日本外科寶函 第25巻 第5号

ARCHIV FÜR JAPANISCHE CHIRURGIE

XXV. BAND, 5. HEFT, 1. SEPT. 1956.

原 著

ENDOCRINOLOGICAL STUDIES ON NEOPLASTIC DISEASES OF THE BREAST IN THE LIGHT OF THE EXCRETION OF URINARY 17-KETOSTEROIDS

by

YUKIHIKO ISEDA

From the 2nd Surgical Division, Kyoto University Medical School
(Director : Prof. Dr. YASUMASA AOYAGI)
(Received for publication June. 11, 1956.)

CONTENTS

Ⅰ. INTRODUCTION

Recently, the number of patients with neoplastic diseases of the breast, especially chronic cystic mastitis (mastopathia chronica) have increased markedly, and these patients are younger than those formerly reported from our clinic. Among the causative factors, our clinical statistics suggest that disturbances of the female reproductive system, and imperfection of sexual life, due to the increase of working women after the second World War play important roles in the increase of chronic

cystic mastitis.

This present study started from these clinical statistical new findings.

The relationship of the breast to the ovary has been recognized since the writings of COOPER in 1829. Since then many investigators have emphasized and extended this observation. Detailed histological studies have been reported since the reports of RECLUS in 1860. Clinically, SCHINZINGER (1889) suggested oophorectomy as part of the treatment of breast cancer. BEATSON (1896) independently reported that in several patients who were castrated alleviation of symptoms and signs was observed.

Since it was demonstrated that the sex hormones were concerned with mammary development and function, it became obvious that they might be of major importance in the genesis of diseases of the mammary gland. The mammary gland must be considered a part of the female reproductive system, and as such is subject to the same stimuli throughout life as the other organs of reproduction. The proliferation and functioning of the parenchymatous tissue of the mammary gland is known to involve the combined activity of several endocrine secretions. Changes in the breast seem to be directly related to those which are seen in the uterus, during the various phases of pituitary and ovarian activity and during pregnancy.

The significance of a relationship between certain types of chronic cystic mastitis and carcinoma of the breast is a subject of much controversy. There is a great deal of complexity and obscurity about the concept of chronic cystic mastitis. Neoplastic, inflammatory and regressive theories have been reported with regard to the concept of chronic cystic mastitis. To end this controversy, in 1927 MOSZKOWICZ standardized biologically as "mastopathia" the dysfunctions of the female reproductive system, but the conditions of these dysfunctions remained obscure.

The endocrine dysfunctions of the female reproductive system in patients with chronic cystic mastitis and the relationship between chronic cystic mastitis and breast cancer were studied in our laboratory, especially the excretion levels of the urinary 17-ketosteroids (17-KS) and the estrogens (by NISHIYA in our laboratory).

II CLINICAL STATISTICAL OBSERVATIONS

The clinical statistical observations have been assembled under seven headings.

Table I Incidence

The Year	Total No. of Patients In Our Surgical Department	No. of Cases with Breast Diseases	Per cent.	The Breast Diseases							
				Inflammation		Chronic Cystic Mastitis		Cancer		Fibroadenoma and Others	
				No. of Cases	Per cent.	No. of Cases	Per cent.	No. of Cases	Per cent.	No. of Cases	Per cent.
1942	3.284	85	2.6%	37	43.5%	9	10.5%	32	37.6%	7	8.4%
1943	3.887	69	1.8%	26	37.6%	9	12.9%	30	43.4%	4	6.1%
1944	3.799	67	1.8%	26	38.8%	13	19.4%	24	35.4%	4	6.0%
1951	4.323	93	2.2%	31	33.3%	16	17.2%	42	45.1%	4	4.4%
1952	4.483	147	3.3%	26	18.0%	**49**	**33.3%**	48	32.6%	24	16.3%
1953	4.968	225	4.5%	34	15.0%	**107**	**47.6%**	58	25.1%	26	12.2%

The clinical data for this study of neoplastic diseases of the breast are based upon patients observed during the past four years.

1) Incidence

Table I shows that the number of patients have recently increased markedly, especially those with chronic cystic mastitis. There is a great divergence between during and after the second World War.

2) Age of incidence

Table II Age of incidence

Age Group	Chronic Cystic Mastitis			Cancer of the Breast		Fibroadenoma of Breast		
	No. of Cases	Unmarried Cases	Per cent.	No. of Cases	Per cent.	No. of Cases	Unmarried Cases	Per cent.
10~19	0		0%	0	0%	2	2	4.8%
20~29	23	9	15.1%	2 (2)	1.8%	**20**	**15**	**65.6%**
30~39	**67**	1	**44.0%**	23 (9)	21.1%	10	1	29.3%
40~49	50		33.2%	**43** (6)	**39.5%**	1		0.3%
50~59	10		6.6%	27	24.8%	0		0%
60~69	2		1.1%	12	11.0%	0		0%
70~79	0		0%	2	1.8%	0		0%
Totals	152	10	100%	109(17)	100%	33	18	100%

( ) : Breast Cancer with Chronic Cystic Mastitis.

Table II shows that chronic cystic mastitis most commonly occurs in the fourth decade, between the ages of 30 to 39 years, breast cancer in the fifth decade, 40 to 49 years, fibroadenomas in the third decade, 20 to 29 years in our clinic. These clinical aspects are younger than those formerly reported in our country.

Fibroadenomas of the breast are found in many unmarried females.

3). Disorders of the sexual life.

Table III shows that the incidence of the imperfection of sexual life is relatively high in chronic cystic mastitis. Separation from husband, widowhood, spinsterdom, birth control, artificial interruption of pregnancy are gradually increased as a result of the increase in number of working women after the second World

Table III Sexual life

Chronic Cystic Mastitis	Living with husband	Married but Separated	Widow	Single	Status unrecorded	Totals (%)
Birth control	6	6	0	0	0	12 (7.89)
Artificial interruption of Pregnancy	3	32	3	0	1	39 (46.71)
Sterility	10	7	2	0	4	23 (15.13)
One child-sterility	3	2	3	0	2	10 (6.58)
Normal	11	7	5	9	3	35 (23.03)
Status unrecorded	0	0	0	0	1	1 (0.66)
Totals (%)	33 (42,76)	54 (55,53)	13 (8,55)	9 (5.92)	11 (7.24)	120

Carcinoma of the Breast	Living with husband	Married but Separated	Widow	Single	Status unrecorded	Totals(%)
Birth control	1	0	0	0	0	1 (0.93)
Artificial interruption of Pregnancy	16	11	3	0	1	31 (28.97)
Sterility	8	7	4	0	2	21 (19.63)
One child-sterility	6	3	3	0	0	12 (11.22)
Normal	22	2	5	3	1	33 (30.84)
Status unrecorded	3	0	0	0	6	9 (8.41)
Totals (%)	56 (52.34)	23 (21.49)	15 (14.02)	3 (2.80)	10 (9.35)	107

War.

4). Menstruation and cyclical symptoms in the mammary gland.

Many investigators have reported that it is known definitely that women who develop cancer of the breast at any period of life have or have had a higher percentage of menstrual disturbances than those who do not. However, as shown

Table IV Menstruation and cyclical Symptoms in mammary gland.

	Chronic Cystic Mastitis		Breast Cancer		Fibroadenoma of the Breast	
	No. of Cases	Per cent.	No. of Cases	Per cent.	No. of Cases	Per cent.
Normal Menstruation	110	75.9%	66	80.5%	27	81.8%
Abnormal Menstruation	35	24.1%	16	19.5%	6	18.2%
Totals	145	100%	82	100%	33	100%
Cyclical Pain and Swelling present	60	44.1%	17	30.9%	8	25.8%
Cyclical Pain and Swelling absent	76	55.9%	38	69.1%	23	74.2%
Totals	136	100%	55	100%	31	100%

in Table IV, in our series the menstrual cycles are normal in 75.9% of patients with chronic cystic mastitis, in 80.5% of those with breast cancer, in 81.8% of those with fibroadenoma of the breast. Cyclical pain and swelling of the mammary gland are found more frequently in chronic cystic mastitis than in other breast diseases.

5). Pregnancy, parturition and artificial interruption of pregnancy.

Table V shows that the incidence of sterility in chronic cystic mastitis is relatively high. In those women who have born children, the process is sometimes seen after a along period of infertility. It is an accepted fact that nulliparous women have a higher incidence of cancer of the breast than those who have born children. The parturition rate in chronic cystic mastitis is relatively low. As already mentioned, the artificial interruptions of pregnancy have increased (Table V).

Table V Pregnancy, parturition, and artificial interruption of pregnancy

Chronic Cystic Mastitis				Carcinoma of the Breast				Fibroadenoma of the Breast			
No. of preg.	No. of cases	No. of birth	No. of cases	No. of preg.	No. of cases	No. of birth	No. of cases	No. of preg.	No. of cases	No. of birth	No. of cases
0	22	0	27	0	18	0	9	0	1	0	2
1	19	1	26	1	13	1	16	1	1	1	3
2	22	2	31	2	11	2	15	2	6	2	7
3	23	3	23	3	12	3	12	3	1	3	2
4	20	4	17	4	9	4	5	4	4	4	2
5	11	5	5	5	9	5	7	5	3	5	0
6 and more	22	6 and more	10	6 and more	14	6 and more	12	6 and more	0	6 and more	0
Totals	139	Totals	139	Totals	86	Totals	86	Totals	16	Totals	16

No. of artificial interruptions of pregnancy	No. of cases	No. of artificial interruptions of pregnancy	No. of cases	No. of artificial interruptiors of pregnancy	No. of cases
0	57	0	46	0	6
1	29	1	15	1	3
2	19	2	4	2	5
3	9	3	3	3	1
4	1	4	0	4	0
5	2	5	0	5	0
Totals	117	Totals	68	Totals	15

6). Lactation

The question of lactation is also of great importance. It is held by some observers that early weaning of the child or faulty lactation for various reasons conduces to the development of breast tumor.

Table VI Lactation

	Chronic Cystic Mastitis		Carcinoma of the Breast	
	Cases	Per cent.	Cases	Per cent.
Normal laction	14	20.6%	18	33.9%
Faulty lactation	54	79.4%	35	66.1%
Totals (%)	68	100%	53	100%

7). Past gynecological diseases

Table VII Past gynecological diseases

	Chronic Cystic Mastitis		Carcinoma of the Breast		Fibroadenoma of the Breast	
	Cases	Per cent.	Cases	Per cent.	Cases	Per cent.
Past gynecological diseases present	56	38.1	25	32.9	3	9.1
Past gynecological diseases absent	91	61.9	51	67.1	30	90.9
Totals (%)	147	100	76	100	33	100

Table VII shows that diseases of the pelvic organs are accompanied by breast diseases in about 35% of cases. The association of breast cancer with lesions in the pelvis is similar to that observed in chronic cystic mastitis.

These clinical statistics suggest that patients with neoplastic diseases of the breast, especially chronic cystic mastitis, may show variations in hormone excretion.

III. THE DETERMINATION OF URINARY 17-KS EXCRETION

1. *Methods of research*

1). The subjects of this study

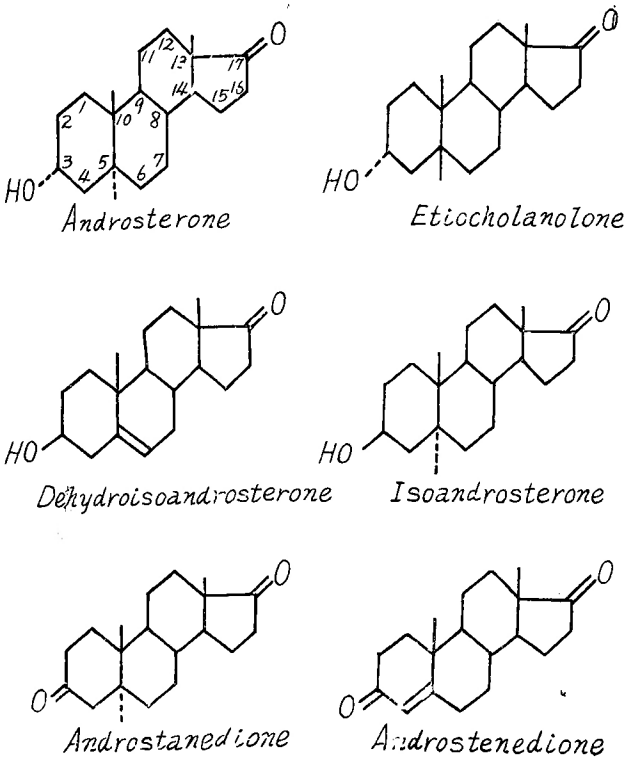
Determination of the urinary excretion of the 17-KS was carried out in patients with neoplastic diseases of the breast observed during the past four years. In in-patients these were determined every day throughout the menstrual cycle; in patients with amenorrhea for three or four weeks; in out-patients, every three or four days throughout the menstrual cycle.

As controls urinary excretion of the 17-KS was measured in normal female subjects and in various surgical patients in our clinic.

In addition, investigation of the clinical statistics and histological examination of mammary tumors were performed.

Furthermore, the ratio of urinary estrogen to 17-KS (the sex hormone balance) was determined throughout the menstrual cycle in neoplastic diseases of the breast.

Fig. 1. The more commonly occurring urinary 17-Ketosteroids



2). 17-KS

The 17-KS are characterized by a common structure called the cyclopentanoperhydrophenanthrene nucleus. They differ only in the side chain, and their configuration is shown in Figure 1. The more important urinary 17-KS are shown in Figure 1.

In 1935 ZIMMERMANN devised a colorimetric chemical reaction which takes advantage of the fact that d-metadinitrobenzene reacts with ketone groups to form a dark red compound. This reaction is the basis of the colorimetric reaction for the determination of 17-KS.

It should be emphasized that besides the mere presence of biologically active material, these colorimetric reactions also detect bio-

logically inert steroids which are degradation products of the active ones.

The 17-KS were estimated according to MIYAKE's method (MIYAKE's modification of Drekter-Pearson's method) in our laboratory.

Procedure. Place 20 cc of a 24 hour urine specimen and 6 cc of concentrated hydrochloric acid in a 125 cc ERLENMEYER flask and stopper the flask in a water bath at 80°C. for 30 minutes, cool and transfer 10 cc of the hydrolysate to a 100 cc separatory funel. Add 20 cc anaesthetic ethyl ether and shake the funnel for 60 seconds. Remove the urine. Wash the ether once with 20 cc of 10 per cent NaOH and once with 20 cc of distilled water ; shake for 30 seconds with each wash. Remove 10 cc of ether, evaporate the 10 cc, and assay by means of ZIMMERMANN's reaction. In our determinations, ZIMMERMANN's reaction was performed as follows. Add 0.8 cc of 1 per cent m-dinitrobenzene absolute alcohol solution and 0.6 cc of the 8 N KOH solution to the dried extract. Keep the solution in a water bath whose temperature is 25°C. for 20 minutes. After 20 minutes dilute the solution with 2 cc of diluent ; the diluent consists of three parts of absolute alcohol to one part of water. Read the diluted solution in a 0.5 cm cuvette in a photoelectric colorimeter (A-K-A SHIMAZU, made in Japan) using a green (EG) and violet (Ev) filter. Use the blank containing absolute alcohol, m-dinitrobenzene and potassium hydroxide as the zero setting.

In our laboratory, the color correction was made by the method of FRASER and TALBOT. As the colorimetric assay procedures were applied to crude neutral urine extracts, the color correction equation of FRASER et al. (1941) was used for eliminating the error of overestimation of the ketonic steroids, contributed by other interfering chromogens. The standard crystalline steroids used were ketonic dehydroisoandrosterone, and nonketonic testosterone acetate.

$$\text{Corrected green reading} = \frac{Ki\,E_G - Ev}{Ki - Ks}$$

E_G is extinction obtained with green filter.

Ev is extinction obtained with violet filter.

Ki is Ev/E_G for testosterone acetate. $Ki = 1.28$

Ks is Ev/E_G for pure 17-KS (dehydroisoandrosterone). $Ks = 0.392$

$$\therefore \text{17-KS mg/24h} = \frac{1.28\,E_G - Ev}{0.888} \times C \times S \times U$$

C = coefficient of density of the dehydroisoandrosterone

$$= \frac{\gamma\ (\mu g)}{E} = 144.1 \text{ (the } \mu\text{g. of the aliquot divided by the density)}$$

$$S = \frac{\text{urinary sample (cc)}}{\text{used for color reaction}} \cdot \frac{1}{}$$

$$= \frac{1}{20 \times \frac{10}{20+6} \times \frac{10}{20}} = 0.26$$

U = amount of 24-hour urine specimen (l/day)

$$\therefore \text{17-KS mg/24h} = \frac{1.28\,E_G - Ev}{0.888} \times 37.46 \times U \text{ (l)}$$

2. *Urinary 17-KS excretion in normal subjects.*

According to the method used in our investigation, the normal values for adult males (35 cases) between the ages of 20 and 60 years ranged from 7.4 to 18.1 mg with a mean of 12.05 mg per 24 hour urine specimen; the normal female value (60 cases) in the same age group is from 5.3 to 14.0 mg with a mean of 7.97 mg and the standard deviation from the mean value of these two groups are 3.25 mg and 2.50 mg respectively.

In our laboratory, it was decided that the normal 17-KS limits in female must be from 5.0 to 14.0 mg per 24 hours.

3. *Urinary 17-KS excretion in various surgical patients.*

For control purposes, estimations of the urinary excretion of 17-KS in various surgical patients in our clinic are shown in Table Ⅷ. The 17-KS excretion is also affected by a number of nonspecific processes. Debilitating illness, inanition and hepatic impairment are usually associated with definitely lowered urinary 17-KS. A great deal of research on adrenocortical function has been done and the physiological values of the urinary 17-KS in homeostasis and in "stress" have recently been reported by many investigators, but the values of 17-KS obtained do not always agree. It is considered that diminished 17-KS are related to the lack of sufficient nourishment, hepatic impairment, and hypofunction of the hypophysio-adreno-gonad system.

Table VIII The Urinary Excretion of 17 Ketosteroids in Various Surgical Diseases. (1)

Diseases	Age	Sex	17-KS (mg/24h)	Diseases	Age	Sex	17-KS (mg/24h)	Diseases	Age	Sex	17-KS (mg/24h)
Cancer of the stomach	63	M	9.26	Fistula of the gall	61	M	4.55	Cancer of the prostate	65	M	8.53
〃	48	F	2.56	Cancer of the liver	59	M	3.40	Abdominal neurosis	32	F	7.48
〃	56	F	2.93	Cholelithiasis	41	M	11.39	〃	18	F	3.86
〃	41	M	10.25	Infectious hepatitis	22	M	7.27	〃	38	F	1.47
〃	62	F	0.76	〃	47	F	3.97	〃	28	M	5.24
〃	55	M	1.65	〃	22	F	4.33	〃	40	F	4.63
〃	61	M	1.32	Jaundice	22	F	2.88	〃	42	F	5.89
〃	73	M	2.85	Gastroptosis	21	F	9.05	Fistula of the duodenum	35	F	3.43
Cancer of the oesophagus	61	M	3.46	Ulcer of the stomach	45	M	9.28	Cancer of the pancreas	59	M	3.97
Cancer of the rectum	63	M	8.88	Ulcer of the duodenum	51	M	6.43	Morbus Basedowii	26	M	11.49
Cancer of the anus	54	F	19.78	〃	43	M	7.03	Struma nodosa	25	F	4.76
Cancer of the colon	63	M	6.68	Hypertrophy of the prostate	63	M	7.38	〃	28	F	5.32
Cancer of the gallbladder	57	F	0.31	〃	60	M	11.58	Struma simplex	19	F	9.93
〃	55	M	3.75	〃	71	M	7.51	〃	18	F	14.21
Fistula of the gall	48	M	5.35	〃	59	M	11.98	Struma maligna	46	M	17.12

Table VIII The Urinary Excretion of 17-Ketosteroids in Vavious Surgical Diseases. (2)

Diseases	Age	Sex	17-KS (mg/24h)	Diseases	Age	Sex	17-KS (mg/24h)	Diseases	Age	Sex	17-KS (mg/24h)
Struma maligna	41	F	6.02	Idiopathic gangrene	33	M	9.02	Retentio testis abdom. bilateral.	22	M	6.17
Scrofula	22	F	7.92	〃	41	M	7.95	Myositis ossific. progressiva	2	M	0.89
Tuberculosis of the lung	31	F	8.18	〃	37	M	3.71	Scleroderma diffusa	41	F	6.62
〃	24	M	10.79	〃	28	M	3.00	Bronchiale Asthma	27	M	2.55
〃	29	F	10.36	〃	38	M	3.85	〃	22	M	9.94
Stenosis of the mitral valve	30	M	3.67	〃	40	M	8.10	〃	31	M	7.09
〃	31	F	7.94	〃	37	M	5.48	Tumor of the hypophysis	25	F	3.32
Tumor of the mediastinum	51	F	2.20	〃	39	M	7.01	Chorioepithel. malignum	40	F	3.20
〃	46	F	8.60	Appendicitis perforativa	18	F	6.32	〃	27	F	8.14
Aplastic anemia	47	F	1.44	Abscess of the periproct	26	M	11.60	Cancer of the uterus	45	F	5.62
Lymphatic Leukemia	18	M	4.53	Fistula ani	36	M	10.32	Sarcoma of the uterus	61	F	3.41
Splenomegaly	19	F	7.96	〃	40	M	7.30	Tumor of the ovary	27	F	5.34
〃	22	M	2.48	Sarcoma of the sacrum	27	F	4.05	Tumor of the ovary (Krukenberg)	40	F	19.17
〃	25	F	3.12	Nephrosis	22	M	1.74				
Hemolytic Jaundice	19	F	9.44	Retentio testis abdom. dext.	24	M	10.16				

4. *Urinary 17-KS excretion in patients with neoplastic diseases of the breast.*

1). Chronic cystic mastitis (mastopathia chronica)

A study of 102 cases of chronic cystic mastitis revealed that the excretion of urinary 17-KS was usually low (65.7%). Figure 2 shows the diminished output of 17 -KS observed in 67 of the total 102 cases. The diminished output of 17-KS in all age groups is shown in Table Ⅸ.

The low 17-KS output in patients should be due to deficient adrenal androgen production or to metabolic error. There are, however, no findings in these patients which suggest obvious adrenal, pituitary, or thyroid insufficiency. We also considered the possibility that hepatic impairment, either generalized or as a specific enzyme deficiency, might be responsible. A battery of sensitive liver function tests gave no evidence of diffuse hepatic impairment in these patients.

2). Carcinoma of the breast

A study of 86 cases of carcinoma of the breast revealed that the excretion of urinary 17-KS was usually normal (70.9%). Figure 3 shows the diminished output of 17-KS observed in 25 of the total 86 cases. The 25 cases with low 17-KS output consisted of 12 cases of breast cancer with chronic cystic mastitis and 13 cases of breast cancer without chronic cystic mastitis. There were 16 cases of breast cancer with chronic cystic mastitis (malignant transformation of chronic cystic mastitis) out of 86 cases of breast cancer. In these cases, the excretion of the urinary 17-KS was usually low (Fig. 3, Table Ⅸ), and the clinical liver function tests resembled those in cases of chronic cystic mastitis. Except for these 16 cases of breast cancer, the diminished output of 17-KS in all age groups is shown

Fig. 2. Urinary 17-KS excretion in chronic cystic mastitis. (102 cases)

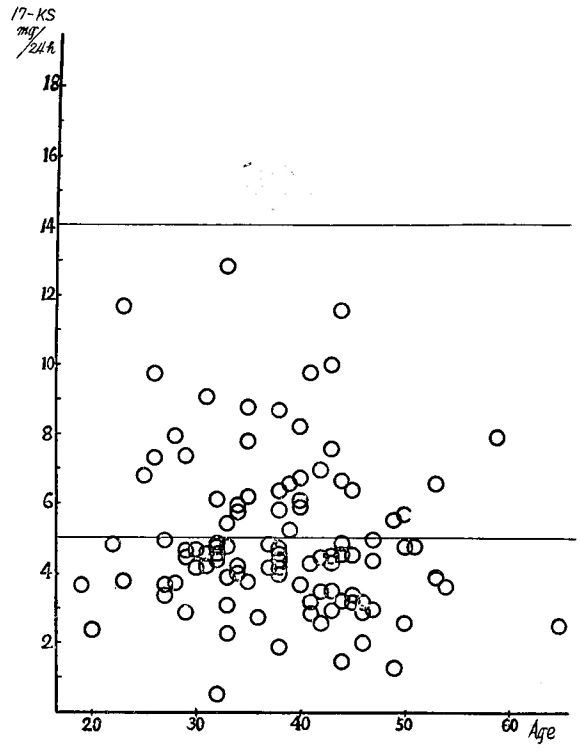


Table IX Diminished 17-Ketosteroids in neoplastic diseases of the breast.

Chronic cystic mastitis

Age group	~19	20~29	30~39	40~49	50~59	60~69	Totals
Total cases	1	16	39	37	8	1	102
Diminished Cases	1	10	25	25	5	1	67
Per cent.		62.5%	64.1%	67.6%	62.5%		65.7%

Cancer of the breast with chronic cystic mastitis

Age group	20~29	30~39	40~49	50~59	Totals
Total cases	2	8	6	0	16
Diminished cases	1	7	4	0	12
Per cent.		87.5%	66.7%		75.0%

Cancer of the breast without chronic cystic mastitis

Age group	30~39	40~49	50~59	60~69	70~79	Totals
Total cases	8	31	18	11	2	70
Diminished cases	1	4	3	4	1	13
Per cent.	12.5%	12.9%	16.7%	36.4%		18.6%

Fig. 3. Urinary 17-KS excretion in carcinoma of the breast. (86 cases)

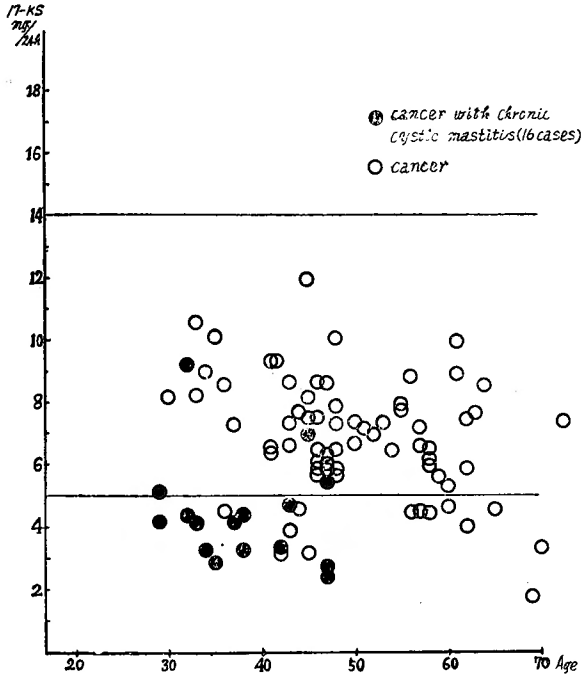
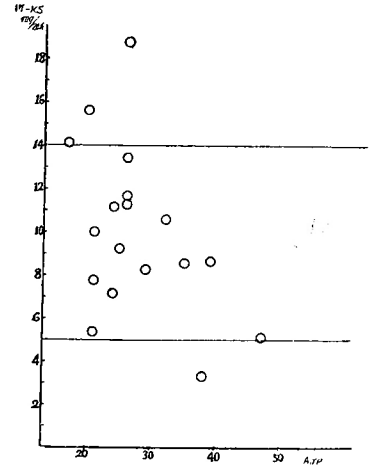


Fig. 4. Urinary 17-KS excretion in fibroadenoma of the breast. (18 cases)



in Table Ⅸ. The 17-KS values in 13 cases of breast cancer diminished as the patients grew older. In these groups of 13 cases of breast cancer, hepatic impairment was found in 8 cases, in 5 of which there were pleural and osseous metastases.

3). Fibroadenomas of the breast.

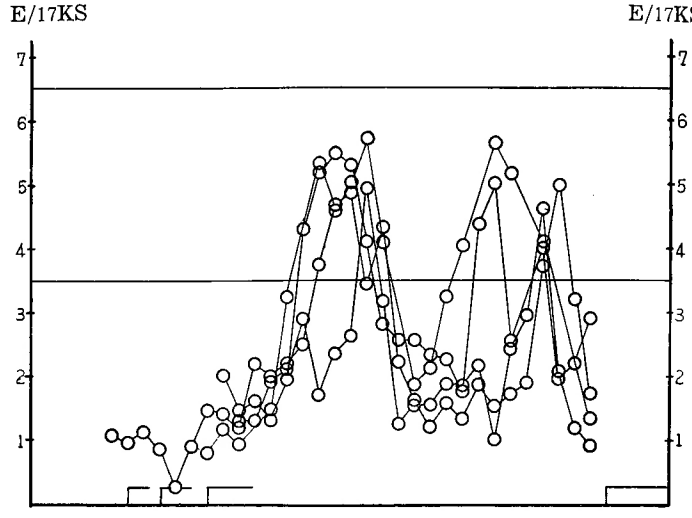
A study of 18 cases of fibroadenoma of the breast revealed that the excretion of 17-KS was usually normal. Figure 4 shows the diminished and increased output of 17-KS observed in cases 1 and 3 of a total of 18 cases. One of the cases with diminished output was had chronic cystic mastitis histologically.

Ⅳ. SEX HORMONE BALANCE IN PATIENTS WITH NEOPLASTIC DISEASES OF THE BREAST.

As already mentioned, the urinary excretion of 17-KS was usually low in chronic cystic mastitis, but in breast cancer the urinary excretion of 17-KS was usually normal. In these contrasting data, we must examine the urinary sex hormone balance, especially the monthly curves and the averages of the hormone balance.

Simultaneous chemical measurements of urinary estrogens (K. NISHIYA studied the urinary estrogens by fluorometry in our laboratory) and of 17-KS have been reported in this paper.

Fig. 5. Urinary sex hormone balance throughout the menstrual cycle in normal females



1. *In normal females*

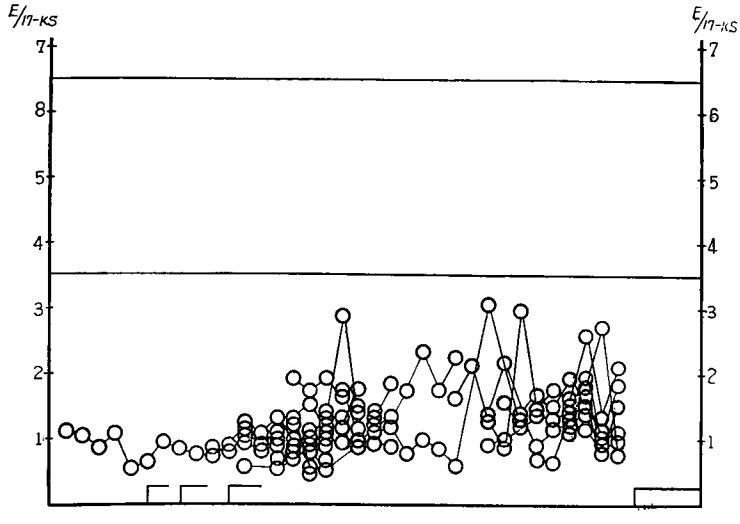
Studies on the urinary sex hormone balance (Estrogens (γ) divided by 17-KS (mg.)) throughout the menstrual cycle have been carried out in normal females. The monthly curves of hormone balance resembled those of the normal estrogen excretion (Fig. 5). The normal peak balance ranged from 3.5 to 6.0. Except for the peak balance, the averages of the hormone balance ranged from 0.5 to 2.0.

2. *In patients with neoplastic diseases of the breast*

1). Chronic cystic mastitis

In chronic cystic mastitis, the monthly curves of the hormone balance were definitely atypical in a high percentage of cases (in 38 cases of a total of 48 cases). (79.2 %). The normal peak balances were absent in 13 cases (Fig. 6), the peak balances of regular balance curves were higher than 6.5 in 14 cases (Fig. 7), the peak balances of irregular balance curves were higher than 6.5 in 5 cases (Fig. 8), the peak balances of irregular balance curves were lower than 6.5 in 6 cases (Fig. 9), and normal peak balances with regular balance curves were present in 10 cases (Fig. 10).

Fig. 6. The normal peak balances are absent in chronic cystic mastitis. (13 cases)



Except for the peak balance, the averages of

Fig. 7. The peak balances of regular balance curves are higher than 6.5 in chronic cystic mastitis. (14 Cases)

Fig. 8. The peak balances of irregular balance curves are higher than 6.5 in chronic cystic mastitis. (5 cases)

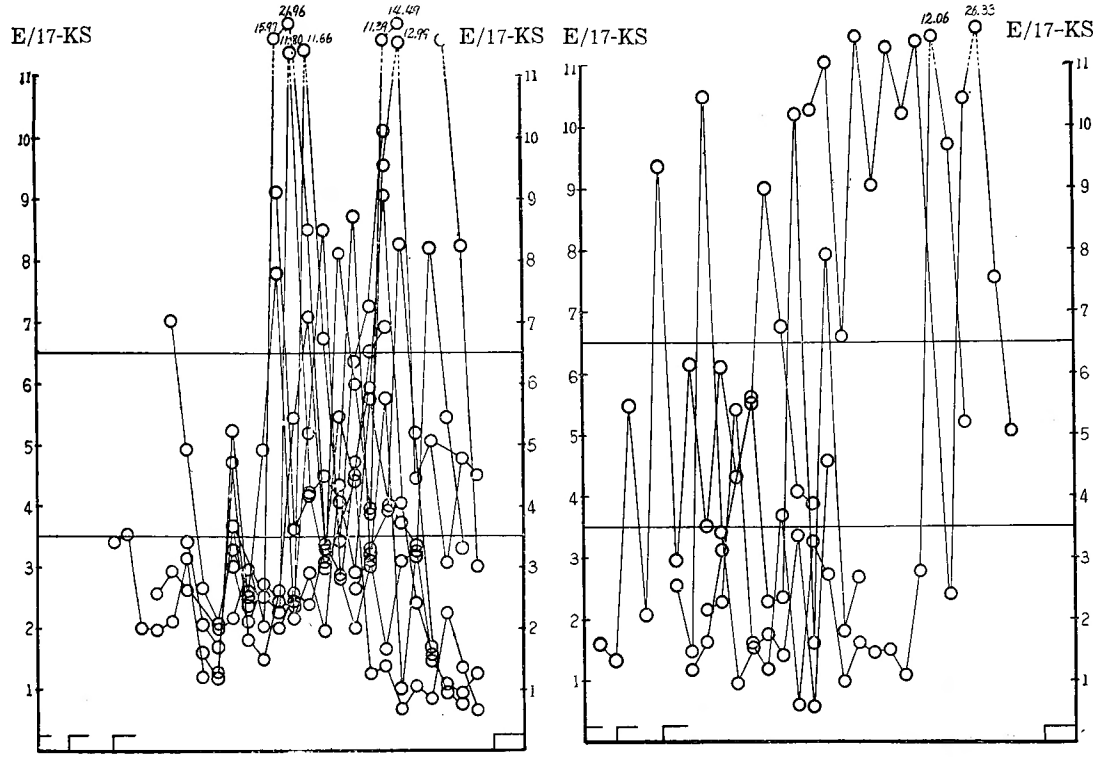


Fig. 9. The peak balances of irregular balance curves are lower than 6.5 in chronic cystic mastitis. (6 cases)

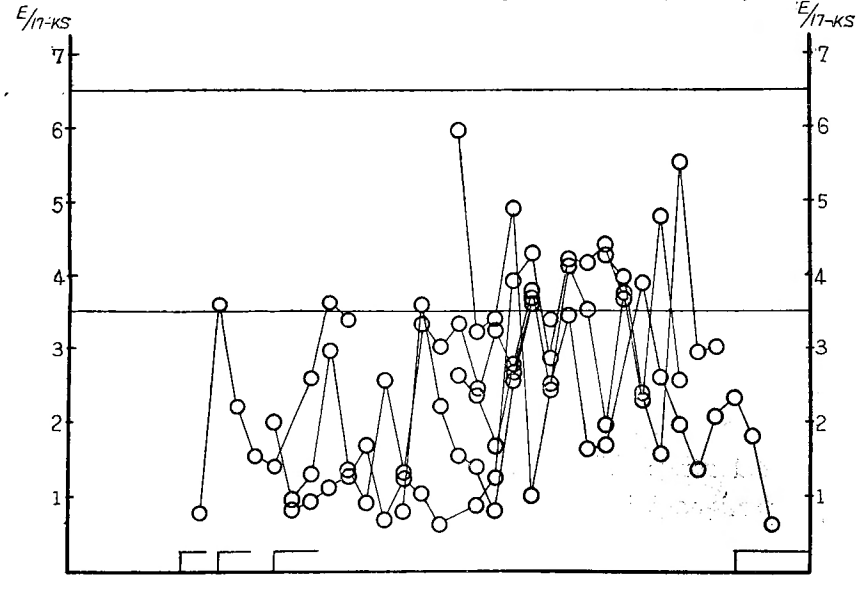


Fig. 10. Normal peak balances with regular balance curves in chronic cystic mastitis. (10 cases)

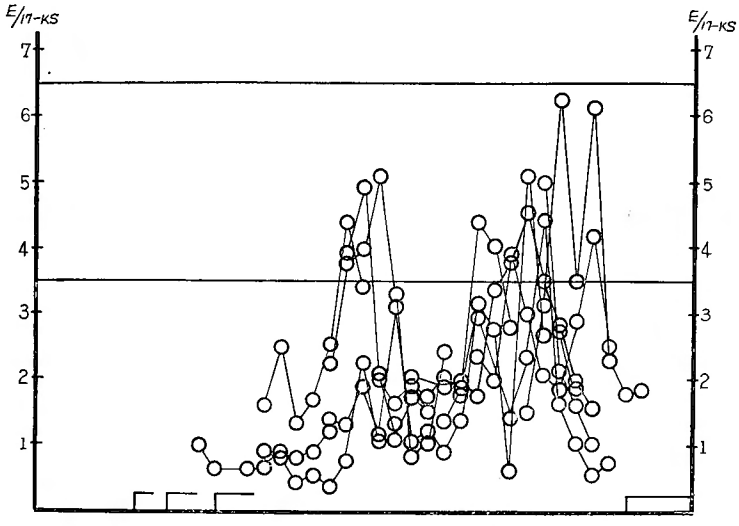
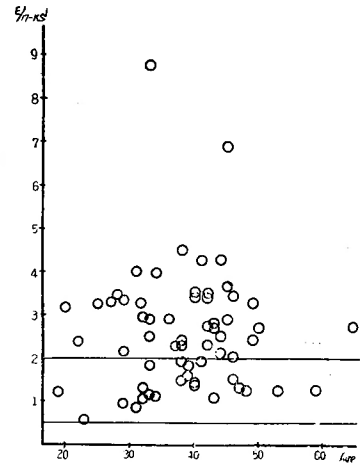


Fig. 11. Averages of hormone balance in chronic cystic mastitis, excluding peak balances. (62 cases.)



hormone balance were higher than normal (Fig. 11). For example, the averages of hormone balance were higher than 2 (relative hyperestrogenism) in 40 of a total of 62 cases. In cases of urinary normoandrogenism, it was found that urinary hyperestrogenism was present in only 3 cases, giving us an imbalance with relative hyperestrogenism.

2). Carcinoma of the breast

In carcinoma of the breast, the monthly curves of hormone balance were usually within the normal range (in 29 cases of a total of 52 cases). (55.8%) Normal peak balances with a regular balance curve were present in 6 cases (Fig. 12), normal peak balances were absent in 23 cases of amenorrhea (Fig. 13). On the other hand, normal peak balances were absent in 13 cases (Fig. 14), peak balances of regular balance curves were higher than 6.5 in 5 cases (Fig. 15), and peak balances of irregular balance curves were lower than 6.5 in 5 cases (Fig. 16).

Breast cancer with chronic cystic mastitis was present in 9 cases of the 52 cases of breast cancer. In these cases, the monthly curves of the hormone balance were similar to those of chronic cystic mastitis (Table X). Except for the 9 cases of breast cancer with chronic cystic mastitis, the sex hormone balances in breast cancer were definitely within the normal range (67.4%).

Except for the peak balance, the averages of hormone balance were usually within the normal range (Fig. 17). When the averages of hormone balance were higher than 2, malignant transformation of chronic cystic mastitis was found in 4 cases out of 8.

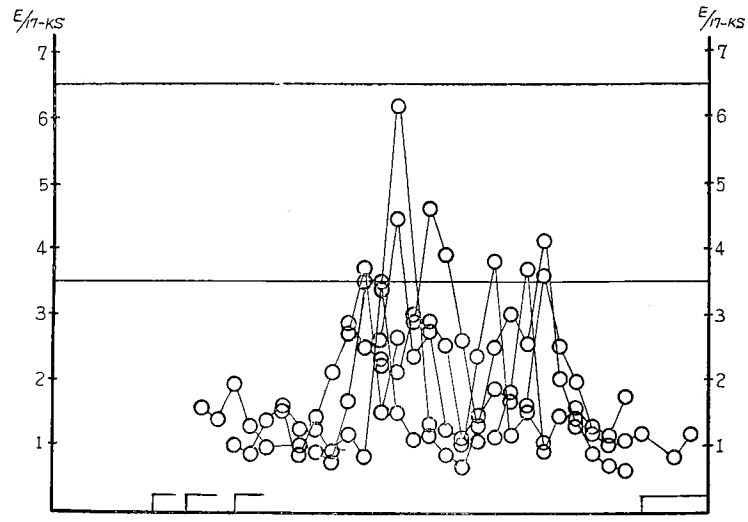


Fig. 12. Normal peak balances with regular balance curves in carcinoma of the breast. (6 cases)

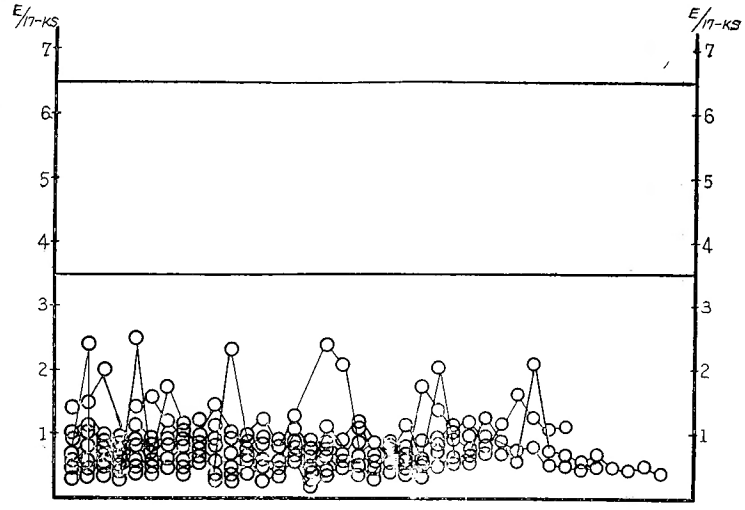


Fig. 13. The normal peak balances are absent in carcinoma of the breast with amenorrhea. (23 cases)

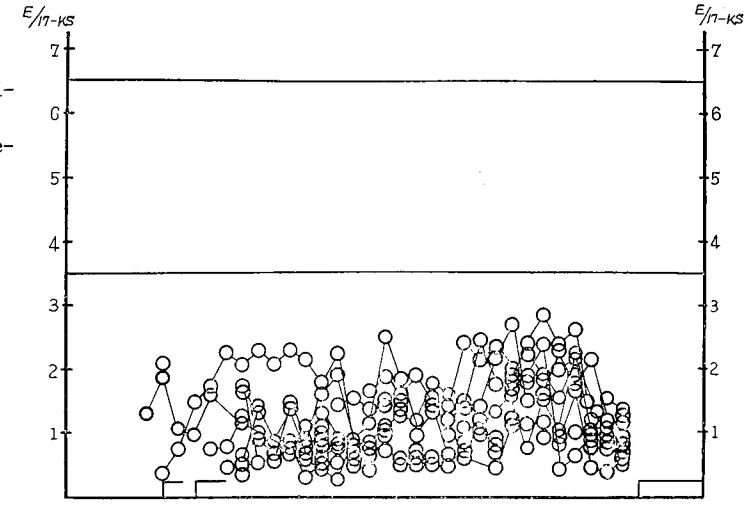


Fig. 14. The normal peak balances are absent in carcinoma of the breast. (13cases)

Fig. 15. The peak balances of regular balance curves are higher than 6.5 in carcinoma of the breast. (5 cases)

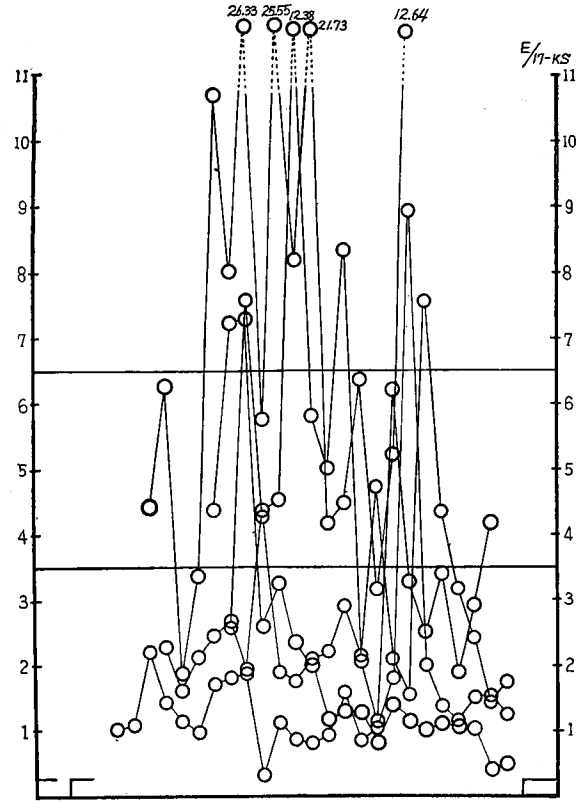


Fig. 16. The peak balances of irregular balance curves are lower than 6.5 in carcinoma of the breast. (5 cases)

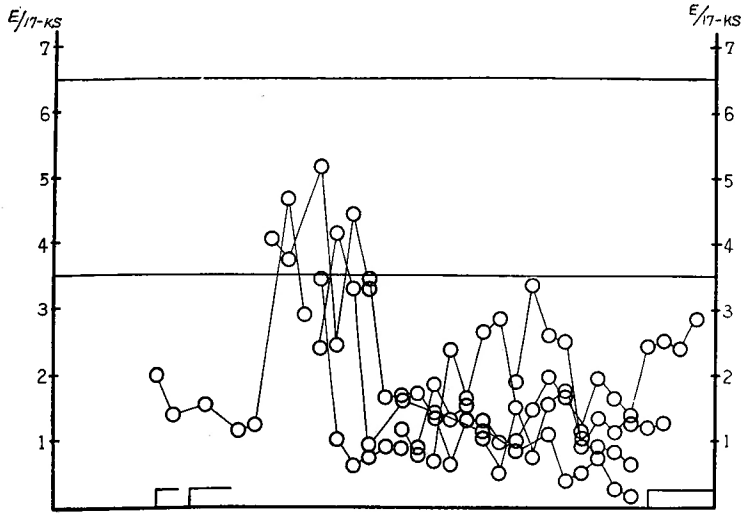
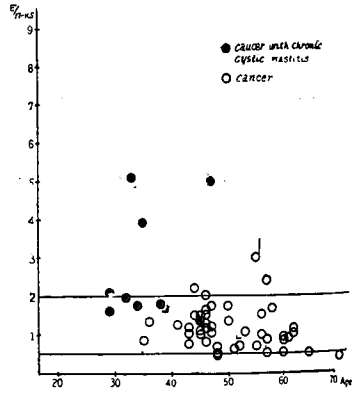


Fig. 17. Averages of hormone balance in carcinoma of the breast, excluding peak balances. (53 cases)



3). Fibroadenomas of the breast.

In fibroadenomas of the breast the monthly curves and averages of hormone balance were usually within the normal range (Figs. 18, 19).

These results are summarized in Table X.

Fig. 18. The monthly curves of hormone balance in fibroadenomas of the breast. (6 cases)

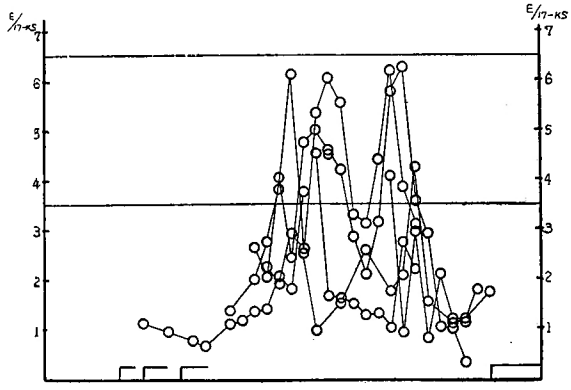


Fig. 19. Averages of hormone balance in fibroadenoma of the breast, excluding peak balances. (15 cases)

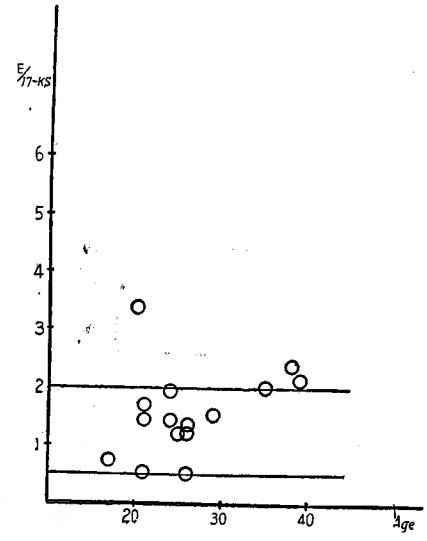


Table X Sex hormone balances in neoplastic diseases of the breast

			Chronic cystic mastitis	Breast cancer	Fibroadenoma
Monthly curves of hormone balance	Normal	Normal peak balance	10	6	6
		Absent peak balance with amenorrhea	0	23	0
	Abnormal	Absent peak balance with regular menstruation	13	13(3)	0
		Peak balance higher than 6.5 (with regular balance curve)	14	5(4)	0
		Peak balance higher than 6.5(with irregular balance curve)	5	0	0
		Peak balance lower than 6.5 (with irregular balance curve)	6	5(2)	0
Totals			48	52(9)	6
Averages of sex hormone balance, excluding peak balances	More than 2 (Relative hyperestrogenism)		40	8(4)	4
	Less than 2 (Normal balance)		22	45(5)	11
Totals			62	53(9)	15

( ) : Breast cancer with chronic cystic matitis.

V. DISCUSSION

The data detailed in this article may be summarized briefly as follows: A study of the urinary excretion of 17-KS in chronic cystic mastitis and in breast cancer with chronic cystic mastitis revealed that the excretion rates were low. A study of the urinary excretion of 17-KS in breast cancer revealed that the excretion rates were normal. A study of the urinary excretion of 17-KS in fibroadenomas of the breast revealed that the excretion rates were normal.

The concurrence of low 17-KS outputs with normal biologic androgen activity and normal liver function in chronic cystic mastitis (mastopathia) appears to be a new endocrine finding. In current endocrine theory, this finding implies either failure of both gonadal and adrenal androgen production, or a more obscure disturbance in steroid production or metabolism.

Recently, we have read other reported studies of the 17-KS excretion in neoplastic diseases of the breast, but the other reports are not in accord with ours.

In our clinic, the ratio of urinary estrogens to 17-KS has been determined in neoplastic diseases of the breast for the purpose of research in steroid metabolism.

Continuous daily determinations of urinary sex hormone balance (E/17-KS) in patients with neoplastic diseases of the breast have not yet been reported.

In chronic cystic mastitis and breast cancer with chronic cystic mastitis, the monthly curves and averages of the hormone balance were definitely atypical (relative hyperestrogenism). In breast cancer and fibroadenomas of the breast, the monthly curves and averages of the hormone balance were usually within normal limits.

Urinary excretion levels of the sex hormones represent only the end products of steroid metabolism. It has not yet been proved whether or not they give a true index of the blood levels, the rate of secretion or destruction, or the utilization of the hormones by the tissues. The data in our laboratory suggest that the patients with chronic cystic mastitis may excrete estrogens and 17-KS, in a different fashion from individuals without the diseases, but the patients with cancer may excrete the sex hormones normally. It is clear that alterations in excretion eevels or the specific type of hormone isolated are not necessarily characteristic for patintes with cancer.

It is conceivable that the formation of carinogenic agents from hormones may occur as a result of a faulty metabolism due to a change in the physiologic state of the host. Lack of a steroid hormone, which normally stimulates the breast, may lead to degenerative or regressive changes, which might then allow other agents to act. The etiologic factors of such abnormal steroid metabolism in chronic cystic mastitis are considered the abnormal stimuli to hypophysis, adrenal cortex, gonad and liver. Among the abnormal stimuli, suggested as playing an important role in the development of abnormal steroid metabolism, are the artificial interruption of pregnancy, abortion, sterility, birth control, pelvic and liver diseases. These

abnormal stimuli have recently increased as a result of the increase of working women after the second World War.

From the foregoing data, it can be concluded that there is no proof that the sex hormones are the direct cause of carcinoma of the breast, but it is possible and likely in some cases that they are indirectly responsible, in as much as they may produce precancerous changes or may provide a suitable substrate so that another agent may act.

Ⅵ. SUMMARY

1). The 24-hour urinary excretion of 17-KS in patients with neoplastic diseases of the breast was determined by Miyake's method.

2). A study of the urinary excretion of the 17-KS in chronic cystic mastitis and in breast cancer with chronic cystic mastitis revealed that the excretion rates were low.

3). A study of the urinary excretion of 17-KS in breast cancer and in fibroadenomas of the breast revealed that the excretion rates were normal.

4). Studies of the sex hormone balance (E/17-KS) throughout the menstrual cycle were carried out in patients with neoplastic diseases of the breast.

5). In chronic cystic mastitis and in breast cancer with chronic cystic mastitis, the monthly curves of hormone balance were definitely atypical in a high percentage of cases. Except for the peak balances, the averages of the hormone balance were higher than those of normal values.

6). In cancer of the breast and in fibroadenomas of the breast, the monthly curves of the hormone balance were usually within the normal range. Except for the peak balances, the averages of the hormone balance were definitely normal in a high percentage of cases.

7). As the result of these observations, we conclude that in the majority of chronic cystic mastitis, there were abnormal steroid matabolism with hypoandrogenism. On the other hand, in the majority of breast cancer, there were no striking differences from normal steroid metabolism.

In conclusion, I wish to thank Dr. Kyozo Masuda the lecturer of our clinic and Prof. Dr. Miyake of Gifu University for their guidance throughout the period of this study.

REFERENCES

1) Adachi, H.: Estrogen and Cancer. Clinical Endocrin., (Horumon to Rinsho, in Japanese), **2**; 1741, 1954. 2) Beatson, G. T.: On the Treatment of Inoperable Cases of Carcinoma of the Mamma. Lancet, **2**; 104, 1896. 3) Callow, R. K.: The Chemical Estimation of Neutral 17-KS. J. Endocrin., **5**; 117, 1948. 4) Dingemanse, E. et al.: The Clinical Method for Chromatographic Colorimetric Determination of 17-KS in Normal Adult. J. Clin. Endocrin., **12**; 66, 1952. 5) Dobriner, K. et al.: Abnomal Alpha Ketosteroid Excretion in Patients with Neoplastic Disease. Science, **99**; 494, 1944. 6) Drekter, I. J. et al. The Rapid Method for Determination of Total Urinary 17-KS. J. Clin. Endocrin., **7**; 795, 1947. 7) Drekter, I. J. et al.: The Determination; Preparation of Pigment-free Extracts and Simplified Procedure for Esimation of Total 17-KS. J. Clin. Endocrin. **12**; 55, 1952. 8) Escher, G. C.. Hormone Therapy in Advanced Mammary Carcinoma. The Med. Cin.North A., **36**; 681, 1952. 9) Fujimori, M.: Relationships between

Brest Cancer and Endocrine Functions. Endocrin.Meeting, (Naibunpitsu no Tsudoi, in Japanese), **3**; 567, 1953. 10) Fujimori, M. et al. : On the Relationship between the Endocrine Functions and the Precancerous Condition of Breast Cancer. Clin. Surg., (Rinsho Geka in Japanese), 8; 561, 1953. 11) Fujimori, M. et al. : On the Relationship between the Endocrine Functions and the Precancerous Conditions of Breast Cancer. J. Jap. Surg. Soc., **54**; 219, 1953. 12) Fujimori, M. et al. : On the Relationship between the Endocrine Functions and the Precancerous Conditions of Breast Cancer : Report 2. Especially about the Role of Hypophyseo-ovarian System. J. Jap. Surg. Soc., **55**; 533, 1954. 13) Fujimori, M. et al. : Precancerous Conditions of Breast Cancer. from the Histochemical and Endocrinological Point of View, Especially about the Studies of the Nucleic Acids Metabolisum. J. Jap. Surg.,Soc., **56**; 596, 1955. 14) Glass, S. J. et al. : Sex Hormone Changes Associated with Liver Disease. Endocrin, **27**; 749, 1940.

15) Hatta, O. et al. : Clinical Investigation on 17-ketosteroids in Urine of Surgical Patients. J. Jap. Surg. Soc., **55**; 515. 1954. 16) Holtorff, A. H. et al: The Colorimetric Estimation of 17-KS and Their Application to Urine Extracts. J. Bio. Chem., **135**; 377, 1940. 17) Ishiyama, S. : Hormone Therapy on the Cancer of Breast. Clin. Endocrin., (Horumon to Rinsho, in Japanese), **1**: 540, 1953. 18) Jailer, J. W. : Diagnostic Significance of the 17-KS. The Med. Clin. North A., **36**; 757, 1952. 19) Kier, L. C. et al. : Endocrine Relationships in Benign Lesions of the Breast. Annals of Surg., **135**; 782, 1952. 20) Kita, Y. : Studies on the Influences of the Sexual Hormone upon Mammary Cancer; 1. Oophorectomy on Mammary Cancer. J. Jap. Surg. Soc., **54** 323, 1953.

21) Kita, Y. : Studies on the Influences of the Sexual Hormone upon Mammary Cancer; 2. Transplantation of Testis on Advanced Mammary Cancer. J. Jap. Surg. Soc., **55**; 341, 1954. 22) Kuru, M. . Precancerous Condition. J. Jap. Soc., **53**; 537, 1952. 23) Kobayashi, S. et al. : Change of Urinary 17-Ketosteroids Excretion in Cancer Patients. Clinic. Endocrin., (Horumon to Rinsho, in Japanese), **2**; 1693, 194; 24) Keinesberg, S. et al. : The Excretion of 17-KS; Normal Values in Relation to Age and Sex. J. Clin. Endocrin., **9**; 436, 1949.

25) Lewis, B. D. et al. : Gynecomastia, Virginal Hypertrophy and Fibroadenomas of the Breast. Annals of Surgery, 100; 779, 1934.

26) Lewis, B. D. et al. : The Relation of Chronic Cystic Mastitis to Carcinoma of the Breast. Surg. Gyneco. and Obst., **66**; 300, 1938.

27) Masuda, K. et al. : Endocrinological Studies on Mastopathia. J. Jap. Surg. Soc., **54**; 221, 1953. 28) Masuda, K. et al. : Mastopathia and Sex Hormone. Shinryo in japanese, **6**; 891, 19 53. 29) Masuda, K. et al. : Endocrinological Studies on Neoplastic Diseases of the Breast. J. Jap. Surg.Soc., **55**; 534, 1954. 30) Masuda, K. et al. : Endocrinological Studies on Neoplastic Diseases of the Breast. Rinshogeka in Japanese, **10**; 1, 1955. 31) Masuda, K. et al. : Endocrinological Studies on Neoplastic Diseases of the Breast. J. Jap. Surg. Soc., **56**; 593, 1955. 32) Masuda, K. et al. : Estimation of Steroid Estrogens by Fluorometry. Saishinigaku in Japanese, **9**; 80, 1954. 33) Masuda, K. et al. : Neoplastic Disease of the Breast and Hormone. Shinryo in Japanese, **8**; 349, 1955.

34) Miyake, T. et al. : Clinical Availability of the Zimmermann Reaction. Folia Endocrin. Jap., **26**; 122, 1951. 35) Moszkowicz, L. : Ueber dem Monatlichen Zyklus der Brustdruse. Arch. f. Klin. Chir., **142**; 374, 1926.

36) Nathanson, I. R. : The Relationship of Hormones to Diseases of the Breast. Endocrinology of Neoplastic Diseases; **138**; 1947, Oxford University Press, New York.

37) Nathanson, I. T. : Hormonal Treatment in Cancer. Med. Clin. North A., **34**; 1409, 195;

38) Nishiya, K. : Endocrinological Studies on Neoplastic Diseases of the Breast in the Light of the Excretion of the Urinary Estrogens. (unpublished) 39) Ono, F. : Some Clinical Studies on the Measurement of Urinary 17-KS. Endocrinological Meeting, (Naibunpitsu no tsudoi in Japanese), **3**; 613, 1954.

40) Ochiai, K. : Cortisone and Cancer. Clinical Endocrin., (Horumon to Rinsho in Japanese) **2**, 1194, 1954. 41) Pearlmann, W. H. : Steroid Excretion in Cancerous and Noncancerous Persons; 17-KS. Endocrin., **30**; 270, 1942.

42) Procter, I. M. et al. : The Relation of Chronic Cystic Mastitis to Malignancy. Surg. Gyneco. and Obst., **70**; 671, 1940. 43) Ross, M. et al. : The Urinary Excretion of Estrogens and Androgens by Women with Carcinoma of the Breast. Cancer Research, **1**; 52, 1941.

44) Saltzstein, H. C. et al. : Benign Tumors of the Breast. J. A. M. A., **140**; 997, 1949.

45) Schinzinger, A.: Centralbl. f. Chir., **16**; 55, 1889. 46) Selye, H.: Textbook of Endocrinology. **77**; 1947, Acta Endocrinologica. Inc. Montreal, Canada. 47) Sommer, S. C. et al.: Ovarian Influence upon Survival in Breast Cancer. Arch. of Surg., **67**; 916, 1953.
48) Soejima, Y.: Beitraege zur Mastopathie. Archiv fur Japanische Chirurgie, **20**; 737, 1943. 49) Talbot, N. B. et al.: The Colorimetric Assay of Total α- and β-17-KS in Extracts of Human Urine. J. Biol. Chem., **132**; 595, 1940. 50) Talbot, N. B. et a.: Chromatographic Separation and Colorimetric Determination of Alcoholic and Nonalcholic 17-KS in Extracts of Human Urine. ibid, **139**; 521, 1941.
51) Talbot, N. B. et al.: Elimination of Errors in the Colorimetric Assay of Neutral Urinary 17-KS by Meanes of a Color Correction Equation. J. Biol. Chem., **143**; 211, 1942.
52) Takemoto, H. et al.: Neoplastic Diseases of the Breast and Sex Hormone. J. Jap. Surg Soc., **55**; 536, 1954. 53) Taylor, H. C.: The Relation of chronic Mastitis to Certain Hormones of the Ovary and Pituitary and Coincident Gynecological Lesion. Surg. Gyneco. and Ost., **62**; 129, 1936. 54) Taylor, H. C.: et al. Estrogen and 17-KS Excretion in patients with Breast Carcinoma. Cancer Research, **3**; 180, 1943. 55) Whitehouse, B.: Mastopathia and Chronic Mastitis. Surg. Gyneco. and Obst., **58**; 278, 1934. 56) Wanke, R.: Die Mastopathia Chronica in Neuerst Betrachtung. Deutsch. Zeitsch. Chir., **250**; 234, 1938.
57) Yasogawa, M. et al.: Clinical Studies on the Cause of Gynecomastia. J. Jap.Surg. Soc., **55**; 535, 1954. 58) Yamamoto. T.. Endocrinological Studies on Neoplastic Diseases of the Breast. J. Jap. Surg. Soc., **55**; 536, 1954.
59) Zimmermann, W. Eine Farbreaktion der Sexualhormone an der ihre Anwendung zur Quantitativen Colorimetrischen Bestimmung. Ztschr. f. Physiol. Chem., **233**; 257, 1935.

和 文 抄 録

尿中 17-Ketosteroids 排泄状態よりみた乳腺腫瘍特にマストパチー Mastopathie の内分泌学的研究

京都大学医学部外科学教室第2講座（青柳安誠教授 指導）
大学院学生 伊 勢 田 幸 彦

外科領域に於て前癌状態として注目され且つ最近，特にその発生数が増加し，その発生年令の若くなつたマストパチーを中心に，線維腺腫，乳癌患者について尿中 Androgen 即ちその指標となる尿中 17-Ketosteroids（以後 17-KS）排泄量の消長，及び Estrogen と17-KSとのバランスを検討して次の結果を得た．

1. マストパチーに於ては，尿中 17-KS 排泄量の低下しているものが多く，全例の 65.7%に低下例を認めた．

2. 普通乳癌に於ては，尿中 17-KS 排泄量は正常値を示すものが多く，全例の 81.4%が正常であつた．たゞマストパチーから移行したと考えられるものに於ては，尿中 17-KS 排泄量の低下しているものが多く全例の 75.0%に低下例を認めた．

3. 乳腺線維腺腫に於ては，尿中 17-KS 排泄量は殆んど全例に於て正常値を示し，少数例に於て，やゝ高値を示した．

4. 尿中両性ホルモンのバランスから観察すると，マストパチー及びマストパチーから移行したと考えられる乳癌では，バランスの消長に異常を認めるものが多く，而も 17-KS 低下による相対的エストロゲン過剰を認めるものが多かつた．

乳癌では，両性ホルモンのバランスは正常を示すものが多かつた．

線維腺腫に於ても，両性ホルモンのバランスは正常を示すものが多かつた．

5. 尿中 17-KS 低下による相対的エストロゲン過剰という Steroidhormone の代謝障碍は，その標的臓器である乳腺に特異的な変化マストパチーを惹起させるものと考える．