%) of them followed by hypofunction (25.0%). Cortical lipid was found to be +2 to +3 in majority of effective cases, while being recorded as +1 in many of ineffective cases. As a whole in effective cases lipid granules had a tendency to become fine in size or to decrease in number. On the other hand, finding of hyperfunction was obtained much in the patients having a longer period of interval between onset of breast cancer and treatment by surgical endocrine therapy and in those of the fifth decade. This result would support Huggins' assumptions that the longer the time elapsed until relapse, the more

effectiveness of the therapy could be expected and that the therapy was effective in patients of relatively higher age.

The metastasis of the cancer in the adrenal glands was observed in 6 of 23 cases (26%) which could be examined for bilateral organs, two thirds of them having bilateral metastasis. Moreover the metastasis was noted in 13 of 58 totally extirpated adrenal glands (22.4%), being located chiefly in medulla in all the cases. The frequency of metastasis of breast cancer to adrenal glands in the postmortem was reported to be 58% by Glomset[27], 31% by Warren[73] and 20% by Willis[78], while it was reported in operated cases to be 25% by Huggins[39], by Pyrah[55] and 55% by Cade[10]. The frequency of the metastasis varies considerably depending on reporters, because in not so few cases it is usually difficult to distinguish metastatic lesion from the normal tissue of adrenal medulla. Particularly it is possible to overlook small metastatic lesion to the adrenal medulla. However it is presumed that the variety in occurrence of the metastasis will be mostly due to the case selected. In the present cases the metastasis of cancer to adrenal glands was detected in higher proportion in the cases having metastasis to the remote organs.

There has been a few reports concerning the change in human adrenal glands brought by the ovariectomy. Sirtori stated that the hyperplasia of zona reticularis became evident in the cases of breast cancer where a long time had elapsed since ovariectomy. On the other hand, there have been many reports[1)2)72)79] describing that the ovariectomy can cause atrophy of the adrenal cortex in mouse or rat. Our experience on 5 cases of castrated women (before menopause) disclosed a tendency of decrease in adrenal weight, and in width of cortex and findings of normal or lowered function from histological and histochemical viewpoint. It is presumed that these results are caused by a lack of activating activity of estrogens on adrenal glands. As far as these points are concerned, it is needed to continue further observations for a long time by using many more cases.

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Explanation of Photo.

PHOTO. 1. New generation of cortical cells at the subcapsular zone. Small, chromatin-rich cells which seem to be an intermediate form between capsular and cortical cells appear in quantity, gradually changing to zona glomerulosa cells with clear foamy

protoplasm.

PHOTO. 2. Within the capsule germinal cells of cortex cause the metaplasia, forming a group of young cortical cells, which further develops to capsular adenoma, a group of clear cells like those of zona gromerulosa.

PHOTO. 3. Intracapsular nodular hyperplasia (capsular adenoma), usually consisting of small, gromerulosa-like cells with a tendency of Sudan-phobia. They abound in the adrenal gland showing a strong tendency of hyperplasia.

PHOTO. 4. Accessory adrenal cortical tissue. Intracapsular nodules gradually increase in size, moving outward until they protrude outside the adrenal capsule to form accessory adrenal glands. Most of them are relatively large, some being characterized by 3 zones in the cortex.

PHOTO. 5. Nodular hyperplasia within the cortex. It is considered that this was formed with intracapsular nodules which increased in size and protruded into the cortex. In general it consists of bright large cells.

PHOTO. 6. Capsular trabeculae. A portion of the capsule extends into the cortex to form capsular trabeculae. New production of cortical cells takes place vigorously.

PHOTO. 7. Mosaic or network-like structure. Fascicular arrangement of usual cortical cells is completely disturbed, foamy hypertrophic large cells gathering closely each other to form a mosaic structure.

PHOTO. 8. Sudan III staining. It is observed that rough lipid granules are filled in both cortex and cortical nodules.

PHOTO. 9. Sudan III staining. The outer layer of z. fasciculata and inner layer of z. reticularis are filled with fine lipid granules. Cortical nodules and cortex are similar in the staining charactcristics.

PHOTO. 10. Cortical tissue having staining characteristics similar to inner zone of the cortex with compact protoplasm appears sometimes in the fat surrounding the adrenal gland. Because the tissue directly change to the fatty tissue without having capsule and a number of probably intermediate cells appear from it, the tissue is considered to be produced by metamorphosis from the fatty tissue. This finding will suggest extremely elevated function of the cortex.

PHOTO. 11. Hyperemia of sinusoids. Capillary hyperemia and enlargement are noted in each region of subcapsular, fasciculata, and reticular zones.

PHOTO. 12. Sudan III staining. Rough granules are filled in the whole cortex covering from gromerulosa to reticular zones. Generally, there are many cases showing cortical hypofunction.

PHOTO. 13. Sudan III staining. Almost no fat granules are noted except in the most inner layer of reticular zone. Generally there are many cases with cortical hyperfunction.

PHOTO. 14. Sudan III staining. Fine granules are scattered spottedly. There are many cases with such a finding, varying in the extent. In general, there are a number of cases with noticeable hyperfunction.

PHOTO. 15. Ascorbic acid. The acid is noted as black fine granules, being contained in abundance in compact cells. The photo shows one having increased ascorbic acid.

PHOTO. 16. A case with adrenal cortical hyperplasia. Giri-like appearance and marked multiplication of cortical cells are noted.

PHOTO. 17. A case with adrenal cortical adenoma. In the left adrenal gland, spherical adenoma about 4 mm in diameter was found. This case was markedly improved by surgical endocrine therapy.

PHOTO. 18. Metastasis of cancer. Metastases of cancer to the adrenal gland were noted in high frequency. Most of them were considered to arise primarily in the medulla in nodular form. Surrounding adrenal cortex mostly showed hypofunction.

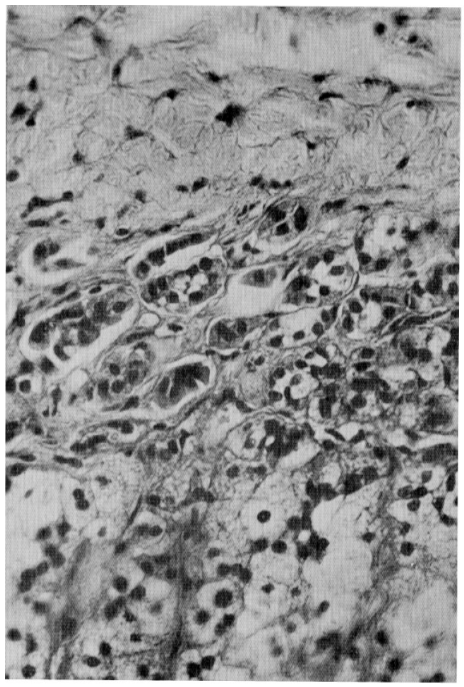


Photo. 1

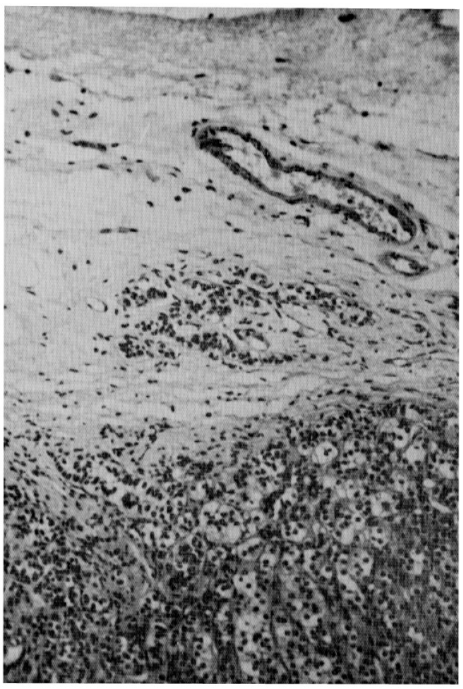
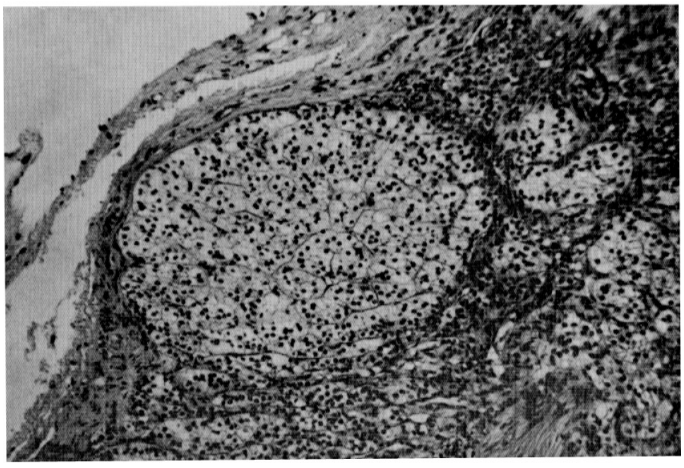


Photo. 2

Photo. 3

Photo. 4



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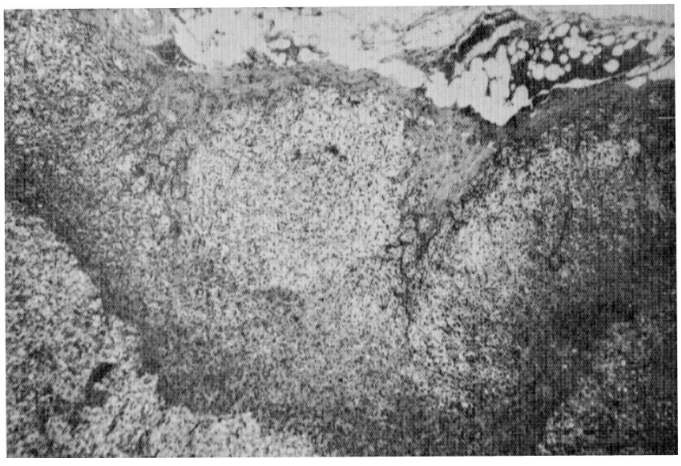

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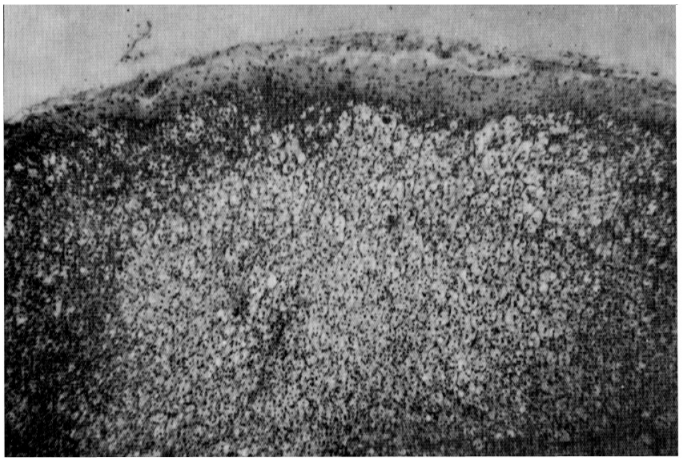
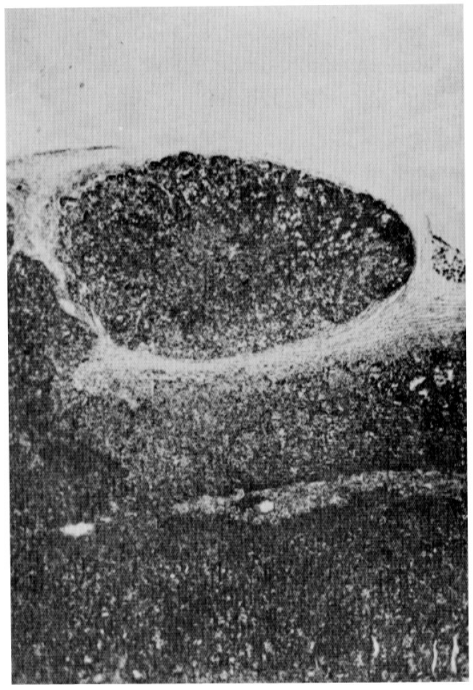
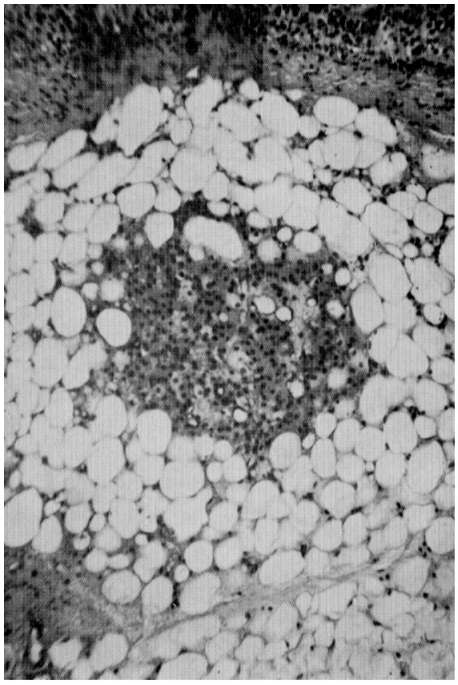


Рното. 7



Рното. 8

Рното. 9



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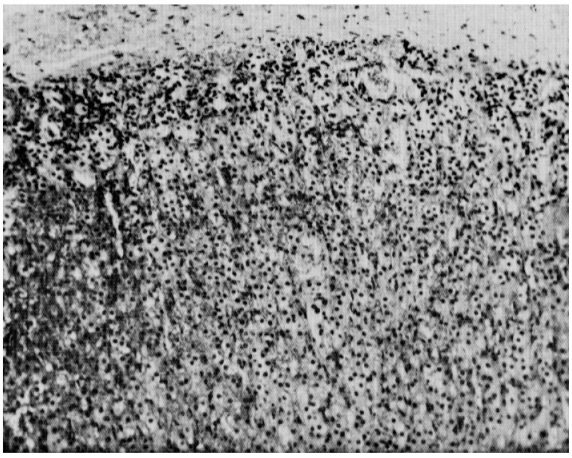

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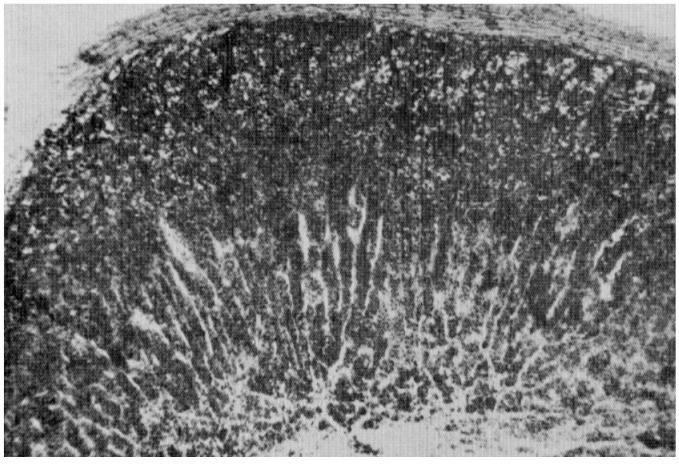

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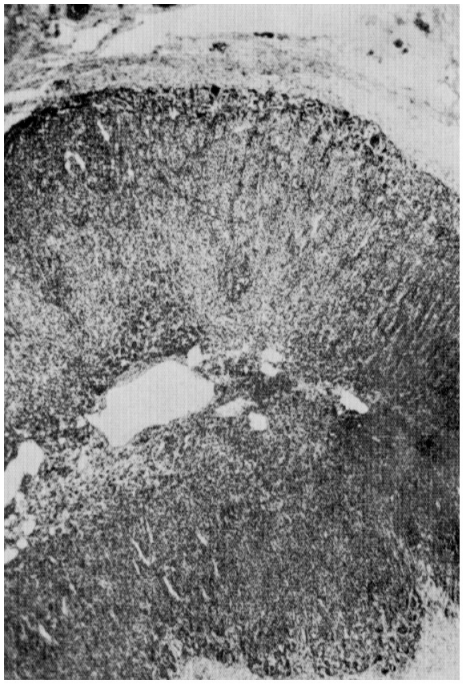


Photo. 13

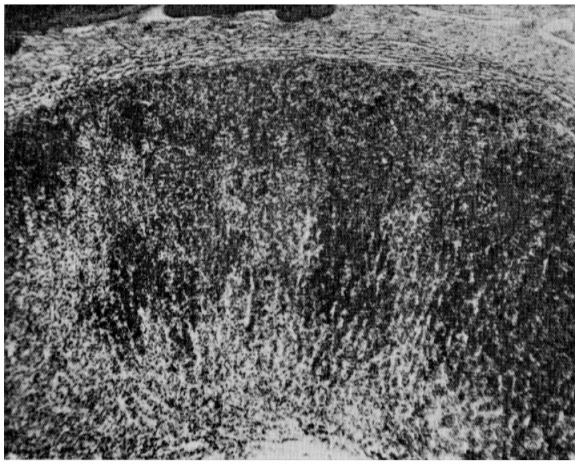


Photo. 14

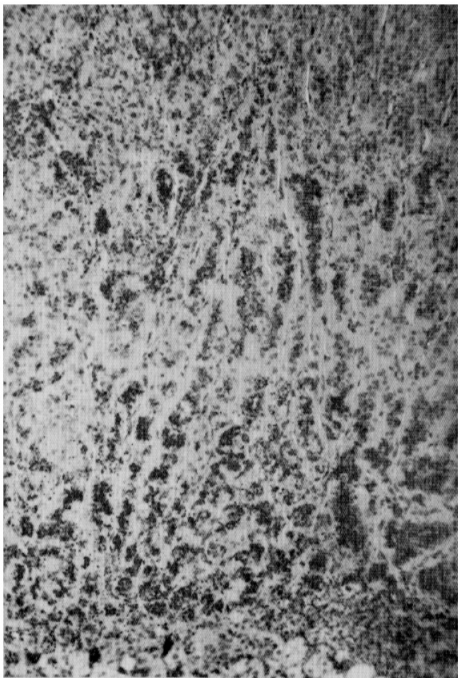
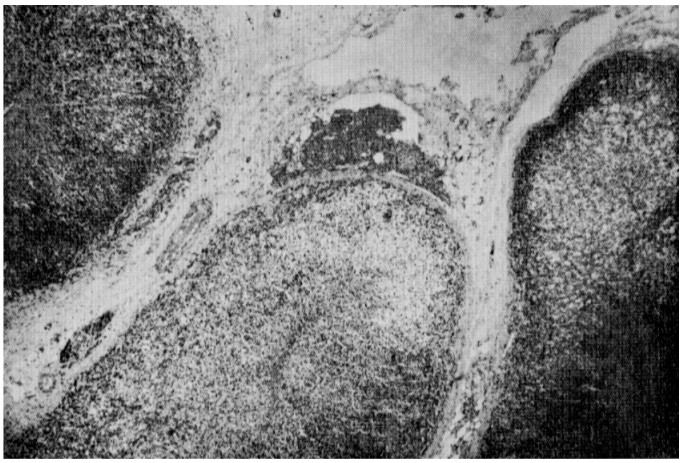


Photo. 15



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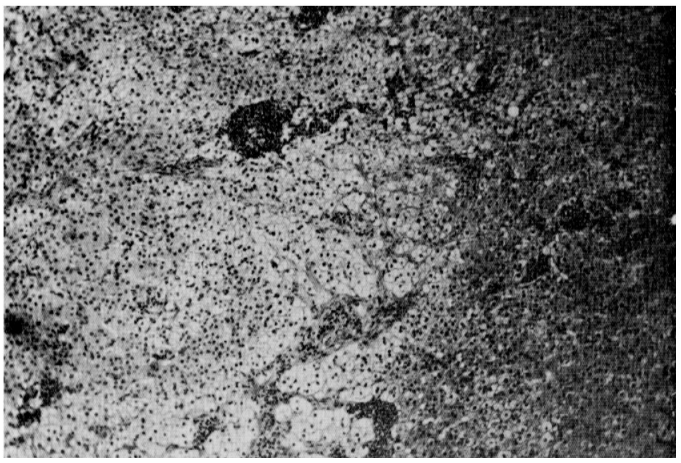

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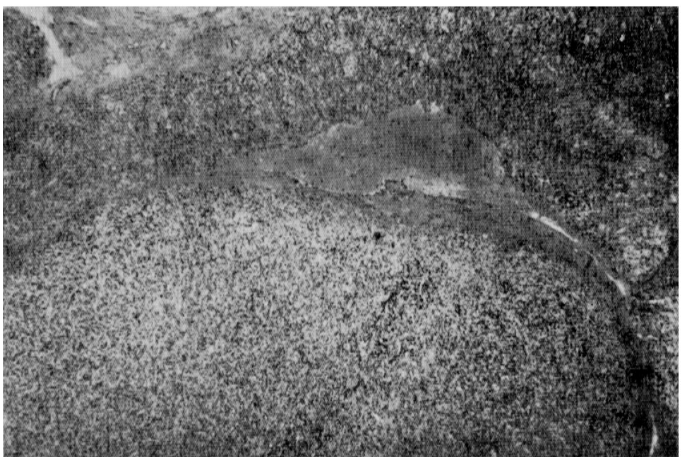

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