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LSD 1030

ENDOCRINOLOGICAL STUDIES ON THE PERIODIC PSYCHOSES

By

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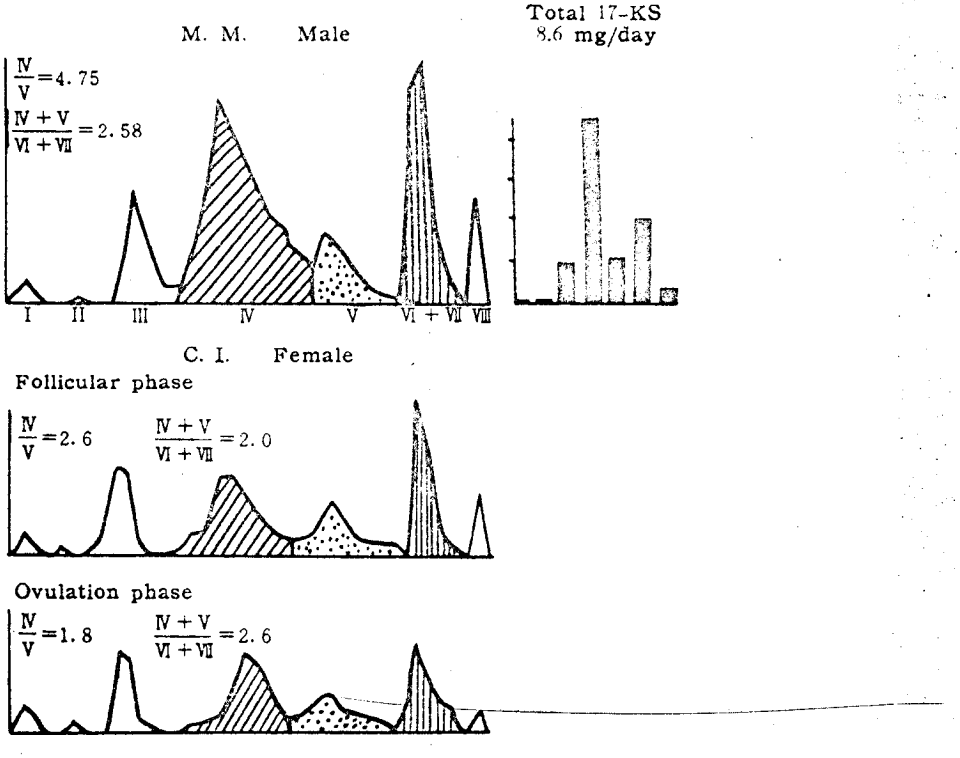
We would like to discuss briefly a few problems concerning the metabolism of steroid hormones and liver function in female periodic psychoses.

The chromatographic pattern of fractions of urinary 17-KS of normal adults has two characteristics: first, there is a greater amount of the androsterone (IV) than of the etiocholanolone (V), and second, the gonadal fractions as a whole are predominant over the 11-hydroxy-17-KS fractions (VI+VII) (Fig. 1). Periodic psychotics showed various abnormal



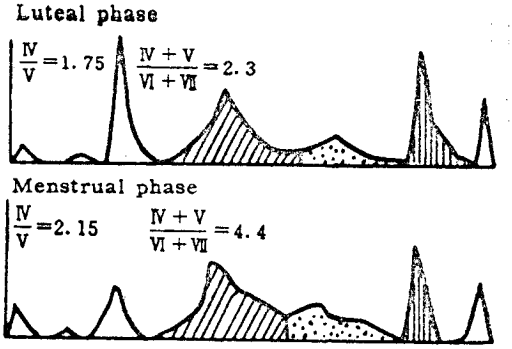


Fig. 1. Fraction Pattern of Urinary Neutral 17-KS in Normal Controls.

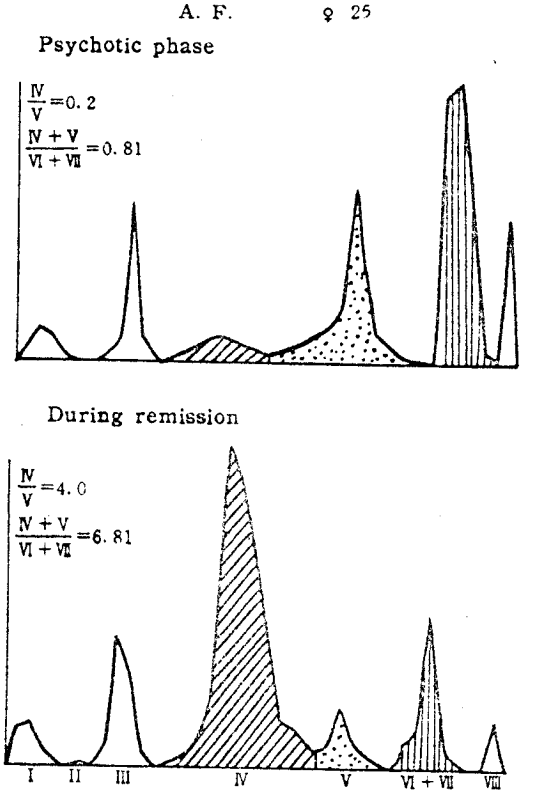


Fig. 2. Fraction Patterns of Urinary 17-KS in Periodic Psychosis.

patterns in such a way that the androsterone was less than the etiocholanolone (Fig. 2), the gonadal fractions were less than the 11-hydroxy-17-KS fractions (Fig. 3), and the amount of every fraction was extremely

T. H. ♀ 40.
Periodic psychosis

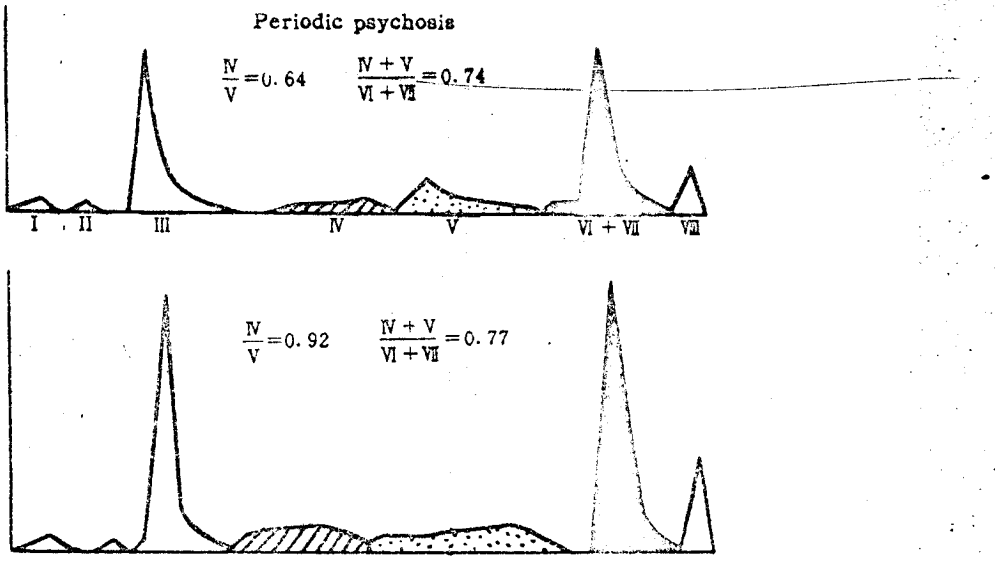
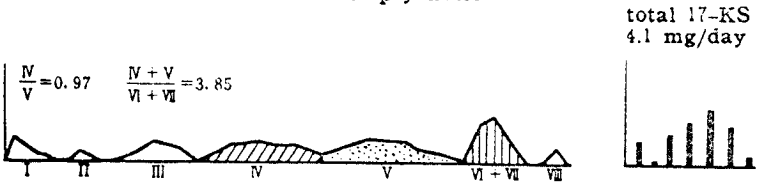


Fig. 3.

K. H. ♀ 59
Periodic psychosis



Y. M. ♀ 21
Simmonds' disease

Fig. 4.

reduced as is in the case of *Simmonds'* disease (Fig. 4); the most characteristic thing being the fact that the androsterone was less than the etiocholanolone. The pattern in the patient usually returned to normal during the lucid interval (Fig. 5).

In view of the fact that the androsterone and the etiocholanolone

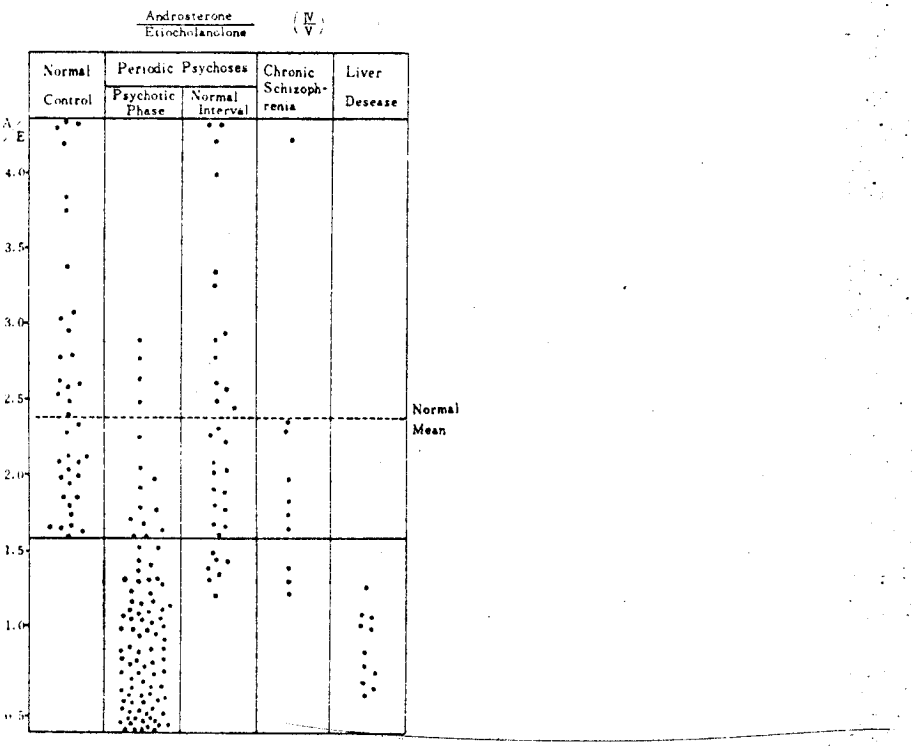


Fig. 5.

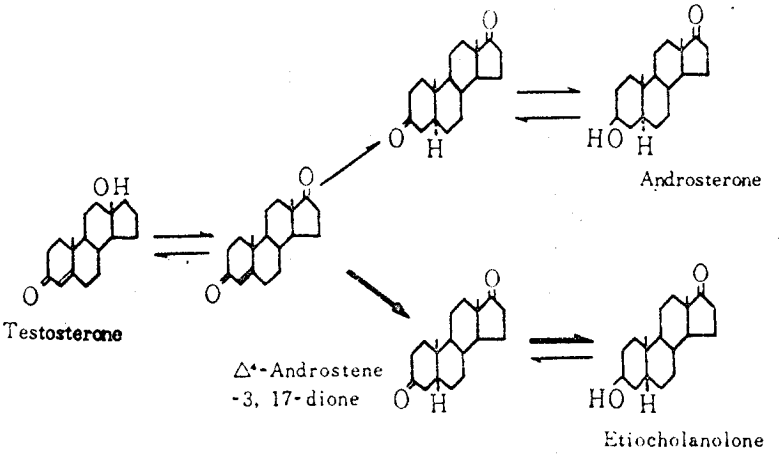


Fig. 6. Metabolic pathway of Testosterone.

have an isomeric structure and that their common precurser is testosterone, one possible explanation of our findings mentioned above may be that testosterone is metabolized dominantly to androsterone in normal

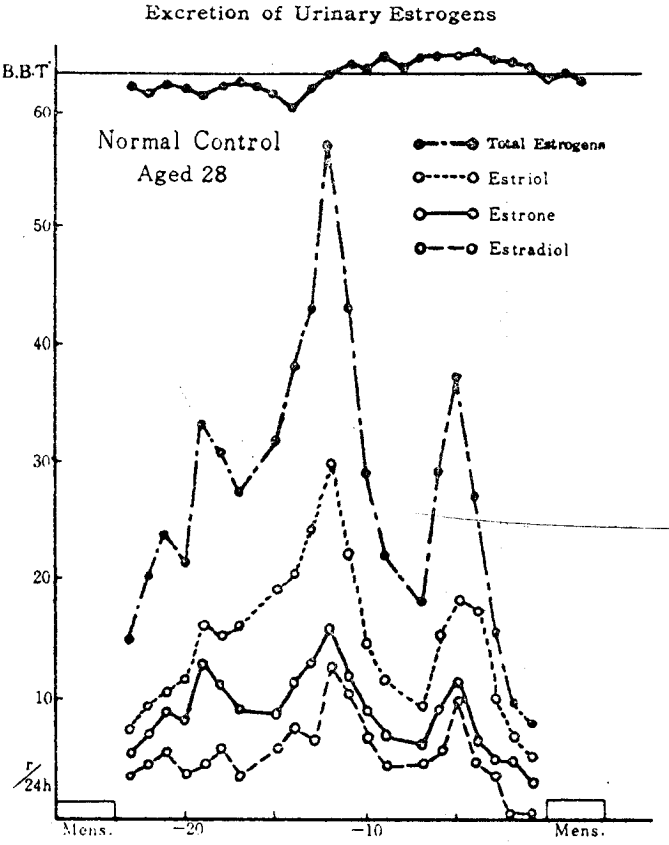


Fig. 7.

Tab. 1. Fraction Patterns of Estrogen in Urin of Normal Control

Name	Age		E.D. γ/24h	E.O. γ/24h	E.T. γ/24h	E.D. / E.D.	E.O. / E.D.	E.T. / E.D.
T. M.	28	follicular phase	4.8	10.6	15.9	1	2.2	3.3
		luteal phase	4.5	7.2	10.4	1	1.6	2.3
Y. I.	32	follicular phase	7.5	13.7	20.3	1	1.8	2.7
		luteal phase	8.5	14.3	19.1	1	1.8	2.4
K. K.	24	follicular phase	6.0	10.9	17.0	1	1.8	2.8
		luteal phase	5.3	6.9	13.3	1	1.3	2.5
Mean		follicular phase	6.1	11.7	17.7	1	2.0 ±0.2	3.0±0.3
		luteal phase	5.9	9.5	14.3	1	1.55±0.25	2.4±0.1

adults but under abnormal conditions the pathway to the etiocholanolone becomes dominant (Fig. 6).

Let us turn to the problem of estrogen excretion. Fig. 7 shows a curve for urinary excretion of estrogens in a normal female. It has two

Excretion of Urinary Estrogens
Periodic psychosis. Aged 17

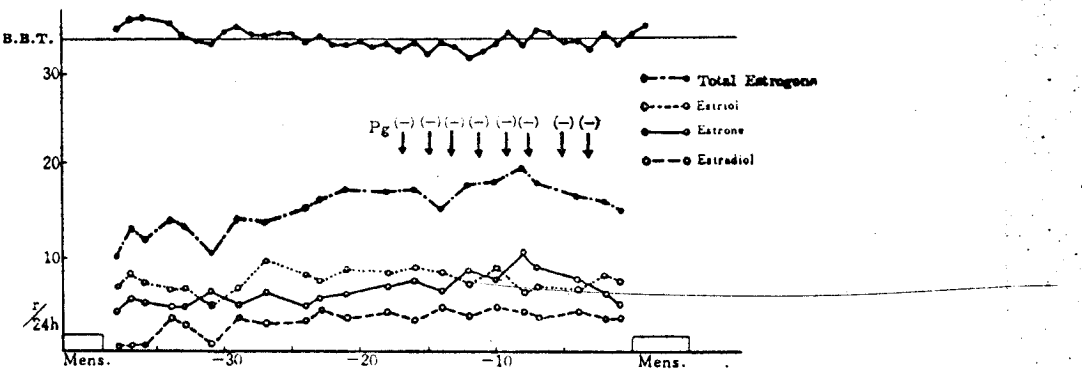


Fig. 8.

Excretion of Urinary Estrogens

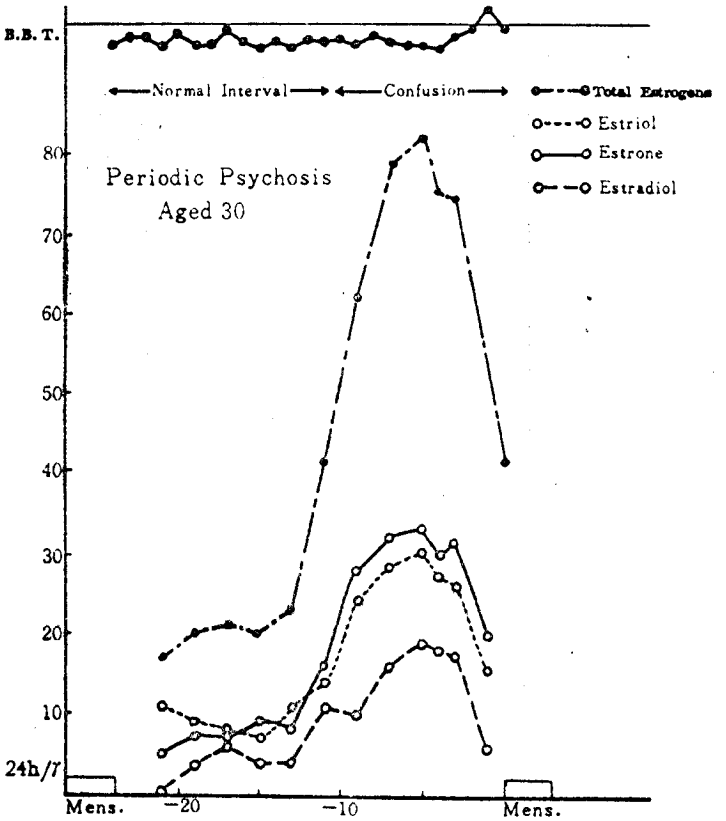


Fig. 9.

peaks corresponding to ovulational and premenstrual phases. The ratios between estradiol, estrone, and estriol are approximately 1.0, 2.0, and 3.0, respectively (Tab. 1). The excretion of pregnandiol during the luteal phase amounts to one to five milligrams. In periodic psychoses, estrogen excretion no longer showed two regular peaks, but the pattern was irregular in various fashions (Fig. 8, 9), and sometimes the pregnandiol excretion was too low to be determined. The ratio between the estrogen fractions was found to be abnormal in psychoses, namely, the amount of estrone was larger than that of estriol. Similar irregularity in pattern and abnormal ratio among estrogens have been reported also in cases of liver diseases (Tab. 2).

Tab. 2. Fraction Patterns of Estrogen in Urine
Periodic Psychoses, Post-Partum Psychoses, Liver Diseases

Name	Age		E.D.	E.O.	E.T.	
K. N.	15	follicular phase	1	1.4	0.9	Periodic psychoses
		luteal phase	1	1.4	1.1	
Y. N.	17	follicular phase	1	3.0	3.8	
		luteal phase	1	4.7	5.7	
M. N.	30		1	1.9	1.5	
T. H.	17		1	1.2	0.6	
T. H.	40		1	2.2	0.9	
K. S.	40		1	3.3	2.7	
M. W.	17		1	1.8	1.2	
S. H.	16		1	2.5	2.1	
E. M.	24		1	2.6	2.2	
H. A.	20		1	2.1	1.6	
M. O.	32		1	1.9	1.7	
S. N.	42		1	2.2	1.7	
F. K.	36		1	2.8	2.2	
M. O.	21		1	3.6	2.3	
E. H.	17		1	2.3	3.1	
K. T.	15		1	2.1	2.8	
M. O.	24		1	5.8	4.6	Post-partum psychoses
K. H.	25		1	2.5	1.8	
N. N.	26		1	3.2	2.7	
T. M.	28		1	3.1	2.5	
K. N.	24		1	2.6	1.8	
K. K.	24		1	1.9	2.2	
S. S.	37		1	1.5	0.8	Liver diseases
T. M.	25		1	2.2	1.2	
H. H.	27		1	1.7	1.1	
M. O.	36		1	1.9	1.6	

From the findings mentioned above we may say that in periodic psychoses, disturbances not only exist in the gonadal system but also in the metabolism of sex steroids.

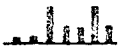
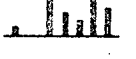
The next experimental data we would like to present are those of

Tab. 3. Excretion Rates and Fractions Pattern of 17-KS after 50 mg Testosterone Administration

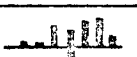
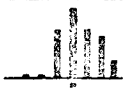
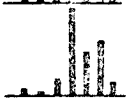
	Name	Sex	Age	A/E before adm.	During 24 hrs after administration	
					Excretion rates	A/E
Normal control	B. F.	♂	29	3.08	45.0%	3.46
	N. F.	♀	36	2.54	44.0	2.64
	K. I.	♂	31	1.99	41.9	3.64
	Y. K.	♀	27	1.75	33.8	1.88
	T. N.	♀	19	1.56	25.1	2.05
	R. I.	♀	26	1.65	23.5	1.92
	T. H.	♀	16	2.05	22.0	6.83
Patients who showed abnormal pattern of 17-KS fractions	M. Y.	♀	36	0.45	31.3	0.48
	Y. T.	♀	59	1.08	20.7	1.18
	K. I.	♀	38	1.20	19.0	1.30
	S. F.	♀	25	1.42	18.9	1.26
	T. K.	♀	26	0.82	17.9	1.18
	F. K.	♂	30	0.39	13.9	1.20
	K. Y.	♀	51	1.02	13.5	1.28
	K. N.	♀	24	0.65	12.1	0.68
	C. S.	♀	26	0.69	8.7	0.68

17-KS excretion after administration of testosterone. Fifty milligrams of testosterone were administered intramuscularly to patients who showed an abnormal pattern of 17-KS excretion. After administration of testosterone the patients, as compared to normal controls, showed low excretion rates of 17-KS with abnormal patterns as was mentioned above, namely, with less androsterone than etiocholanolone (Tab. 3). We have

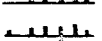
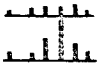
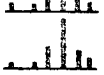
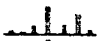
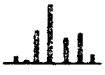
Tab. 4.

Name	Sex	Age	Diagnosis	Fraction Patterns I II III IV V VI VII	Total 17-KSmg	$\frac{IV}{V}$	$\frac{IV+V}{VI+VII}$
O. Y.	♀	47	Hepatic Cirrhosis		4.3 mg/day	0.89	0.37
K. Y.	♀	51	Hepatic Cirrhosis		5.32 mg/day	1.03	0.85
A. O.	♂	48	Hepatic Cirrhosis		2.63 mg/day	0.62	2.64
T. M.	♂	45	Hepatic Cirrhosis		4.4 mg/day	0.65	1.96
Z. M.	♂	45	Hepatic Cirrhosis		7.5 mg/day	1.41	0.72
M. H.	♂	53	Hepatic Cirrhosis		0.54 mg/day	1.25	0.37
S. Y.	♂	51	Hepatic Cirrhosis		2.62 mg/day	0.73	0.72

Tab. 5.

Name	Sex	Age	Diagnosis	Fraction Patterns I II III IV V VI VII	Total 17-KSmg	$\frac{IV}{V}$	$\frac{IV+VI}{VI+V}$
Z. N.	♂	58	Serum Hepatitis,		4.63 mg/day	0.59	1.54
			Recovery State		8.47 mg/day	2.33	2.0
Y. T.	♀	59	Acute Hepatitis,		3.89 mg/day	1.08	1.33
			Recovery State		6.07 mg/day	1.06	0.95
T. H.	♂	21	Acute Hepatitis,		4.9 mg/day	0.76	0.61
			Recovery State		0.75 mg/day	2.5	2.63
I. U.	♂	30	Infections Hepatitis Recovery State		9.6 mg/day	1.45	2.85
S. T.	♂	21	Cholangiolitic Hepatitis		9.18 mg/day	2.1	2.37

Tab. 6.

Name	Sex	Age	Diagnosis	Fraction Patterns I II III IV V VI VII	Total 17-KS	$\frac{IV}{V}$	$\frac{IV+V}{VI+VI}$
Y. M.	♀	22	Simmonds' Desease,		4.03 mg/day	0.18	0.66
Y. K.	♀	25	Pituitary Dwarfism		2.02 mg/day	1.0	1.58
F. I.	♀	30	12/XI 1959 Diencephalic Disorder 15/XII 1959		6.29 mg/day	0.48	4.03
					6.31 mg/day	0.47	4.1
M. Y.	♀	25	Anorexia nervosa		8.25 mg/day	2.09	2.24
Y. P.	♂	35	Hypothyreoidism		13.21 mg/day	5.27	2.64
Y. N.	♂	17	Hypothyreoidism		4.13 mg/day	3.0	2.17
N. K.	♂	35	Diabetes mellitus		9.51 mg/day	3.03	2.56
F. I.	♀	24	Diabetes mellitus		10.1 mg/day	2.6	3.27

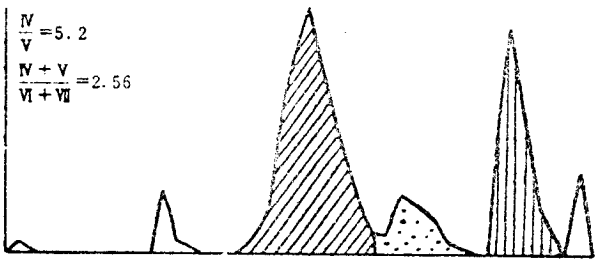
also examined the patterns of 17-KS excretion in liver diseases. In almost all of the liver diseases subjected to examination, the patterns were found to be abnormal in the same way as was observed in periodic psychoses (Tab. 4, 5). It follows that the abnormal patterns of 17-KS

and estrogen excretion which were observed in periodic psychoses may be attributed to a metabolic disturbance of the liver (probably a disorder of the oxidation-reduction enzyme system). However, whether the disorder of the liver is the primary factor or whether there exists some other factors which have influence on the liver function, is still open to question.

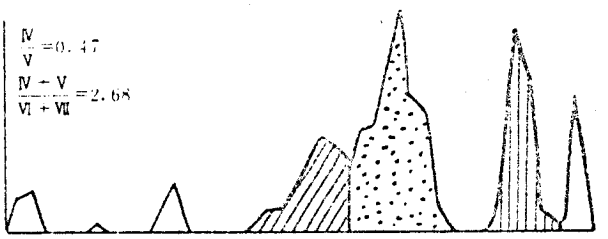
With the latter possibility in the mind, we have examined 17-KS fractions in various endocrine diseases. As can be seen in Tab. 6, *Simmonds'* disease, pituitary dwarfism and diencephaloses (diencephalic disorders) gave abnormal patterns just like those mentioned above for periodic psychoses, while the other diseases gave a normal pattern. This may suggest that hypothalamopituitary control is also involved in the metabolic function of the liver.

In the next place, we have examined 17-KS patterns in the so-called LSD experimental psychoses. Normal subjects who showed a normal pattern of urinary 17-KS before administration of lysergic acid diethylamide-25 were selected and 100 gamms of LSD-25 were administered orally to each person. Urine was collected 24, 48, and 72 hours after administration. It was found in all cases that during the first 24 hours the androsterone was markedly reduced and the pattern of fractions was abnormal in a similar way as was observed in periodic psychoses, but it returned to a normal state after 48 to 72 hours (Fig. 10, 11, Tab. 7). Since LSD-psychosis has been thought to be a sort of acute diencepholosis (*Stähelin*) and the main sites of action of LSD have been pointed out to be the liver, hypothalamus and adrenal medulla, the results of our experiment mentioned above seem to present quite an interesting problem as to the mechanism of action of this drug and the pathology of acute psy-

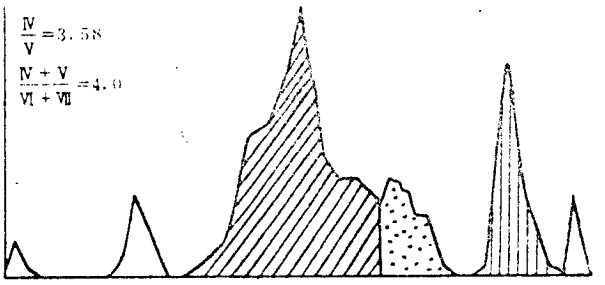
Y. S. ♂ 25



Before administration of LSD



During the 1st 24hrs after adm. of LSD



During the 2nd 24hrs after adm. of LSD

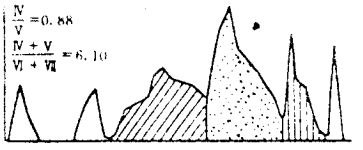
Fig. 10. Fraction Patterns of 17-KS in LSD_{25}-Model-Psychoses.

F. K. ♂ 30

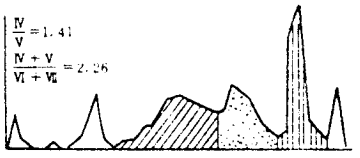
Before administration of LSD

During the 1st 12hrs after adm. of LSD

During the 1st 24hrs after adm. of LSD



During the 2nd 12hrs after adm. of LSD



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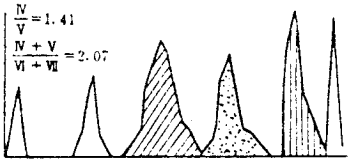
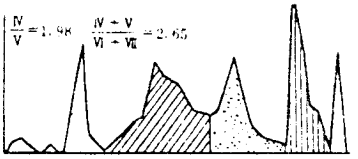


During 48hrs after adm. of LSD



During the 3rd 24hrs after adm. of LSD

Fig. 11. Fraction Patterns of 17-KS in LSD_{25}-Model-Psychoses.

Tab. 7. 17-KS Fraction Patterns of so-called LSD_{25}-Psychoses

Name	Sex	Age	Androsterone Etiocholanolone				
			Before	0–12 hrs	12–24 hrs	24–48 hrs	48–72 hrs
Y. K.	♂	31	2.42	2.04	1.3	1.45	–
F. K.	♂	30	2.46	–	0.35	1.41	1.98
			–	1.66	0.88	1.41	–
Y. S.	♂	25	5.2	–	0.47	3.58	–
S. T.	♂	17	3.33	–	0.69	2.93	–
. U.	♂	30	2.45	–	0.48	0.81	1.55

choses. Finally, we as well as other authors (*Gjessing, Mall, Danziger*) confirmed that thyroid hormone had a prominent effect for the periodic psychoses, especially for the frequently relapsing types. In such cases it is found that administration of thyroid hormone worked increasing upon androsterone and normalized metabolic pattern of androgen. From these results the hypothesis is made that one of the effect of thyroid hormone might be mediated by the normalization of metabolism of the steroid hormone in the liver.

As a conclusion from our experimental results, we would like to say that the abnormal patterns of androgen and estrogen fractions found in acute or periodic psychoses may be explicable in terms of disorder of the liver and also that of the hypothalamic function. Thus the mutual relationship between the liver and the hypothalamus comes into question, but it is still uncertain which of them is the primary factor.

However, it is considered that the disorder of the liver is not the primary factor on the development of periodic psychoses but it is an aspect of the breakdown of hepato-cerebral homeostasis.