OBSERVATIONS ON THE RELATION BETWEEN INSULIN COMA DOSAGE AND PROGNOSIS IN SCHIZOPHRENIA.

By R. K. Freudenberg, M.D., D.P.M.,
Physician-Superintendent, Netherne Hospital, Coulsdon, Surrey.

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The evidence for somatological differences between various types of schizophrenia and its different stages of severity or chronicity is still scanty and often contradictory. The present investigation mainly concerns itself with endocrinological factors. Kraepelin, already, suggested disturbances in the endocrine system. The incidence of schizophrenia in different age-groups, especially its steep rise at puberty, reaching its peak at 20 in men and 25 in women and the rapid decline of its occurrence after these ages (Haas, 1938), has for a long time pointed to the sex steroids as an important factor in the pathology of this disorder. Hemphill *et al.* (1944, 1945, 1948) found an atrophy of the testes in many cases of schizophrenia, and considered the severity of the testicular change to be proportional to the severity of the psychosis. They suggest that the testicular lesions are not the cause of schizophrenia, but probably effects of the " pathogenic process " and related to hypothalamic or pituitary function. In confirmation of these findings Hoskins and Pincus (1949) observed the output of androgen in schizophrenics to be significantly lower than in normal men. Sears (1937) made similar observations in females, and found that the blood-œstrin level of female schizophrenics was much lower than in normal women. Possibilities for primary endocrinological factors suggest themselves; the " pathogenic process " can, however, still be primarily a psychological " stress " in this new constellation or a combination of both, or the effect of another central disturbance. Some of our somatological findings can, therefore, tentatively be interpreted as related to or identical with the primary stress or others only as secondary correlates or results, though the present state of our knowledge does not yet allow a final decision as to what is primary and what only secondary. Recent evidence on the relationship of sex hormones and insulin (Houssay, 1951) suggests that oestrogens have a " sensitizing " and androgens a " desensitizing " effect. An investigation into the insulin sensitivity in clinically different schizophrenic groups and the two sexes expressed in the amount of insulin needed to produce a hypoglycaemic coma should, therefore, throw some light on other endocrinological mechanisms.

Method.

In insulin coma treatment of schizophrenia, the insulin dosage is gradually increased until high enough to produce a coma within three hours after the injection, characterized by the absence of purposeful responses. The first dose producing a coma is referred to as the initial coma dose. As the dosage needed to produce comas fluctuates during the course of treatment, the maximal and minimal dose was also recorded. Treatment responses were assessed by questionnaire and/or interview. Atypical cases of schizophrenia, of the pseudoneurotic type or cases with marked manic-depressive, anxiety hysteric or obsessional features were always treated separately. The body index type was determined with the help of the Rees-Eysenck formula. The other data are self-explanatory from the tables. The weight referred to is always the one before treatment commenced. All findings were statistically evaluated.

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Results :

TABLE I.—*Sex Differences.*

	Male means.	Female means.	Differences.	*t.*	*df.*	*p.*
Initial dosage	433·8	199·9	233·9	4·445	82	<·01
Maximal dosage	496·6	257·7	238·9	4·163	81	<·01
Minimal dosage	144·7	128·4	16·3	1·181	81	<·05

Note on degrees of freedom.—There were 14 good- and 18 poor-response males, and 36 good- and 17 poor-response females. The fluctuations in degrees of freedom arise because certain measurements were missing in the case of some females.

TABLE II.—*Light Males* vs. *Heavy Females.*

(Mean male weight—56·15 kgm. Mean female weight—66·15 kgm. All females heavier than all males.)

	Light male means.	Heavy female means.	Difference.	*t.*	*df.*	*p.*
Initial dosage	686·7	175·0	511·7	3·011	19	<·01
Maximal dosage	771·1	240·0	531·1	2·710	18	<·02

TABLE III.—*Sex Differences in Response Grades : Schizophrenics.*

Response Grades.	1.	2.	3.	4.	5.	Totals.
Males	3	12	32	3	18	68
Females	15	21	19	6	17	78
Probability that difference in proportions is accidental	<·01	>·05	<·01	>·05	>·05	

TABLE IV.—*Sex Differences in Response Grades : Atypicals.*

Response Grades.	1.	2.	3.	4.	5.	Totals.
Males	—	—	3	1	—	4
Females	4	5	8	—	—	17
Probability that difference in proportions is accidental	>·05	>·05	>·05	>·05	—	

TABLE V.—*Differences between Female Schizophrenics and Female Atypicals of All Grades.*

	Mean schizs.	Mean atypical.	Difference of means.	*t.*	*df.*	*p.*
Body index	110·310	113·250	2·940	1·664	85	>0·05
Weight	56·870	53·824	3·046	1·741	92	do.
Initial dosages	208·08	178·82	29·26	1·265	93	do.
Maximal dosages	262·37	226·47	35·90	1·304	91	do.
Minimal dosages	128·09	91·88	26·21	2·701	90	<0·01

TABLE VI.—*Differences between Good-response and Poor-response Patients.*

	Good response means.	Poor response means.	Difference of means.	*t.*	*df.*	*p.*
Male weight	67·69	65·52	2·17	·565	30	>·05
Female weight	57·65	57·15	0·50	·277	50	do.
Male body-index	101·3	101·5	0·2	·124	30	do.
Female body-index	108·9	110·2	1·3	·578	47	do.
Male initial dosage	380·0	475·6	95·6	·715	30	do.
Female initial dosage	191·2	218·2	27·0	1·224	51	do.
Male maximal dosage	452·9	541·7	88·8	·602	30	do.
Female maximal dosage	243·6	289·4	45·8	1·682	50	do.
Male minimal dosage	156·4	135·6	20·8	·780	30	do.
Female minimal dosage	121·1	144·7	23·6	1·574	50	do.

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TABLE VII.—*Comparison between Male and Female Schizophrenic Patients, Grades 1 and 2.*

	Male mean.	Female mean.	Difference of means.	*t.*	*df.*	*p.*
(a) *Under 6 months :*						
Initial dosage	476·67	185	291·67	4·327	26	<0·01
Maximal dosage	558·33	243·182	315·148	4·358	26	do.
Minimal dosage	171·67	119·54	52·13	2·531	26	<0·05, >0·01
(b) *Over 1 year :*						
Initial dosage	356·67	160	196·67	2·220	7	>0·05
Maximal dosage	428·33	226·67	201·66	2·175	7	do.
Minimal dosage	171·67	100	71·67	1·234	7	do.

TABLE VIII.—*Comparison between Male and Female Schizophrenic Patients, Grade 3.*

	Male mean.	Female mean.	Difference of means.	*t.*	*df.*	*p.*
(a) *Under 6 months :*						
Initial dosage	278·57	210	68·57	1·013	10	>0·05
Maximal dosage	308·57	252	56·57	·944	10	do.
Minimal dosage	121·43	140	18·57	·535	10	do.
(b) *Over 1 year :*						
Initial dosage	352	265	87	1·134	21	>0·05
Maximal dosage	458	328·76	129·24	·972	21	do.
Minimal dosage	148	146·25	1·75	·064	21	do.

TABLE IX.—*Comparison between Male and Female Schizophrenic Patients, Grades 4 and 5.*

	Male mean.	Female mean.	Difference of means.	*t.*	*df.*	*p.*
(a) *Under 6 months :*						
Initial dosage	260	198·57	61·43	·729	10	>0·05
Maximal dosage	274	232·86	41·14	·528	10	do.
Minimal dosage	94	138·57	44·57	1·284	10	do.
(b) *Over 1 year :*						
Initial dosage	540	206·25	333·75	1·888	20	>0·05
Maximal dosage	620·714	273·75	346·96	1·769	20	do.
Minimal dosage	143·57	126·25	17·32	·585	20	do.

TABLE X.—*Comparison between Male Grades 1 and 2 (short duration of illness) and Male Grades 4 and 5 (long duration of illness).*

	Under 6 months. Grades 1 and 2 mean.	*Over 1 year.* Grade 4 and 5 mean.	Difference of means.	*t.*	*df.*	*p.*
Initial dosage	476·67	540·0	63·33	·287	18	>·05
Maximal dosage	558·33	620·71	62·38	·258	18	do.
Minimal dosage	171·67	143·57	28·10	·831	18	do.

TABLE XI.—*Comparison between Female Grades 1 and 2 (short duration of illness) and Female Grades 4 and 5 (long duration of illness).*

	Under 6 months. Grades 1 and 2 mean.	*Over 1 year.* Grade 4 and 5.	Difference of mean.	*t.*	*df.*	*p.*
Initial dosage	185·0	206·25	21·25	1·042	28	>·05
Maximal dosage	243·18	273·75	30·57	·994	28	do.
Minimal dosage	119·54	126·25	6·71	·367	28	do.

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TABLE XII.—*Body Index Figures.*

	Mean I.B.	S.D.I.B.	N.
Rees-Eysenck normals . . .	100·10	5·82	100
,, ,, neurotics . . .	102·44	6·97	400
Netherne schizophrenics . . .	101·39	6·34	68

VERBAL INTERPRETATION OF TABLES.

Table I.—The mean initial and maximal doses for males are higher than those for females to a degree that is most significant statistically. The sex difference in minimal dosage is not statistically significant, though the mean for females remains lower.

Table II.—The males, as a group, are significantly heavier than the females, but the sex difference in initial and maximal dosages cannot be attributed to this difference in mean weight. If the twelve females above the midpoint between male and female mean weights are contrasted with the nine males below the midpoint, two groups result in which all females are heavier than all males and in which the female mean weight approximates the total male mean, the male mean weight to the total female mean. The male initial and maximal dosages remain higher than the female to a statistically significant extent.

Table III.—Shows differences in treatment response grades between male and female schizophrenics.

Grade 1 = Total recovery.
Grade 2 = Social recovery.
Grade 3 = Social defect.
Grade 4 = Family invalid.
Grade 5 = Hospital invalid.

The response grades correspond to the classification of Guttmann, Mayer-Gross and Slater (1939):

Total recovery = Freedom from symptoms and signs, return to previous social environment and to previous or equivalent occupation.

Social recovery = Return to previous social environment and to previous or equivalent occupation, in spite of the presence of minor signs and symptoms, such as irritability, shyness, shallowness of affective response, etc.

Social defect = Presence of minor symptoms, as over, incapacity to carry out work of previous level, and failure to maintain self in the same degree of social adaptation.

Family invalid = Presence of well-marked symptoms, incapacity to carry out any useful occupation, but manageable at home.

Hospital invalids = The inmates of mental hospitals, some continuously since the end of treatment, some relapsed after a temporary recovery.

The proportion of female schizophrenics giving therapeutic response 1 is significantly greater than the proportion of male schizophrenics doing so. The proportion of females giving response 3 is significantly less than the proportion of males. There are no significant differences between the sexes in the proportions giving responses 2, 4 and 5.

Table IV.—This indicates that among atypicals there are no significant differences between the sexes in the proportions giving the various therapeutic responses. The comment with regard to the small number of males is again relevant. The proportion of females giving responses 1 and 2 is definitely greater than the proportion of males. Amongst all atypicals of both sexes only one patient showed response 4, and none response 5.

Table V.—This indicates that there are no significant differences between schizophrenic and atypical females in regard to body-index, weight, initial or maximal dosage, though the schizophrenics show significantly higher minimal dosages. All atypical dosage means are lower.

Table VI.—If all atypicals are excluded, no statistically significant differences within each sex are seen between good (response grades 1 and 2) and bad (response grades 3 and 4) response patients as regards weight, body-index and insulin dosage, though insulin coma dosage means are higher in the poor-response cases except for the male minimal dosage.

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Table VII.—Once response 1 and 2 cases are classified according to duration of illness, it becomes evident that the initial, maximal and minimal dosage in patients with a duration of illness of less than six months is significantly lower in females than in males. This difference is not seen once if the duration of illness is more than one year.

Tables VIII and IX.—Treatment responses 3, 4 and 5 show no significant difference in dosage whether the duration of illness is long or short.

Tables X and XI.—A comparison between response grades 1 and 2 with a duration of illness of less than six months, and response grades 4 and 5 with a duration of illness of over one year, reveals no statistically significant differences within each sex, though there is a trend for the dosage means to be higher in the group having a poor response and long duration of illness.

Table XII.—The Netherne schizophrenics do not differ significantly either in mean or in standard deviation from the Rees-Eysenck normals, nor from the Rees-Eysenck neurotics.

Summary of Chief Findings.

(1) *Sex and Dosage.*

The mean initial and maximal dosages for males are significantly higher than those for females, whatever the therapeutic effect, and this is independent of weight.

(2) *Sex and Therapeutic Effect.*

(*a*) Significantly more females than males make a total recovery. (Response grade 1.)

(*b*) Significantly more males than females exhibit the response—social defect. (Response grade 3.)

(*c*) There are no significant differences between the sexes in the numbers of social recoveries, family invalids and hospital invalids. (Response grades 2, 4 and 5.)

(3) *Sex, Dosage, Therapeutic Effect and Duration of Illness.*

(*a*) Females showing the therapeutic responses 1 and 2 have a significantly lower initial, maximal and minimal insulin coma dosage than males, as long as duration of illness is less than six months.

(*b*) Males and females show no significant differences in mean initial, maximal and minimal dosages between any therapeutic effects, if the duration of illness is over one year.

(4) *Dosage: Schizophrenics versus Atypicals or "Pseudoschizophrenics."*

(*a*) Atypicals or "pseudoschizophrenics" generally show better treatment responses than do schizophrenics. No response grade 5 occurs amongst atypicals and only one response grade 4.

(*b*) Female schizophrenics show a significantly higher mean minimal dosage than female atypicals, whose dosage means for initial and maximal doses also remain lower, though not to a statistically significant degree.

Tentative Analysis.

Let there be a factor "x" which brings about lower initial maximal or minimal coma dosages, and a factor "y" which brings about a good therapeutic response. Then findings 3(*a*) and 4(*a*) and (*c*) suggest strongly but do not conclusively prove that "x" and "y" are either identical or closely dependent on each other.

Findings 2(*c*) and 3(*b*) can be accounted for by postulating a factor "z" in whose presence the therapeutic value of "$y = x$" is nullified. If factor "$x = y$" is identified with endocrine events, factor "z" might plausibly be identified with chronicity, expressed in duration of illness, or severity of illness—(findings 3(*a*) and (*b*)). Finding 4 suggests that factor "$x = y$" is more strongly operative in atypicals than in schizophrenics. This factor appears more strongly linked with female sex (findings 1, 2(*a*) and (*c*).

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Discussion.

General Endocrinological Considerations.

In considering endocrine mechanisms it is important to attempt a dynamic evaluation of the situation. The different hormones of the anterior pituitary, usually referred to as trophic, stimulate their respective target glands, and hypersecretion of the trophic hormone leads to hypersecretion and hyperplasia of the target gland. After prolonged stimulation the target gland may become refractory to stimulation. Target gland hormones inhibit the production of their corresponding trophic hormones. The responses of body-cells vary considerably to the different hormones, and are dependent on innate genetically determined factors as well as environmental ones (Williams, 1950). The sensitivity of the endorgan is of great importance in assessing the quantitative and qualitative effect of a hormone. The mechanism of release is another important factor, and whether this is inhibited or sensitized. Some authors (Sackler *et al.*, 1951), therefore, also talk of an operational activity of a particular hormone determined by all these factors, and the inhibiting or activating influences of different hormones on each other.

The different mechanisms determining the sensitivity to insulin were reviewed by several authors (Martin, Martin, Lyser and Strouse, 1941; Smeto, 1948; Axelrod, Lobe, Orton and Meyers, 1947). Anterior pituitary extracts are known to be antagonistic to insulin (Williams, 1950). This is probably effected by more than one pituitary hormone (Young, 1944). Marked resistance to insulin develops during treatment with such extracts. This effect does not occur in adrenalectomized animals. Hypophysectomy leads to insulin hypersensitivity (Houssay and Biasotti, 1941). Patients suffering from Addison's disease are known to be extremely sensitive to insulin. Recent evidence suggests, however, that the action of insulin is antagonized both directly by the pituitary and indirectly through the adrenal cortex (Williams, 1950). Oestrogens also influence anterior pituitary function. Clinically and experimentally they were found to stimulate initially and later to depress. If given in large doses over a prolonged period the ovaries may eventually become inactive (Everett, 1950). There is also some evidence that oestrogens depress the release or effectiveness of the diabetogenic principle (Williams, 1950). This might explain why diabetes is much more common in males than in females and, further, why the incidence in females rises in later decades. It is, for instance, found that menopausal diabetes responds favourably to oestrogen therapy (Thorn and Forsham, 1950). An increase in insulin requirements occurs if testotesterone is given to diabetics (Thorn and Forsham, 1950). The incidence of diabetes in partially depancreatized rats is also diminished by oestrogens and increased by androgens. Oestrogens and androgens appear to be antagonistic in this respect (Houssay, 1951). The pituitary can, however, be inhibited by testosterone also, though it is less sensitive to it than to oestrogen. Large doses of testosterone were found to lead to a reduction of the sperm count presumably by a depression of gonadotrophin output (Engle, 1942). As mentioned above, there is evidence to show that this antagonism does not affect the "diabetogenic principle."

Results of General Endocrinological Interest.

Houssay (1951) concludes that "substances with oestrogenic effect decreased the incidence of diabetes . . . following subtotal pancreatectomy, androgens on the contrary increased it." Sex differences in insulin coma dosage are probably explained by similar mechanisms. Excessive adrenal hormone can also be the cause of diabetes (Cushing syndrome, Archard Thiers syndrome and adrenal tumour). The insulin resistance seen in many diabetics can be due to an increased output of the anterior pituitary or the adrenal cortex. The necessity for large insulin coma dosage can at times be explained in this manner. High initial and maximal insulin coma dosages may be required because of a strongly effective suprarenal cortical hormone. Little fluctuation in the coma dosage may indicate a strong reserve power, and low minimal dosages signs of refractoriness or exhaustion.

If the effects of high insulin dosage used in insulin coma treatment are looked upon as a special instance of a "stress response," then the fluctuations and differences in response can also be interpreted in terms of the "general adaptation

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syndrome." This syndrome according to Seyle (1950) has three stages, the alarm stage, the stage of resistance and the stage of exhaustion. High doses are then an instance of a highly effective alarm stage characterized by a discharge from a strong adrenocortical reserve and very low doses one of exhaustion.

In the present investigation an attempt is made to explain the change in insulin sensitivity on an endocrinological basis; this is probably a simplification.

Results with Reference to Endocrinological Mechanisms in Schizophrenia.

It need hardly be said that our findings cannot be claimed as definitely specific for schizophrenia as other diagnostic categories were not examined; some can only be tentatively assumed as acting in a more specific manner. It is also possible that the type of clinical syndrome may depend on other physiological characteristics of the tissues especially affecting central nervous system function. These are probably determined by constitutional factors, which again result from an interplay between genetic and environmental influences. If the latter conception is true, it also follows that different pathological endocrine processes may result in similar psychological syndromes, or that different psychological syndromes may be related to the same endocrine pathology. This hypothesis appears the most likely explanation of the evidence collected by various workers in this field.

Meduna (1950) states that the schizophrenias responding favourably to shock therapy are better classified as pseudoschizophrenias, because of special clinical characteristics such as similarities with the oneiroid state of Mayer-Gross or other atypical features referred to above. Refractory cases are, according to Meduna, suffering from an "endogenous schizophrenia." Meduna believes that prognostically favourable groups also have certain endocrinological features, e.g.,

(1) A sustained blood-sugar curve in the intravenous glucose tolerance curve.
(2) A positive diabetic-like blood-sugar curve in the Exton-rose test.
(3) Resistance to insulin in the intravenous insulin-tolerance test.
(4) An increased anti-insulin factor in the blood.

He suggests that all this may be explained by an overactivity of the anterior pituitary. Other authors (Hoskins, 1946) state that differences in glucose tolerance curves are consistently related only to different degrees of emotional tension. Cases with marked tension showed the most sustained curves. These conditions are more predominant in prognostically favourable cases and, therefore, need not be explained by an "anti-insulin factor." If Meduna's interpretations were correct, a need for larger doses of insulin to produce comas in prognostically favourable cases should be revealed. Our findings do, however, show the opposite. Atypical cases (symptomatic or pseudoschizophrenias) have lower coma dosage means than typical schizophrenias. They also show the best response grades. The fact that the minimal doses are significantly lower in atypical cases may indicate that true schizophrenias with a comparatively short duration of illness have a greater operational effectiveness of suprarenal pituitary function. Tsai, Bennett, May and Gregory (1950) found eosinopenia as an indication of a release of suprarenal cortical hormone during insulin coma treatment. Is then a favourable response to treatment associated with a decrease of cortical hormone activity from an abnormally high down to a lower normal level? The release of the hormone during hypoglycaemia may also be related to the reactivation of the psychosis often seen at the beginning of treatment.

Our finding that there is a greater number of good responses amongst female patients than amongst males and at the same time that the latter generally require higher dosages does point to the sex steroids as an important factor in this mechanism. Is the more potent inhibitory effect of the oestrogen on the anterior pituitary related to better prognosis? Is one justified in assuming an initial overactivity of the pituitary, possibly explained by the experimental findings showing an initially stimulating effect of oestrogen on pituitary function, as an aetiologic factor for the development of the psychosis? Sackler, A. M., *et al.* (1950) came to similar conclusions. In favour of this hypothesis they quote the observation that A.C.T.H. or cortisone have led to psychotic reactions. They also found that sex steroids raised eosinophil levels, the greatest increase occurring in those patients attaining improvement. As adrenocortical hormones are known to lower the eosinophil level, sex hormones are believed to have in this respect an anti-adreno-

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cortical effect. Similar observations (Sackler *et al.*, 1950) are reported with lymphocyte/neutrophile ratios which became higher following steroid therapy in favourably responding cases. An increased adrenal cortical activity occurs during insulin coma treatment, electroconvulsion therapy and electronarcosis (Ashby, 1949; Mitchelson and Hutchins, 1948; Parsons *et al.*, 1949; Rees, 1949). As mentioned before, experimental findings show that oestrogens initially have a stimulating effect on the anterior pituitary. This might occur with the onset of puberty when the organism is flooded with sex steroids, and if the response to this stress is abnormal it might also serve as an explanation for the rise in incidence of schizophrenia at this period of life. Previous studies on the sex incidence of schizophrenia are of great interest in this connection. Haas (1935) found that amongst a total of 15,433 male and 10,228 female admissions during 1924–1933 the diagnosis of schizophrenia could be made in 13·3 per cent. of the males and in 28·03 per cent. of the females, or 100 male first admissions corresponded to 123·2 female ones. The conclusion was therefore reached that the incidence of schizophrenia was higher in females than in males. The sex difference amongst first admissions does vary in the different age-groups. Haas (1938) found that in the age-groups of 16–20 females were more frequent than males. In the age-group of 20–25 the figure for males was found higher, and during the involutional period it is again the females who are greater in number. Dayton (1940) and Malzberg (1940, 1943) made a similar investigation, but calculated these figures per 100,000 population. Their results can, therefore, be taken as more reliable. They also found a higher incidence for females during the involutional period, but in contrast to Haas a greater number of males in the age-group from 10–39. The period during which oestrogens have their maximum activity, therefore, seems to have a certain protective influence, possibly by inhibiting anterior pituitary activity. M. Bleuler's (1950) observations of acromegaloid signs in schizophrenia also point in this direction. He found the incidence of schizophrenia in acromegaloid subjects three times greater than in other members of the investigated families. The opposite was found in Simmond's disease. An acute schizophrenic psychosis may in other words be related to a hyperactivity of the pituitary with its resultant effects on target glands. All this appears contradictory to Hoagland and Pincus's (1949) views that a deficient suprarenal function is either causative or somehow related to the pathogenesis of schizophrenia. How can this discrepancy be explained? It has been found that recent cases of schizophrenia do not show this deficiency (Reiss, 1950) with nearly the same frequency. L. Rees (1951) used desoxycortone acetate and ascorbic acid in schizophrenia without effect. Contrary to Hoagland and Pincus, the response to A.C.T.H. was found positive in over 70 per cent. of all cases. Hoagland and Pincus's findings might, therefore, apply to a later stage of the disease, following overstimulation in the initial stages. The target glands might then have become refractory or exhausted, or the sensitivity of the endorgans or tissues in general altered in the course of the disease process. The 14 patients investigated all had a comparatively short duration of illness; only rarely were any with more than one year's duration of illness given insulin coma treatment.

Most workers believe that a specific organic pathology underlying each psychopathologic syndrome is unlikely (Bleuler 1951). Differences in psychopathological syndromes are rather explained by constitutional factors or different sensitivities to the organic disturbance. The evidence in support of pituitary hyperactivity and its effects in the pathology of schizophrenia is so far only suggestive and further research is required to confirm it.

Summary.

(1) Lower insulin coma dosages have a tendency to be correlated with a good therapeutic response.

(2) Female schizophrenics of less than six months duration of illness needed lower dosages than males of the same duration of illness. This difference disappears with a longer duration of illness.

(3) Female schizophrenics in our series showed a better prognosis than males.

(4) Atypical cases had the lowest minimal dosages and the best therapeutic response.

(5) The body-index type was not significantly correlated with prognosis, neither was weight.

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(6) The chief findings are tentatively discussed.

(7) Our findings suggest the therapeutic use of sex steroids possibly in combination with insulin coma treatment.

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