THE ENDOCRINE CONCOMITANTS OF SCHIZOPHRENIA*

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In attacking the problem of the relationship of endocrine function to the schizophrenias and other mental diseases, we have avoided the elementary conception that certain hormones are responsible for special psychological traits and have reached the following conclusions. First, the quality of the mental disturbance depends mainly on a genetically conditioned personality pattern, various individuals reacting in different ways to the precipitating causes. Second, the hormones come into the whole picture only in so far as the hormone equilibrium of the body determines how far the individual can adjust himself to the increased demands arising out of the occurrence of various precipitating causes (Reiss, 1955). It is therefore understandable that very many, or even the majority of people suffering from severe endocrine disturbance, need not necessarily show any psychopathological changes, since their personality pattern is not so conditioned and no increased demands for adjustment are made by the occurrence of precipitating causes. On the other hand, it is equally understandable that certain disturbances in hormone production and equilibrium, even when clinically obscure, can be decisive for mental breakdown in individuals with the appropriate personality pattern, at the occurrence of precipitating causes.

We would like the investigations which are now reported to be understood in this way, and in order not to complicate matters we shall describe only some of the most elementary changes in the equilibrium between adrenal, thyroid and pituitary glands, for the moment leaving out the results of more complicated investigations which are still in progress.

Much work already published and based on single investigations on groups of patients leads to contradictory conclusions, even though the results presented appear to have statistical significance. The only absolutely true fact emerging from all such investigations is perhaps best illustrated in Figure 1 where the ordinates are left anonymous.

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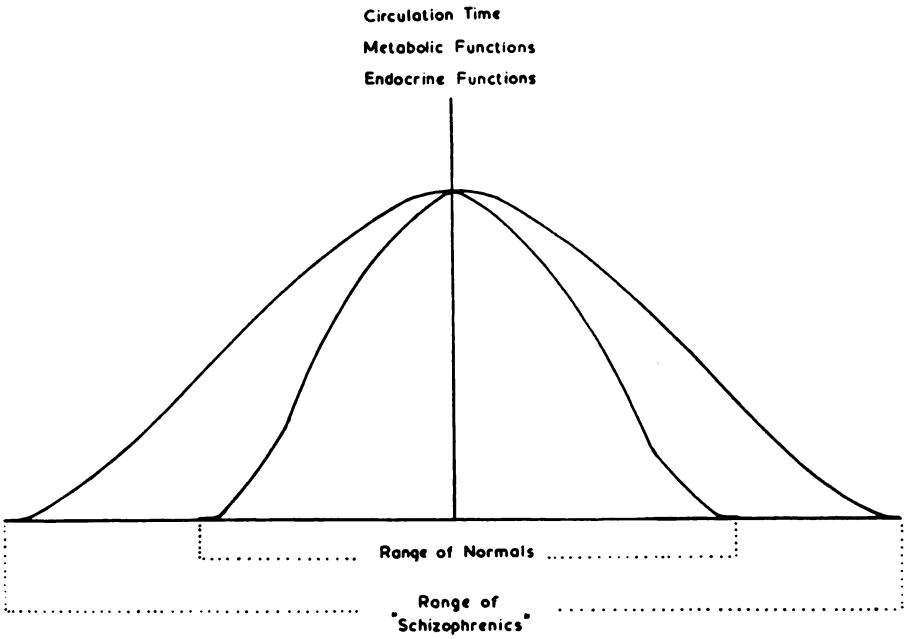


FIG. 1.—Distribution of frequency (vertical axis) of values (horizontal axis) in schizophrenics and non-schizophrenics. Values may be results of single determinations of any parameter, e.g. circulation time, body temperature, basal metabolic rate, blood chemistry, thyroid activity and excretion rate of adrenal cortical hormones. Although schizophrenics and normals may share a common mean value of these parameters, the scatter of values is much wider in schizophrenics than in normals.

This figure can apply to circulation rate, body temperature, basal metabolic rate, blood chemistry, thyroid activity and excretion rate of adrenal cortical hormones. The only fact all these investigations have in common is that the range of the results in schizophrenics is much wider than in normal individuals. In order to obtain reliable results the following approach appears necessary.

1. A better sub-division of clinical types is needed when correlating psychopathological symptoms with biochemical changes. It is not to be expected, for example, that schizophrenics showing great tension should show changes similar to those in quiet, burnt-out schizophrenics.

2. It is necessary to carry out a greater number of determinations on the same patient and to co-ordinate the biochemical and mental state chronologically in the individual case, the technique of "longitudinal section".

3. The investigations should be carried out over a long period of time on a large number of patients and, if possible, using identical techniques, in several hospitals, since certain differences can be seen according to the reception area from which patients are derived.

In this paper, assessments of thyroid function and ketosteroid excretion in schizophrenics are compared with results in non-schizophrenics. Repeated observations, made over varying periods on many patients, are related to changes in mental state and to the results of insulin treatment.

The observations were made on 253 male and 198 female patients in St. Ebba's Hospital, Epsom. Of these, 92 males and 47 females were schizophrenics. For the purposes of this paper, the remaining 161 male and 151 female patients are not grouped according to diagnosis.

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Investigation into Thyroid Function

During the past few years it has become customary to use a radioactive tracer method for assaying thyroid activity by measuring the ability of the gland to take up I^{131}. This procedure gives information concerning only one of the functions of the thyroid, namely, the iodine uptake which precedes the production of thyroid hormone, and we have therefore started to determine the protein-bound iodine in blood as a measure of hormone production. In the investigations to be reported here, results based on measurements of I^{131} uptake are discussed, in accordance with the practice of the majority of endocrinologists who regard this as a reliable measure of thyroid activity. In addition, however, since we have to deal with psychiatric patients, other parameters have been measured in order to provide a cross-check of the results and to enable the reliable detection of borderline cases in whom the thyroid activity is beginning to change. These parameters are as follows (Reiss and Haigh, 1954):

1. The uptake slope of I^{131} during the first hour. This is very often indicative of the I^{131} avidity of the thyroid. The steepness of the uptake curve in the first hour often shows an existing over-function. On the other hand, however, absolute flatness of the curve may be due not only to under-function but also to a suppression of the I^{131} uptake by vasoconstrictor substances circulating in the blood during anxiety states.

2. The amount of I^{131} retained in the thyroid (ring count) 24 and 48 hours after the intravenous injection of the tracer. This is measured with a specially constructed ring counter which, placed round the neck of the patient, permits accurate measurement independently of the distance of the thyroid from any part of the counter (Haigh, Reiss and Reiss, 1954).

3. Twenty-four and 48-hour excretion rates of tracer. This figure permits a cross-check since 24-hour uptake (ring count) and excretion rate amount to about 91 per cent. of the total tracer dose.

It has proved useful to adopt an index of the total thyroid activity (I_t) which represents the quotient of uptake rate in the first hour divided by either the I^{131} excretion rate, or the 24-hour I^{131} retention rate of the thyroid.

We established normal ranges by investigating normal control patients and also by statistical means, calculating the arithmetic mean of the values of the whole hospital population and applying the standard deviation on both sides of the arithmetic mean. The normal ranges are in agreement with the normal ranges established in other hospitals. For instance, the 24-hour I^{131} uptake of the thyroid ranges between 25 and 50 per cent. of the injected dose. Of the patients whose 24-hour uptake falls in this range, 90 per cent. have a normal basal metabolic rate. Some cases where a discrepancy exists between B.M.R. and the tracer values will be discussed later on when undersensitivity to thyroid hormone is discussed.

Figure 2 shows the distribution of the thyroid indices in patients in St. Ebba's Hospital. Results in schizophrenics are compared with those in all the other psychiatric cases. It can be seen that as compared with other males, the male schizophrenic patients show a greater frequency of under-function, while female patients do not. This is shown more clearly in Table I.

Our colleagues in the University Psychiatric Clinic at Zürich, using our method, have carried out similar investigations but exclusively on chronic schizophrenic patients (Bleuler and Stoll, 1956). Their results also appear to be in good agreement with the distribution found in the patients of the Bristol Mental Hospitals as already published (Reiss *et al.*, 1951, 1952, 1953).

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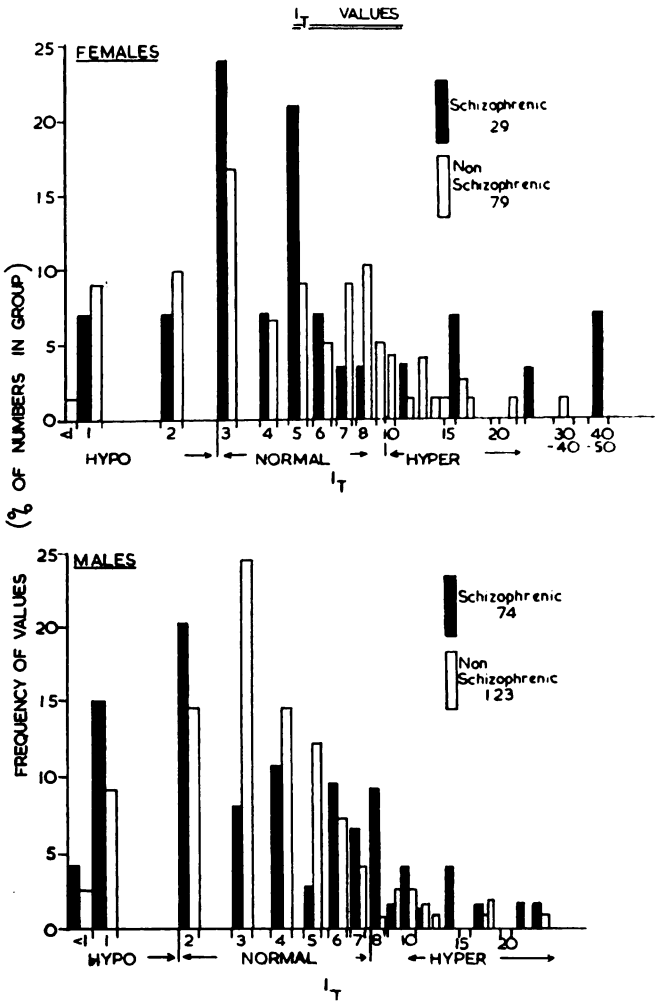


FIG. 2.—Distribution of I_t values (indices of thyroid function) according to sex and mental disorder group. Frequencies of values are expressed as a percentage of number of cases in group.

TABLE I

Thyroid Tests (I_t Values)

Distribution of Results of Tests of Thyroid Function (Thyroid Index, I_t, Reiss and Haigh, 1954) in Schizophrenics and Non-Schizophrenics in St. Ebba's Hospital

	Males		Females	
	Schizophrenics Percentage of 74	Non-Schizophrenics Percentage of 123	Schizophrenics Percentage of 29	Non-Schizophrenics Percentage of 79
Normal	66	79	65	65
Hyper	15	10	21	15
Hypo	19	11	14	20

The distribution in male schizophrenics is significantly different from that in male non-schizophrenics.

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TABLE II

Thyroid Tests (I_t Values)

Distribution of Results of Tests of Thyroid Function (I_t Values) in Chronic Schizophrenics in the University Psychiatric Clinic, Basle

	Males	Females
	Percentage of 90	Percentage of 73
Normal	70	68
Hyper	10	25
Hypo	20	8

The results are not significantly different from those in Table I.

In 1929, Hoskins and Sleeper found hypothyroidism in the small group of patients they investigated, but they made the error of generalizing. In a way, they made the same observation as Langfeldt (1926), that some schizophrenic patients can take large amounts of thyroid, 30 gr. and more a day, without change in their B.M.R. We have also seen some cases that reacted similarly. We were able to go one step further and identify such cases as showing a peripheral under-sensitivity to thyroid hormone. These patients are not necessarily hypothyrotic. On the contrary, their thyroid activity as assessed by tracer investigation may be normal, or even increased, while their B.M.R. is reduced. Their tissues are not sensitive enough to endogenously or exogenously applied thyroid hormone. This state, which is physiopathologically still unexplained, is seen only in certain cases of pituitary under-function, and otherwise by us mainly in schizophrenia.

In some schizophrenics who show thyroid under-function, the under-function is primary, that is, due to the thyroid itself, but in others the under-function is secondary to a pituitary anterior lobe under-function, as previously reported. These two types of cases can be distinguished by treating them with thyrotrophic hormone. Those patients whose thyroids take up more I^{131} after this treatment suffer from secondary thyroid under-function, while those whose thyroids do not take up more I^{131} after this treatment, are primary hypothyrotics (Reiss and Haigh, 1954).

Cranswick (1955) has lately investigated a group of schizophrenic patients who in a statistically significant number of cases did not react to thyrotrophic hormone. He, therefore, assumes that the thyroid of schizophrenics is not sensitive to thyrotrophic hormone. In the light of our previous discussion, it will be understood why such a generalization is not acceptable.

INVESTIGATIONS INTO ADRENAL CORTICAL FUNCTION

Adrenal cortical function and its disturbances are greatly involved in the pathology of schizophrenia. There are still workers who claim that only under-function of the adrenals occurs in schizophrenia, others only over-function. In our opinion such a division of opinion is futile. Not only under-function and over-function but also completely normal function have been seen by us in schizophrenia. In fact, the situation is very similar to that which has just been discussed in relation to thyroid function.

Not only 17-ketosteroids were investigated as a measure of adrenal function, but also various ketosteroid fractions and corticoids. In this paper, however, for simplicity discussion is restricted to the 17-ketosteroid excretion rate in a

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schizophrenic hospital population, and to a correlation of the 17-ketosteroid excretion rate with spontaneous changes in the psychiatric disease and with changes seen after treatment. In the whole schizophrenic population at St. Ebba's Hospital the range of 17-ketosteroid excretion is considerably wider than the normal range generally accepted in the literature (7–18 mg./24 hours). A survey made on 75 schizophrenics over the age of 20 in St. Ebba's showed a range of ketosteroid excretion between 2 and 48 mg. per day: Lingyaerde (1953) similarly reports a very much wider range of excretion in psychiatric patients as compared with controls. In more than 40 per cent. of his patients the excretion rate was below or above the normal range. Figure 3 shows the excretion rate of our schizophrenics as compared with other psychiatric patients, according to age range.

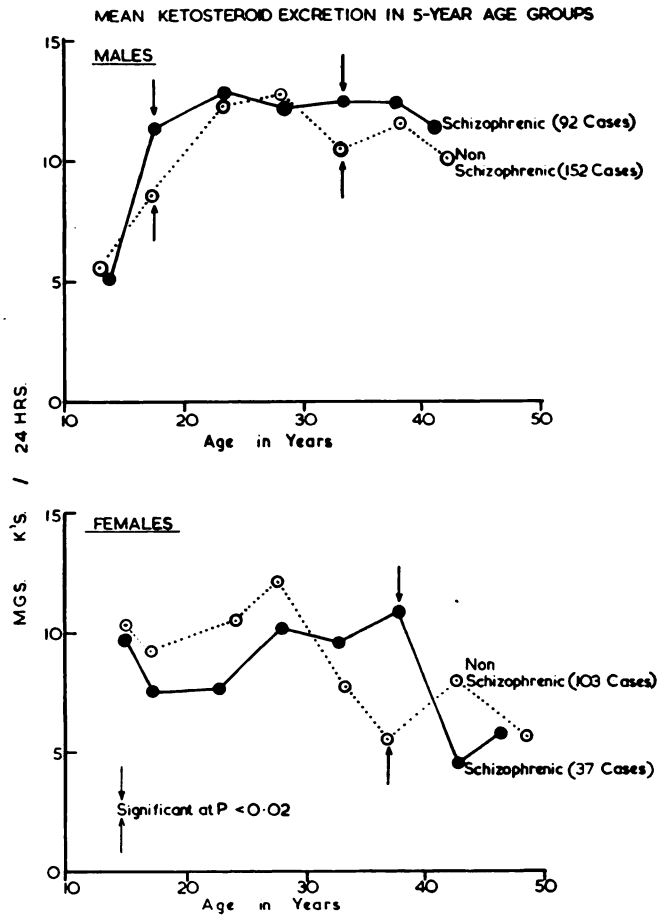


FIG. 3.—Mean 17-ketosteroid excretion rates of schizophrenics and non-schizophrenics according to sex and mean age in quinquennial age groups. The arrows indicate excretion rates that are statistically significantly different when means in the same quinquennium are compared.

Paranoid schizophrenics show a statistically significantly higher ketosteroid excretion rate (Table III). These findings might well be linked with our clinical observation that paranoic women show hypertrichosis more frequently than do other schizophrenics.

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TABLE III
Paranoid and Non-Paranoid Schizophrenics

	Cases	17-ketosteroid Excretion, mg./24 Hours Range	Mean	S.D.	*t*	*P*
Paranoid schizophrenics ..	19	7·3–27·3	16·8	5·4	4·16	0·001
Non-paranoid schizophrenics	45	1·2–26·5	10·1	5·9		

The correlation of a patient's mental state with his ketosteroid excretion rate over long periods has proved to be very informative. Such long-term investigations on individual cases might contribute more to our understanding of the significance of adrenal cortical function in schizophrenia than will the statistical evaluations of single results from groups of cases. Figure 4 shows an example where this was done. There is a distinct association between the more disturbed aggressive phases of a 30-year-old male, and his ketosteroid excretion level.

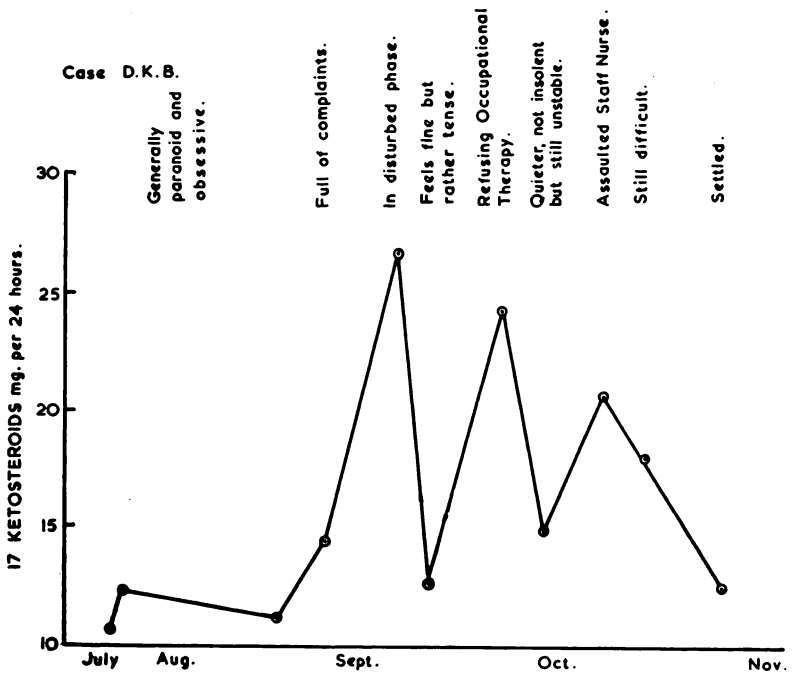


FIG. 4.—Correlation of changes in mental state and in 17-ketosteroid excretion rate. Male schizophrenic, age 30. No treatment during the period of observation. Generally, peaks of excretion were associated with difficult and sometimes aggressive behaviour whilst low excretion rates were associated with quieter behaviour. Thyroid activity: raised (R.C. 62 per cent.) at beginning, becoming normal (R.C. 51 per cent. end of September).

One of the most rewarding results of such correlation was first seen in some cases where the psychiatrist withheld specific treatment to see what a change of environment alone could achieve for the patient when he first came under hospital care and attention. Some of these patients showed a spontaneous remission, and it was most interesting to see how a normal hormone equilibrium,

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including ketosteroid excretion rate and thyroid function, became restored, sometimes even before the mental improvement was finally recognized. Various forms of changes in hormone equilibrium during such spontaneous remissions can be seen in Figure 5. Such investigations are at the moment carried out

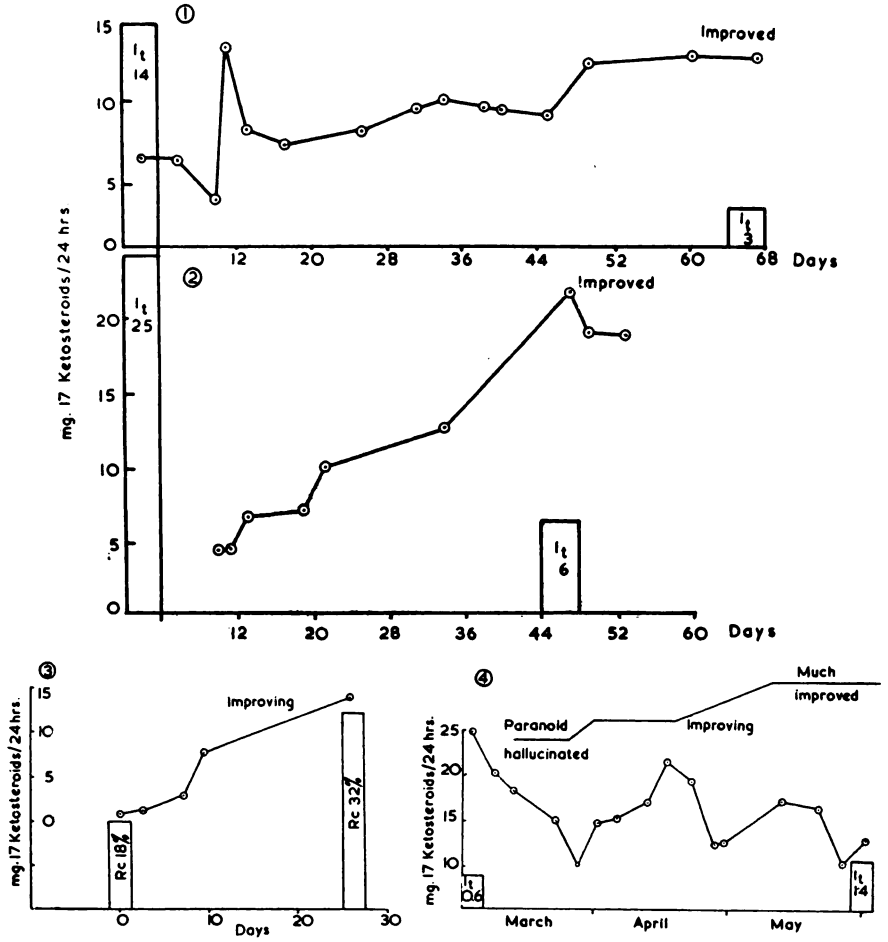


FIG. 5.—17-ketosteroid excretion rates in 4 cases of schizophrenia showing "spontaneous" improvement (i.e. effect of hospitalization without physical treatment). In all cases the tendency is for abnormal excretion rates to become normal. Thyroid activity abnormal at first, also becomes normal. (I_t = thyroid index. R.C. = ring count 24 hours after injection of tracer dose of I^{131}.)

systematically on newly admitted acute patients by various members of our research group. It might well happen in time to come that whenever this normalizing tendency in the function of the thyroid and adrenal cortex is found, it will be possible to advise the psychiatrist to withhold physical treatment, as the patient would be likely to recover spontaneously. A normal hormone equilibrium already existing at the time of admission of the patient to hospital might also quite rightly delay physical treatment, in order to determine if the patient is on the way to spontaneous recovery. Again, a period of observation of the kind described might be useful to some extent in differentiating between a really severe psychopathological state and a mere slight exaggeration of a

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pre-existing personality pattern that will quieten down under hospital care and attention only.

The investigation of the relationship of changes in ketosteroid excretion rate and in thyroid function to the clinical course of events in insulin coma therapy has led to the recognition of the following different types of reaction. Figure 6 shows tracings of ketosteroid excretion during the course of deep

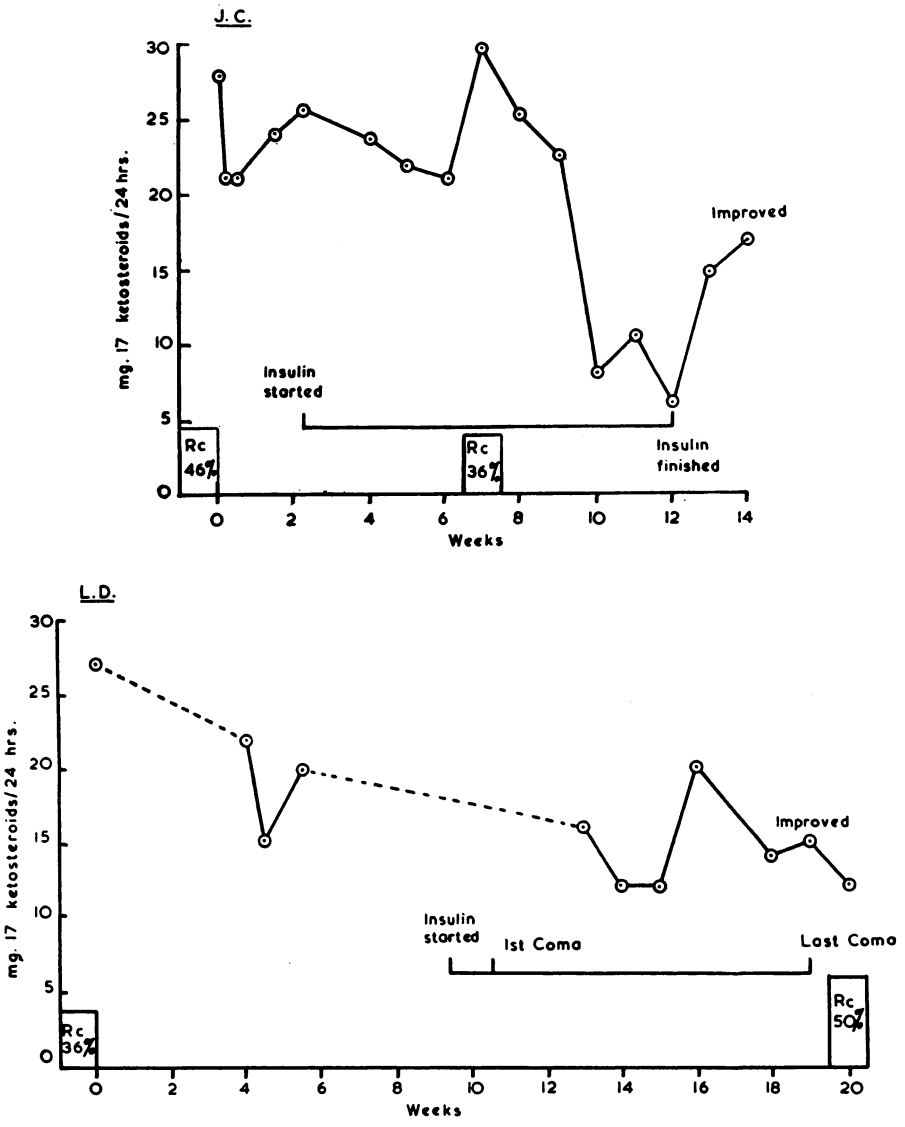


FIG. 6.—17-ketosteroid excretion rates in insulin coma therapy. Type (*i*) The "standard" type of curve in successful therapy. Male schizophrenics: J.C. 29 years of age, L.D. 24 years of age. Note the fall in excretion with final level in normal range. Thyroid function (R.C. = ring count at 24 hours after injection of tracer dose of I^{131}) normal in both cases but showed favourable changes.

insulin coma therapy and afterwards, in two patients who improved under this treatment. This type of curve may be described as the standard curve to be seen

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in really successful insulin coma therapy. Before treatment, the ketosteroid excretion rate was very high, in the upper normal range, or sometimes considerably above it. During insulin treatment the ketosteroid excretion rate—sometimes after a short rise—begins to go down continuously, falling to low levels, occasionally even below the normal range. At this time a certain mental improvement usually occurs. Afterwards the ketosteroid excretion rate remains in the middle normal range. Concomitant with these changes, thyroid function, low at first, increases but remains in the normal range. The patient is much improved and fit for discharge. There are, however, other patients, whose excretion curves are seen in Figure 7, who start exactly as those previously

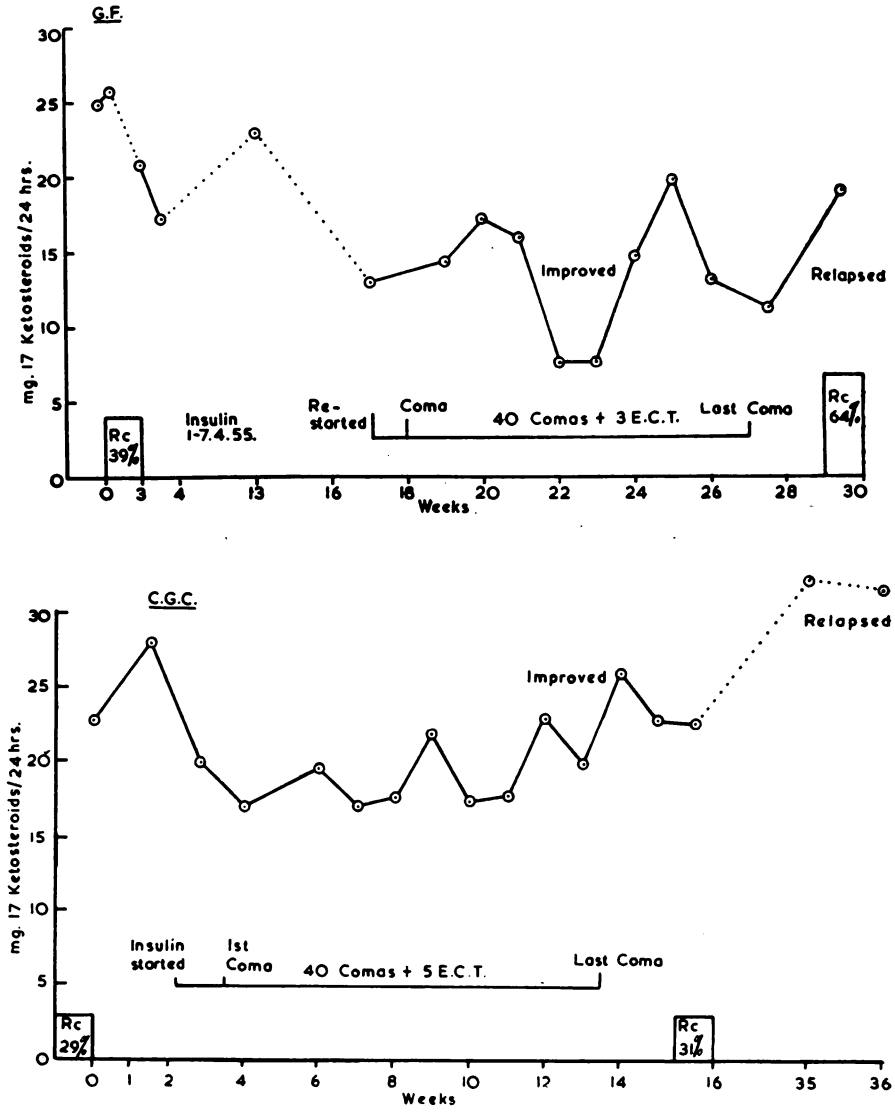


FIG. 7 (*continued overleaf.*)

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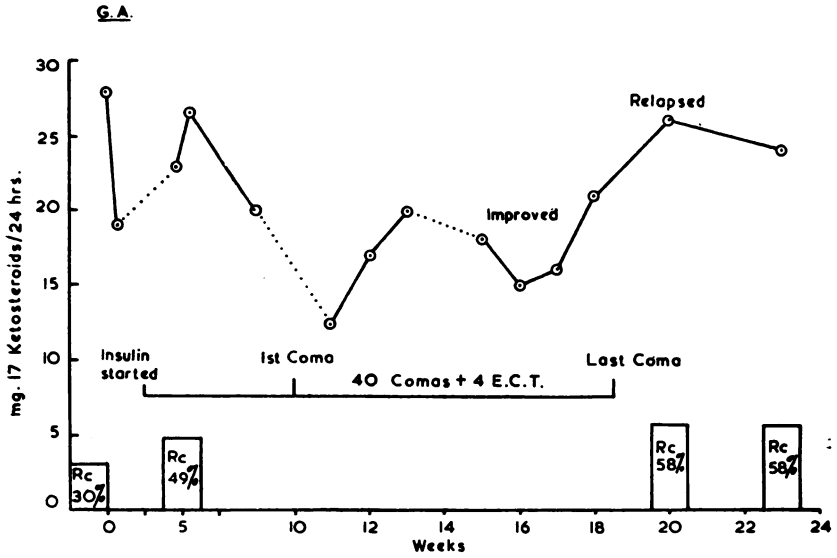


FIG. 7.—17-ketosteroid excretion rates in insulin coma therapy. Type (*ii*) Temporary improvement with relapse after cessation of treatment. Male schizophrenics: G.F. 25, C.G.C. 19 and G.A. 26 years of age. In all cases the fall in the excretion rates during the middle of the treatment is followed by an increase into the higher normal range or even above. Thyroid function is either not improved (C.G.C.) or passes into range of hyper-function (G.F. and G.A.).

mentioned. When the ketosteroid excretion rate becomes low, some mental improvement is noted and is still present when the ketosteroid excretion later shows a rising tendency. At this stage the patient may even be discharged as much improved. In these cases, thyroid function, low at first, remains low or increases above the normal range. If the ketosteroids rise still further the patient relapses and cannot be discharged, or, if discharged, relapses and returns to hospital in a comparatively short time. In several cases, such a course of events was predicted from the laboratory, to the great surprise of the psychiatrist. One might well assume that these two types of patients had originally a hyperfunction of the adrenal cortex, which became exhausted under the continuous stress of insulin coma treatment.

There are, however, other schizophrenics who, to start with, have a very low ketosteroid excretion rate. These are mainly younger patients with retarded development. In only very few of them can the stress of insulin coma therapy raise their ketosteroid excretion rate into the normal range, as seen in Figure 8, a process which is accompanied by mental improvement. In these patients, thyroid function, if normal at first, remains normal, or if abnormal at first, becomes normal. A considerable number of these patients, however, show changes in the ketosteroid excretion rate, as shown in Figure 9. For a short time at first insulin coma therapy can raise the ketosteroid excretion rate, but very soon this falls again below the original level, while thyroid function either remains unchanged, or may go up above the normal range. Mental improvement is never seen in such patients.

Figure 10 shows ketosteroid excretion curves during and after insulin treatment of patients, who, before treatment, had a ketosteroid excretion rate in the normal range. The results of treatment in these cases are very capricious. Sands thought that some patients of this type might have recovered spontaneously without insulin coma treatment. During treatment the first patient shows

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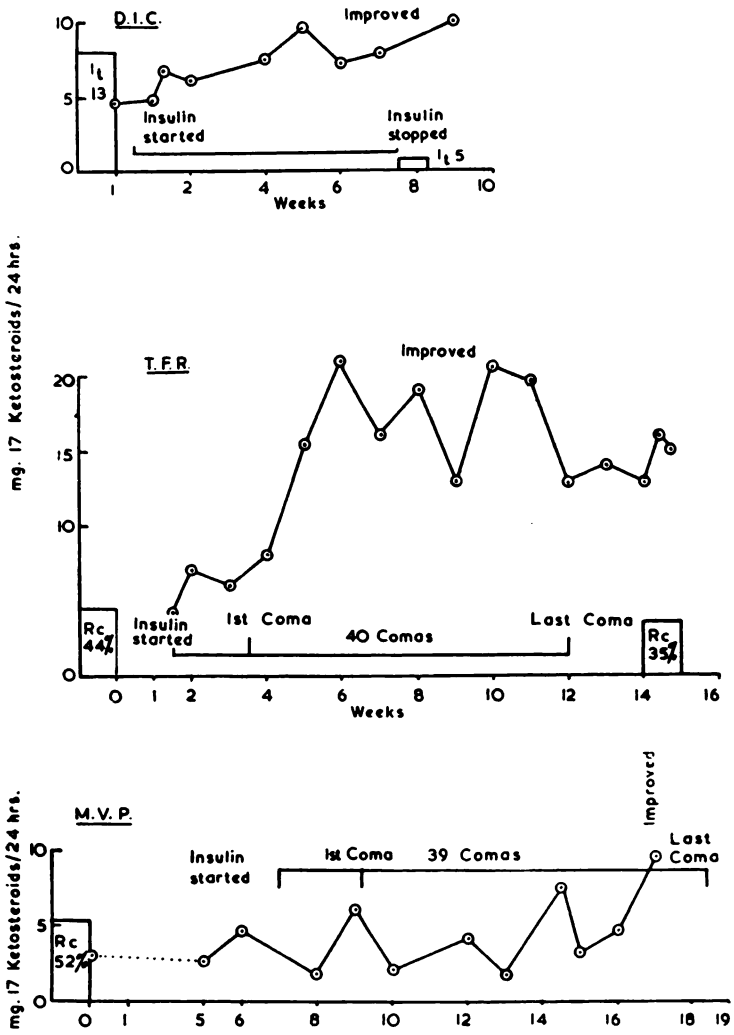


FIG. 8.—17-ketosteroid excretion rates in insulin coma therapy. Type (*iii*) Treatment successful in patients with initially low excretion rates. Male schizophrenics: D.I.C. aged 15, T.F.R. aged 30, M.V.P. aged 17. The 17-ketosteroid excretion rate increases into the normal range. Thyroid function where normal (T.F.R. and M.V.P.) remains normal or where abnormal (D.I.C.) becomes normal.

great fluctuations in the excretion rate. Towards the end of his treatment, however, excretion is in the normal range. The thyroid activity in this patient was above the normal range before treatment and in the normal range at the end of treatment. This patient showed a good improvement. Another patient, however, who also before treatment showed a normal ketosteroid excretion rate, after completion of the treatment had a ketosteroid excretion rate below the normal range. His thyroid activity was above the normal range before treatment and remained so after treatment. This patient did not improve.

Our investigations so far seem to indicate that for improvement to occur by insulin coma treatment, it is essential that the ketosteroid excretion rate and thyroid activity should both come into and remain in the normal range. If one

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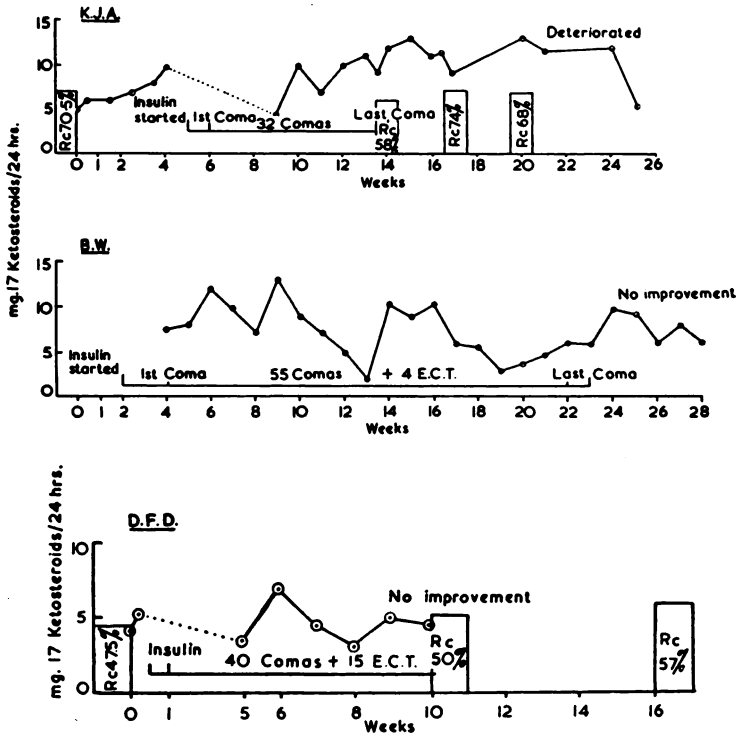


FIG. 9.—17-ketosteroid excretion rate in insulin coma therapy. Type (*iv*) Treatment unsuccessful. Schizophrenics: K.J.A. male, aged 15, B.W. female, aged 22, D.F.D. male, aged 35. Excretion, below normal or in low normal range at beginning, not improved. Thyroid function where normal (B.W. and D.F.D.) remained normal (B.W.) or moved to hyper-normal range (D.F.D.), or where abnormally high remained so (K.J.A.).

of these values is found, at the end of treatment, to be outside the normal range a relapse can be predicted, even if the patient is so well at the time that he can be discharged from hospital.

We conclude, therefore, that the results of these initial investigations of the changes in the adrenal cortex-thyroid equilibrium form a tentative basis for predicting the therapeutic result of insulin coma treatment and of predicting a relapse after treatment. Attempts at prognosis can also be supported by various clinical endocrinological observations. Patients who show high ketosteroid excretion rates, also usually show well developed gonads, sometimes even prematurely developed genitalia and secondary hair distribution, with particularly dense hair on the thighs, and a well-developed beard. In these, the prognosis for a good result from insulin coma therapy is more favourable than in others. Patients with ketosteroid excretion rate below the normal range are often sexually retarded. They have comparatively small testicles, with no cremaster reflex, very little secondary hair and no beard at the age of 19, but the most striking factor is often an open inguinal canal. In these the prognosis for insulin coma therapy is often unfavourable. Although open inguinal canal occurs quite frequently in the normal population, it can always be regarded as an objective sign of a certain degree of immaturity. The testicles need not by any means always be cryptorchic, but there is a possibility that on certain occasions, particularly when the patient lies down for his night's sleep, the testicles are

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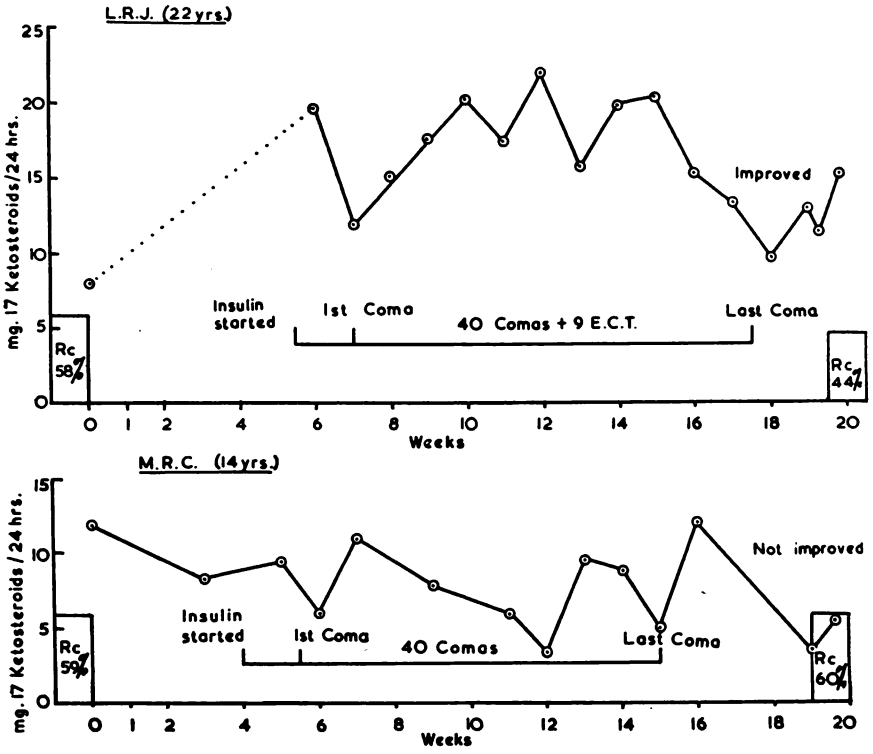


FIG. 10.—17-ketosteroid excretion rates in insulin coma therapy. Type (*v*) Initial excretion in normal range. Male schizophrenics: L.R.J. aged 22. Excretion at first raised, then normalized. Thyroid function initially high became normal. This patient improved with the treatment. M.R.C. aged 14. Excretion tends to be depressed as treatment progresses. Thyroid function above normal and not changed. No improvement.

retracted into the abdomen. Such a process is certainly unfavourable for the normal development and function of the testicles. During our investigations we have not seen one schizophrenic, who had an open inguinal canal, improve after insulin coma therapy. This agrees with the clinical observations of Sands, that insulin coma therapy was unsuccessful in 80 per cent. of his juvenile cases when it was carried out before a certain degree of sexual maturity had been reached.

There is still another state to differentiate. During clinical investigation young men are found not infrequently with a high ketosteroid excretion rate and well developed genitals but with no trace of a beard and no hair on the chest. These are patients whose tissues are insensitive to sex hormone. This under-sensitivity is similar to the under-sensitivity to thyroid hormone mentioned before. The mechanism of peripheral under-sensitivity to a hormone is not yet clear. Gordan (1955) quotes a number of endocrinologists who regarded the disturbed sensitivity to thyroid hormone as a symptom of hypopituitarism.

PITUITARY ANTERIOR LOBE FUNCTION

It is a considerable drawback in the endocrine analysis of schizophrenia that very little work has been devoted to the direct investigation of pituitary anterior lobe functions. This is due to the fact that methods for investigating anterior pituitary lobe hormones in body fluids are not yet sufficiently developed

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to be used as routine research methods. However, our results to date make it quite certain that a primary disturbance of pituitary anterior lobe function in the frame of the neuro-endocrine interrelation is very important. In schizophrenics, thyroid, adrenal and gonadal function can be disturbed simultaneously, a state which can only be due to a disturbance of the function of the pituitary anterior lobe in producing the relevant trophic hormones. It is possible for the production of one trophic hormone to be reduced while others are over-produced, thus resulting in various states of disturbed hormone equilibrium. For instance, there may be increased thyroid activity and decreased adrenal cortical activity, or simultaneous increase of thyroid and adrenal cortical activity and so on.

Many workers nowadays regard schizophrenia as a maladaptation to stress. The role of the anterior pituitary lobe in neuro-endocrine interrelations during stress is well known. Intensive study of individual young male acute schizophrenics, their social background, employment, manner of life, make it seem probable that the high ketosteroid excretion rate often connected with a certain degree of pre-maturity, is the result of intermittent stress conditions, and represents a form of adaptation. These patients come, mainly, from metropolitan reception areas. There is a group of schizophrenics of opposite type with very low ketosteroid excretion rate who are often retarded in their development and subject to continuous stress conditions in various aspects. Their low ketosteroid excretion rate might well be the expression of a state of endocrine exhaustion.

In this connection, it should be noted that in the majority of puerperal cases, with varying psychiatric symptoms, either a very high or a very low ketosteroid excretion rate is found, apparently according to the range of adaptation of the pituitary anterior lobe and adrenal cortex in each individual.

When discussing pituitary anterior lobe function, it is necessary also to consider disturbances in gonadal function in relation to the production of gonadotrophic hormone, since the occurrence of gonadal disturbances in some schizophrenics is known. An association between masturbation and schizophrenia has long been in the minds of some psychiatrists. In the standard psychiatric text-book of Clouston, in 1898, masturbation was even regarded as a cause of what would now be called catatonic schizophrenia. Today it is well established that sexual activity stimulates increased production of gonadotrophic hormone; equally, so can masturbation. It can therefore be regarded as feasible that frequent stress, or the frequent masturbation often seen in schizophrenics could lead to some degree of over-stimulation or exhaustion of the pituitary anterior lobe, and in turn respectively to sexual prematurity, or the arrest of sexual development at various stages.

Discussion

When discussing the results just described, it is necessary to avoid some obvious misunderstandings, which can occur either in analysing primary cause and secondary effect or in the expectation from hormone therapy in psychiatry. If psycho-endocrine research is to become useful in treating mental disease, basic conceptions must be carefully formulated. In any patient, an endocrine disturbance may obviously be primary or secondary in the development of the disease. The neuro-endocrine vicious pathological circle must be continually kept in mind. The precipitation of an acute disorder might be compared with the development of an avalanche, which starts with a slight movement in the snow, and ends by uprooting or destroying all in its path. The results are seen, but not the primary cause. Similarly in mental disease, owing to neuro-endocrine interrelationships it is to be expected that there are always some endocrine

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disturbances accompanying mental disease, even though the initiating cause may be obscure. In fact, it would not be surprising, as investigation methods improve, to find that every acute recent case always showed some abnormal endocrine function.

Hormone therapy should never be regarded as intended to deal with the primary cause, but merely as an attempt to improve a disturbed homoeostasis and enable the patient either alone or with the help of the psychotherapist to adjust himself to the demands of his environment.

Reviewing the results reported in this paper it cannot be doubted any longer that in some schizophrenics endocrine disturbance plays an important role. Thyroid under-function and over-function, as well as normal function, can occur. Claims of positive results of treatment from the thyroid aspect reported in the literature may certainly be correct. We ourselves have some experiences in this direction based, however, on proper indications after appropriate investigation of the patients. The same things can be said about adrenal cortical function.

The results of our investigations into the action of insulin coma treatment are particularly illuminating, and help to put the role of the adrenal cortex in schizophrenia in a better perspective. The success of insulin therapy in patients having a high ketosteroid excretion rate initially, seems consistent with the improvement gained by Allen and Broster (1945) after adrenalectomy in psychiatric patients, mostly paranoid, with hyperadrenalism. Other facts can make this picture even more nearly complete: for example, the administration of cortisone or A.C.T.H. is known to produce psychotic symptoms—apparently in individuals so disposed; treatment with high doses of dehydroisoandrosterone sometimes resulted in aggressiveness and schizophrenic symptoms. In both cases the symptoms disappeared after cessation of treatment. Finally, it must be realized that during puberty, and particularly during adrenarche, huge amounts of ketosteroids are being poured into the blood stream, a state which might be termed physiological hyperadrenalism.

In recent acute cases after definite stress, where there is a low ketosteroid excretion rate, it may not be necessary to give insulin coma treatment, even though several such cases in our group did well on it. This, of course, agrees with clinical experience. Equally, if the patient has a low ketosteroid output with an insidious development of illness, it is usually of little use to give insulin. Finally, one can learn from the changes seen after insulin coma therapy that improvement in the ketosteroid excretion rate alone is not enough, but that also the thyroid function should be normalized in cases where insulin treatment is to prove beneficial.

SUMMARY

1. Variations in thyroid activity in schizophrenics are described. Schizophrenia can be accompanied by normal, under- or over-function of the thyroid.

2. The 17-ketosteroid excretion rate in schizophrenics varies over a wider range than is found in the normal population. As with the thyroid, the adrenal cortex may show normal, under- or over-function in schizophrenia.

3. The correlation of changes in the 17-ketosteroid excretion rate with changes in the mental state has been attempted in individual patients.

4. Paranoid schizophrenics have a statistically significantly higher 17-ketosteroid excretion rate than do other schizophrenics.

5. Changes in adrenal cortical and thyroid function during spontaneous change of mental state have been studied. Normalization of function of both glands is an essential concomitant of spontaneous improvement.

6. Various types of changes in 17-ketosteroid excretion rate and in thyroid function found during insulin coma treatment, have been correlated with therapeutic results.

7. Conclusions concerning the significance of the adrenal cortex in the schizophrenic state are stated and discussed.

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