

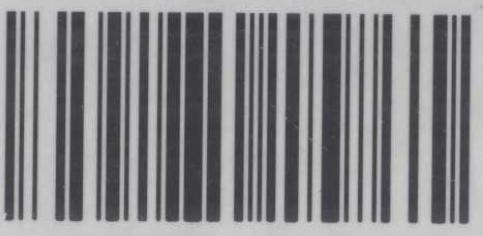
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Psychoendocrinology

Edited By MAX REISS





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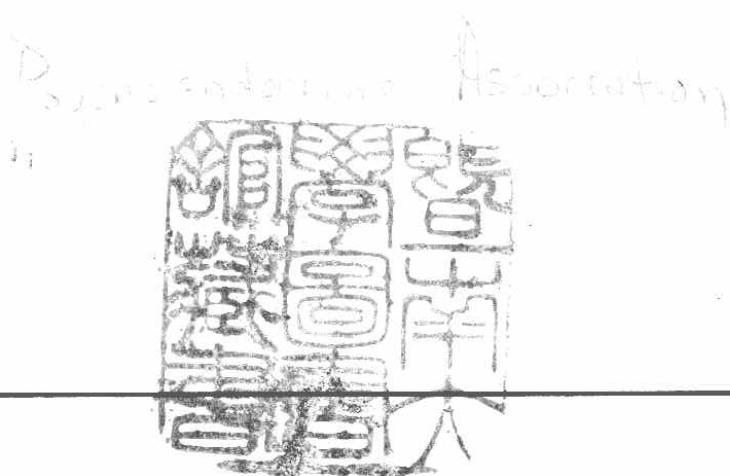
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Psychoendocrinology

Edited By
MAX REISS, M.D., D.Sc.

*Neuroendocrine Research Unit,
Willowbrook State School,
Staten Island, New York*

With 23 Contributors



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FOREWORD

THE SYMPOSIUM on Psychoendocrinology was arranged, within the frame of the 2nd International Congress for Psychiatry at Zurich, to correlate the progress made in the study of endocrine function in psychopathology during the seven years since the 1st International Congress.

The role of endocrine function in psychopathology has been considerably clarified in the last ten years. The chaos which existed then in the conception of endocrine psychiatry led first to disillusionment and then to the realization and appreciation of our ignorance of the influences of endocrine function in psychiatry. Finally, however, new life has started to grow on the ruins produced by the many misconceptions which we are only now beginning to understand. We are closer to the truth. The body and the adaptability, depending upon hormone equilibrium, have finally found their place in the discussion between psyche and mind.

This Symposium represents the first attempt to combine the views and results of clinicians and pure research workers concerned with the psycho-neuroendocrine interrelation. They are working in their hospitals and laboratories in all parts of the world.

Clinicians naturally are most concerned with the value of psychoendocrine investigations in therapy, while laboratory workers are interested in discovering the significance of any correlation that they may have found. The papers in this book were arranged with the clinical lectures first, followed by those more devoted to experimental analysis. Both groups, however, are unanimous, when examining their therapeutic results, in not accepting any results as the final solution but only as one more valuable link in the pathogenetic analysis of mental disease.

THE EDITOR.

Psychoendocrinology

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W. J. TINDALL, M.D., B.Sc., M.R.C.S., L.R.C.P., Organon Laboratories, London. Department of Gynaecology, Royal Free Hospital, London.

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I

PSYCHOENDOCRINOLOGY*

MAX REISS

- I. EARLY MISCONCEPTIONS AND DISAPPOINTMENTS.
- II. ANALYSIS OF PREVIOUS FAILURES AND NEW APPROACH TO THE PROBLEM.
- III. THE SIGNIFICANCE OF THE HORMONE EQUILIBRIUM, THE PERSONALITY PATTERN, AND EMERGENCY SITUATIONS FOR THE PRECIPITATION OF MENTAL DISEASE.
- IV. THE NEUROENDOCRINE INTERRELATION.
- V. THE PATHOGENESIS OF MENTAL DISEASE IN THE LIGHT OF A PSYCHO-ENDOCRINE CONCEPT.
 - 1. The hormone equilibrium during mental breakdown and the acute disease.
 - 2. The hormone equilibrium after one year of the disease process and in chronic patients.
- VI. THE HORMONE EQUILIBRIUM DURING RECOVERY FROM MENTAL DISEASE.
 - 1. Hormone equilibrium during spontaneous improvement.
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 - (a) Electroplexy.
 - (b) Deep coma insulin therapy.
 - (c) Pharmacotherapy.
 - (d) Psychotherapy.
- VII. THE SCOPE OF HORMONE THERAPY.
- VIII. CONCLUSION.

*This paper is based on the following previous publications by the author:
Application of endocrinological research methods in psychiatry: J. Endocrinol., 7, 236, 1951.

Psychological changes connected with spontaneous and experimentally produced alterations in steroid hormone metabolism: Ciba Foundation Colloquia, III, 128, 1952.

The neuroendocrine relationship. J. Ment. Sc., 1944 (January).

Investigations into psychoendocrinology: Int. Record of Med. 166, 196, 1953.

Die Entwicklung der Psychoendokrinologie: Berliner Gesundheitsblatt, 20, 517, 1955.

Psychoendocrinology: J. Ment. Sc., 101, 683, 1955.

The Changing Concepts of the Role of Endocrine Function and Treatment in Psychiatry, a paper read by J. C. Batt and M. Reiss during the Symposium.

PSYCHOENDOCRINOLOGY IS a name used for the study of the interrelation between the functions of the brain and the endocrines. Neither my friends nor I liked this name, but after many discussions we could not decide on an alternative. We even went further, when in 1956 we decided to call our whole research group, consisting of psychiatrists, psychotherapists, psychologists, biochemists, pathologists and endocrinologists, the "Psychoendocrine Association." The name psychoendocrinology was further established at the International Psychiatric Congress in Zurich. The present psychoendocrine concept has developed during the last ten years on the basis of a good deal of trial and error, and much frustration and disillusionment had to be overcome before we felt certain that we were on the right track.

EARLY MISCONCEPTIONS AND DISAPPOINTMENTS

The efforts of all the biochemists and endocrinologists who wanted to find a cause for a psychopathological phenomenon are best likened to the labors of the Danaids or of Sisyphus. Labors and efforts including the evaluation of the sometimes "statistically significant" results, could have been saved had all these workers not been the victims of some serious misconceptions. These misconceptions were originated by endocrinologists and perpetuated and enlarged by psychiatrists.

From the beginning, endocrinology was connected with descriptions of specific psychological sequels of glandular under- and overfunction. Take for example Berthold's classic experiments, in which he was the first to describe the loss of fighting spirit in the cock after removal of the testicles, and its return after reimplantation of the latter. We have learned, however, that it is often misleading to apply too readily experiences we have had in animal experiments to the analysis of human behavior patterns. We know, for instance, that in human beings sex hormones play a less important role in the development of the fighting spirit, and that this psychological phenomenon depends upon a greater multitude of endocrine, psychological, and genetic factors than in animals. On the basis of his experience with the sex drive of animals, the en-

docrinologists tried to treat homosexuality in men with male sex hormones, and were extremely puzzled to find the patient becoming, if anything, more homosexual. They tried to treat frigid women with estrogen, and found that the female sex hormone does not influence the female sex drive, while testosterone, the male sex hormone, often does increase it. Incidentally, Freud pointed out the risk of the gonads themselves being overestimated, and added that the chemical mechanisms concerned are probably more diffuse and complex than the consideration of them alone would make one suppose.

Impotence is, in the mind of many endocrinologists, still most readily associated with underfunction of the testicles. Psychological stress factors which can be the cause of many endocrine changes connected with impotence, are barely considered. Careful study, for instance, of the psychological changes during the development of a hypothyrotic state, which may take several years before becoming clinically recognizable, have shown impotence to be an early symptom during the development of hypothyroidism. The text book description of the psychological concomitants of disturbed thyroid function is still so incomplete as to be misleading. Hypothyroidism is always connected with slowing down of mental processes, hyperthyroidism with anxiety neurosis. Only a few endocrinologists have ever taken the trouble to establish, by careful study of the case history, the great variety of psychopathological changes that can occur during the time needed for the development of the final endocrine status, diagnosed as "major endocrine disorder." The clinical endocrinologist has also spent regrettably little time in considering actually why such a great number of patients, showing a major endocrine disorder, are comparatively little deranged psychologically at a time when others show severe neurotic or psychotic disturbances.

The psychiatrists, some thirty years ago, had an entirely open mind about endocrinological psychiatry and accepted the significance of the various claims made by endocrinologists concerning the causative role of endocrine dysfunction in the development of specific psychopathological disturbances. Kraepelin, one of the

founders of clinical psychiatry expected endocrinology to provide the final solution in the pathogenesis and treatment of some psychiatric disease entities. Freud, too, expressed on many occasions, the hope that endocrinological investigations would supply solutions to many psychiatric problems.

However, all the efforts devoted to endocrinological psychiatry were made in vain. Hoskins and Sleeper (1929), for instance, believed that the development of schizophrenia was due to an underfunction of the thyroid. Unfortunately, they dealt with a small series of schizophrenics who showed low metabolic rates and reacted well to thyroid treatment. On the basis of these results many psychiatrists all over the world started to treat schizophrenics with thyroid preparations, without, however, making sure that they *were* hypothyroidic. There were even psychiatrists in this country who had a whole ward of schizophrenic patients on thyroid therapy. All these people occasionally had a most convincing success, but in the great majority of cases there were failures which discredited the whole treatment. It would be very difficult to convince a psychiatrist today to begin thyroid treatment again now that his youthful enthusiasm has been so greatly dampened.

It must have been most frustrating for the psychiatrist, when he started thyroid treatment of cases which fell psychiatrically into the same disease entity, to find one reacting nicely and the other remaining completely unchanged or even deteriorating. Their experiences with sex hormones must have been similarly disappointing. Some recommended treatment with sex hormones, others castration, but in the end the results were always the same. After the reports of initial successes the treatments were repeated and the results found to be, in the majority of cases, negative—obviously since the treatment was not guided by proper clinical and laboratory investigations—thus the treatment was discredited and the conclusion reached that the mental disturbance in question had nothing to do with sex hormones.

Most disappointing of all was the work carried out on treatment with adrenal cortex hormones. Originally, before the various hormone compounds of the adrenal cortex were isolated and synthe-

sized, a great number of authors reported very encouraging successes of treatment with adrenal cortex extracts in a variety of psychiatric conditions. These were soon forgotten when cortisone was discovered, and reports were made about the psychopathological reactions of some patients who were treated for rheumatism with mammoth doses of the drug. One ought to emphasize that such psychopathological reactions occur apparently only in patients with a certain pathophysiological or mental predisposition. Otherwise, it is obvious that it would occur much more generally. These results, however, made the psychiatrist forget the encouraging experiences he had with adrenal cortex extracts, which obviously contained very little cortisone. If one wants to make a comparison with incidents in the history of endocrinology, it comes to mind that the use of insulin would never have been discovered for the therapy of diabetes had one not gauged the hormone dose according to the patient's blood sugar concentration and the urinary sugar excretion. Otherwise, one would have killed a discouraging amount of patients, and in others effected not the smallest therapeutic result.

Much of this experimental work was begun before satisfactory measuring methods had become available in endocrinology. In any case the investigations were carried out either by psychiatrists who had little understanding of endocrinology and its methods, or by endocrinologists who had little or no experience with mental disease. This was soon realized, and the belief was that the introduction of more modern and progressive endocrine investigation methods, and the isolation and use of biologically active hormones, would greatly contribute to progress in endocrine psychiatry. It was believed that one might find clearly circumscribed endocrine deviations causing depression, schizophrenia, etc. The investigations were carried out in mental hospitals with exact methods, that were progressively improved from a technical viewpoint. However, a feeling of utter frustration must come over anyone, be he psychiatrist or endocrinologist, who attempts to survey the thousands of biochemical and endocrinological investigations into schizophrenia. M. Bleuler (1954) recently undertook just such a survey, but after he had marshalled all the facts he found them so contradictory

that he could not permit himself to draw any definite conclusions. In fact, he was not even sure whether the classic syndrome of schizophrenia had any sort of causal relationship to endocrinology at all, and at a recent meeting dealing with psyche and endocrinology he was rather inclined to separate entirely endocrine psychosis from real endogenous psychosis. A still more recent review by Richter (1957) on the biochemistry of schizophrenia does not show any recognizable trend towards definite deductions. Mayer-Gross and his co-workers (1954), in their recent textbook wrote: "Thyroid, sex glands, adrenal cortex and pituitary have all been suspected as the primary cause of the disturbance, but with no conclusive evidence."

ANALYSIS OF PREVIOUS FAILURES AND NEW APPROACHES TO THE PROBLEM

The causes for the existing chaos in the biochemical and endocrine investigation results became increasingly clear to our research group.

A great number of investigations did not deal with psychiatrically homogenous groups. It would be difficult to find, among their published results, some that are not based on biased samples.

Few of the numerous statistical evaluations of deviations found in, for instance, schizophrenic patients, is valid where the disease entity, schizophrenia, is concerned. Various groups of workers investigating quite different groups of schizophrenics, acute states, chronic states, simple schizophrenia and paranoia, were rather surprised when their "statistically significant" results contradicted the equally "significant" results of other investigators. Many workers also did not realize that so-called "homogenous group," owing to the prevailing system of classification, can contain patients in various states of exhaustion, some of which are excited, some very quiet, etc. One cannot expect to find in such groups significant changes, say, in the blood corticoids, or in other chemical, urine, or blood components.

At an early date, we thought that investigations of greater numbers of the same disease entity, or bigger hospital populations,

would render more valid information. In these large scale investigations, however, the arithmetic means are usually identical with, or very near to those of the control groups, but the range of the results is considerably wider, the standard deviation greater.

Figure 1 illustrates such investigative results. It summarizes the results of our large scale investigations on schizophrenics and can

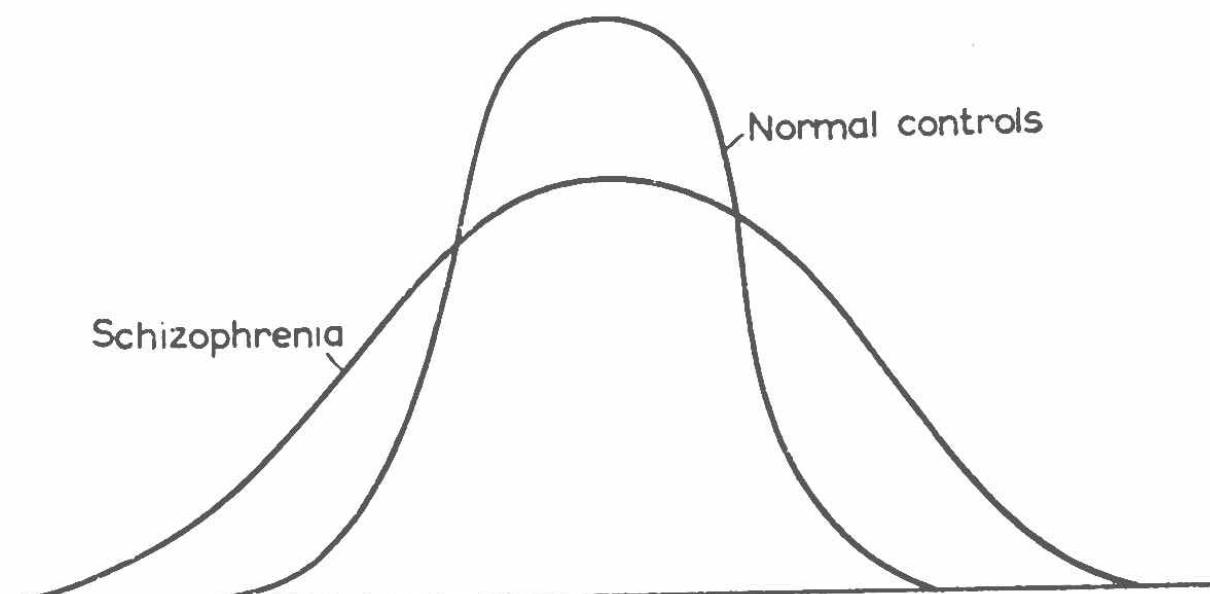


Figure 1

equally apply to blood circulation rate, body temperature, basal metabolism rate, blood chemistry, thyroid activity and excretion rate of adrenal cortical steroids. However, one may draw one final conclusion from these investigative results, namely, that the various biochemical and endocrinological deviations occur much more frequently in mental patients than in the normal population. Such results were achieved by screening the thyroid activity of hospital populations, or a considerable part of them, in Bristol from 1949 to 1953 (Reiss et al.), St. Ebba's Hospital, Epsom from 1954 to 1957 (Sands), the Royal Victoria Hospital, Netley from 1954 to 1956 (Robinson) and Burgholzli, Zurich from 1953 to 1954 (Stoll).

In later investigations more attention was paid to the biochemistry and the endocrinology of the *individual* patient. This change in emphasis evolved from the fact that great diurnal and day to day variations occurred in many patients. In judging steroid hormone production, for instance, these single values were unsuitable

for use in statistical evaluation of cross sections. Further it seemed profitable to investigate the individual patient longitudinally for some time during the deterioration, or improvement, of his mental disturbance. The first results were rather unexpected. It seemed that individual patients with apparently identical psychopathological symptoms showed quite different endocrinological disturbances, under- or overfunction of one gland, or of various glands; alternatively, individuals with the same kind of endocrine disturbance had either no pathopsychological symptoms at all, or quite divergent manifestations of disturbed mentation.

These findings initially shattered every concept we had concerning the role of the endocrines in psychiatry. They later became the starting point of a more productive working hypothesis.

THE SIGNIFICANCE OF THE HORMONE EQUILIBRIUM, THE PERSONALITY PATTERN AND EMERGENCY SITUATIONS FOR THE PRECIPITATION OF MENTAL DISEASE

The variety of the endocrine disturbances that can accompany identical psychiatric disease entities brings to mind experiences with groups of individual soldiers during the war, where the same biochemical change and emergency situation could bring about a variety of neurotic and psychotic reaction patterns. For instance, a group of young men about equal age, in a lifeboat after a shipwreck, are all subject to similar conditions of exposure, starvation and thirst, and to the realization of the uncertainty of their fate. A number of them will not show any psychopathological manifestations at all, others may behave in a very hysterical way, while some may have hallucinations or show all the symptoms of a manic or depressive psychosis. Decisive in their behavior are their preformed personality patterns. In view of what has been described above, namely that identical endocrine disturbance can be accompanied by a variety of psychopathological manifestations, we were forced to draw the conclusion that it is not the quality of the hormone disturbance which determines the type of mental breakdown, but the premorbid personality pattern that is decisive.

In later continuation of the endocrine investigation of mental patients, in which particular attention was paid to the early stages, and the stages intermediate between normal status and a fully developed endocrine disturbance, it was found that the disturbance of one function of one gland rarely occurred on its own, but was usually accompanied by a disturbance of other glands. In other words, a single endocrine disturbance was usually only regarded as an indicator for the disturbance of the whole hormone equilibrium. Therefore, to characterize the hormone equilibrium of a patient attempts were made to investigate the function of at least two glands. Investigation of the functions of the thyroid and the adrenal cortex were within the scope of our group. Simple biochemical investigations were postponed at this time, since it was realized that they give us much less information than the investigation of the hormone equilibrium, which is primarily responsible for the biochemistry of the body. The failure, for example, of some of the best biochemical investigations to lead to any final results is due to the fact that the importance of this sequence was not realized in time. Gjessing, in his admirable research into the changes in nitrogen metabolism, ascribed to the thyroid function the whole responsibility for the most characteristic cyclic changes. That, however, happened at a time when the influence of testosterone, or cortisone, on nitrogen metabolism was not yet known, so that the final solution of the problem still awaits an exact repetition of the original Gjessing experiments, but including control of the adrenal cortex and gonadal function. The same can also be said about any other biochemical component, as for example sugar metabolism, which also depends primarily on the interaction of a number of hormones. There is no doubt that the ductless glands are the main regulators of the biochemical equilibrium of the organism, and the more we learn about their physiology the more we can see how even the simplest metabolic functions are finally dependent on the function of the endocrines, and how the body equilibrium which can ultimately be defined as a tendency to maintain a constancy in the chemical patterns of blood and tissue, is dependent on the cooperative effort of various duct-

less glands. It is obvious that a decrease or increase in the functions of a ductless gland will have its repercussions on the width and stability of the biochemical equilibrium. Thus it must be assumed that the homeostasis of the organism is not an unalterable factor. In some individuals, it can be stretched very far, sufficient for the regulatory demands of enormous efforts, while in other individuals a small effort can lead to a failure of homeostasis. This failure may be followed by severe functional disturbance of some organ systems, among which the brain function plays, of course, a predominant role if one considers that about 30 per cent of the total oxygen consumption of the body takes place there.

Selye's stress and adaptation theory, and E. B. Cannon's theory about the body's regulation towards emergency function, described some small part of all the forces of the organism for maintaining biochemical equilibrium. Cannon's theory, however, was based only on the regulation afforded by adrenal medulla and sympathics, and Selye's gives a prevalence to the anterior pituitary lobe-adrenal cortex axis. Considering the knowledge accumulated about factors contributing to the maintenance of homeostasis a very great number of such adaptation theories could be described at present. It would be wrong to restrict the explanation of the adaptability of the organism to Selye's theory alone. Instead of sticking to such presently well introduced phrases as "adaptation to stress," it would be considerably more productive if more attention were paid to the endocrine and biochemical *adaptation to everyday life* and its demands. A better understanding of the functional endocrinology of everyday life, and sufficient methods to measure the changes taking place should become a most essential basis for the pathogenetic analysis of the development of various mental disorders.

Today it can be safely assumed that the endocrine equilibrium is necessary for the maintenance of normal functions during everyday life, and for the adaptability of the individuals to various emergencies, as they are offered by different psychological and physical stress conditions. It has proved useful to characterize the various elements concerned in the development of mental dis-

turbation in a diagram that during the last year has become more or less the coat of arms of our research group.

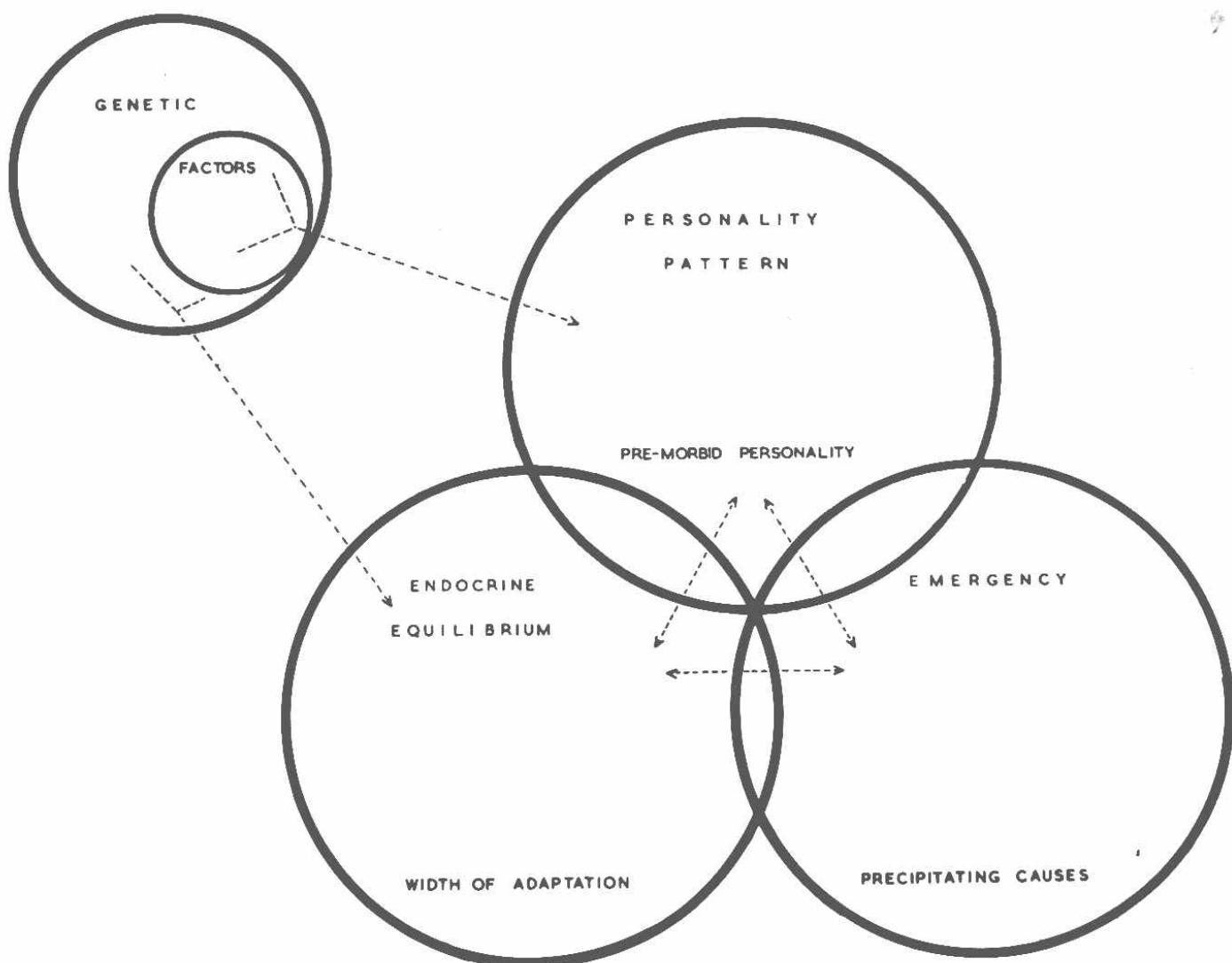


Figure 2

A great number of contradictions which have occurred in the course of the research into endocrine psychiatry can be explained, on the basis of this more dimensional concept. The diagram attempts to schematize the interrelation between personality pattern, emergency situation and endocrine equilibrium. These factors are set inside circles which intersect in order to emphasize the difficulty of separating the various elements. When specifying a primary role of any of these factors one should consider how easily the emergency situation produces endocrine disturbances, or how some endocrine disturbances occur more easily in certain personality patterns. Further, some emergency situations can become, in some

endocrinologically or psychologically predisposed personality patterns, of much greater significance than in others. The endocrine function, the hormone equilibrium, and the width of adaptability, determines when an existing emergency situation will lead to the precipitation of psychopathological phenomena in an individual of a certain personality pattern.

It must be clear that a disturbed hormone equilibrium, even a major endocrine disturbance, need not necessarily lead to any psychopathological manifestations if no emergency situation, a precipitating cause, occurs. But even an emergency situation occurring in an individual with disturbed hormone equilibrium does not necessarily lead to a mental disturbance, if the personality pattern is stable and not primarily schizoid, depressive, etc. The psychoendocrine concept regards the mental breakdown as a pathological exacerbation of various preformed personality traits.

A conception based on this diagram helps us also to understand how various individuals, even if suffering under severe endocrine disturbance, need not necessarily show a mental derangement. Only if some serious emergency situation occurs to which they are unable to adjust themselves, owing to restricted adaptability, can they break down. This breakdown is a mental breakdown in persons of a suitable personality pattern. The quality of the mental breakdown may depend more on the preformed personality pattern than on the quality of the endocrine disturbance.

The diagram intends also to express the dependence of the personality pattern on the genetic factors, and equally the considerable dependence of the endocrine function on genetic factors. It might be as well to compare at this occasion conclusions drawn from genetic conditions concerning endocrinological and psychological factors. This is particularly the case if one looks at the defeatism that various geneticists developed when they found out the inheritance of a psychopathological condition in a patient. For many of them, the problem of pathogenesis and therapy ends at this juncture. That, however, is not so according to our concept. It is known that most severe endocrine conditions, or the inclination to develop them are inherited, but that doesn't mean that

after diagnosing diabetes, for example, in a patient and finding that the disease is inherited, one will shelve the patient as incurable. On the contrary, every diabetic is treated and leads a comparatively normal life whether he has inherited his disease or not. The same consideration can also be made concerning other endocrine disturbances. There is no reason why the trend of our deductions concerning mental disorder should be different. Considering the conditions under which an individual, even with a very unfavorable personality pattern, breaks down mentally, there is no reason to assume that by taking proper care of his hormone equilibrium and paying attention to the various emergency situations, his mental breakdown should not be prevented or treated.

It can be seen that one of the first steps in the formation of our psychoendocrine concept has been to leave behind the original two-dimensional approach made to problems of endocrine psychiatry. The various misconceptions described above encountered by the various workers dealing with the interrelationships between endocrine function and psychopathology, could only arise by sticking too rigidly to the old thought pattern of cause and effect. However, that cannot be done any longer since it has become abundantly clear that a disturbed endocrine function is only one of several links in the development of the mental breakdown.

THE NEUROENDOCRINE INTERRELATION

The psychoendocrine concept is based on the discovery that the activity of the pituitary is related to the function of the hypothalamus. Impulses from the upper brain parts are conducted via the hypothalamus to the pituitary which regulates by means of the various trophic hormones the function of the subordinated glands. The latter act directly on the various organs of the body and also on the brain, influencing in this way again the transmission of the original impulses which in the last resort had influenced the glands. This feedback system closes a neuroendocrine circle, which, in the case of the occurrence of any precipitating causes, can become a vicious circle. Emotions and psychic traumata can, on this pathway, influence the total endocrine function of the body.

There are some things, of course, not yet clarified, for instance, why in some women, after a psychic trauma, the periods stop, while others develop hyperthyrotic changes, etc. It seems that the type of endocrine reaction to emotions and traumata is genetically determined in the individual.

Disturbances in the neuroendocrine circle need not necessarily include the pituitary in the first instance. They can, particularly under conditions of acute stress, start also in the periphery by mobilization of large quantities of vaso motor substances. It has been shown that certain endocrine reaction to stress takes place at the same rate in hypophysectomized and normal control animals (Badrick et al 1955).

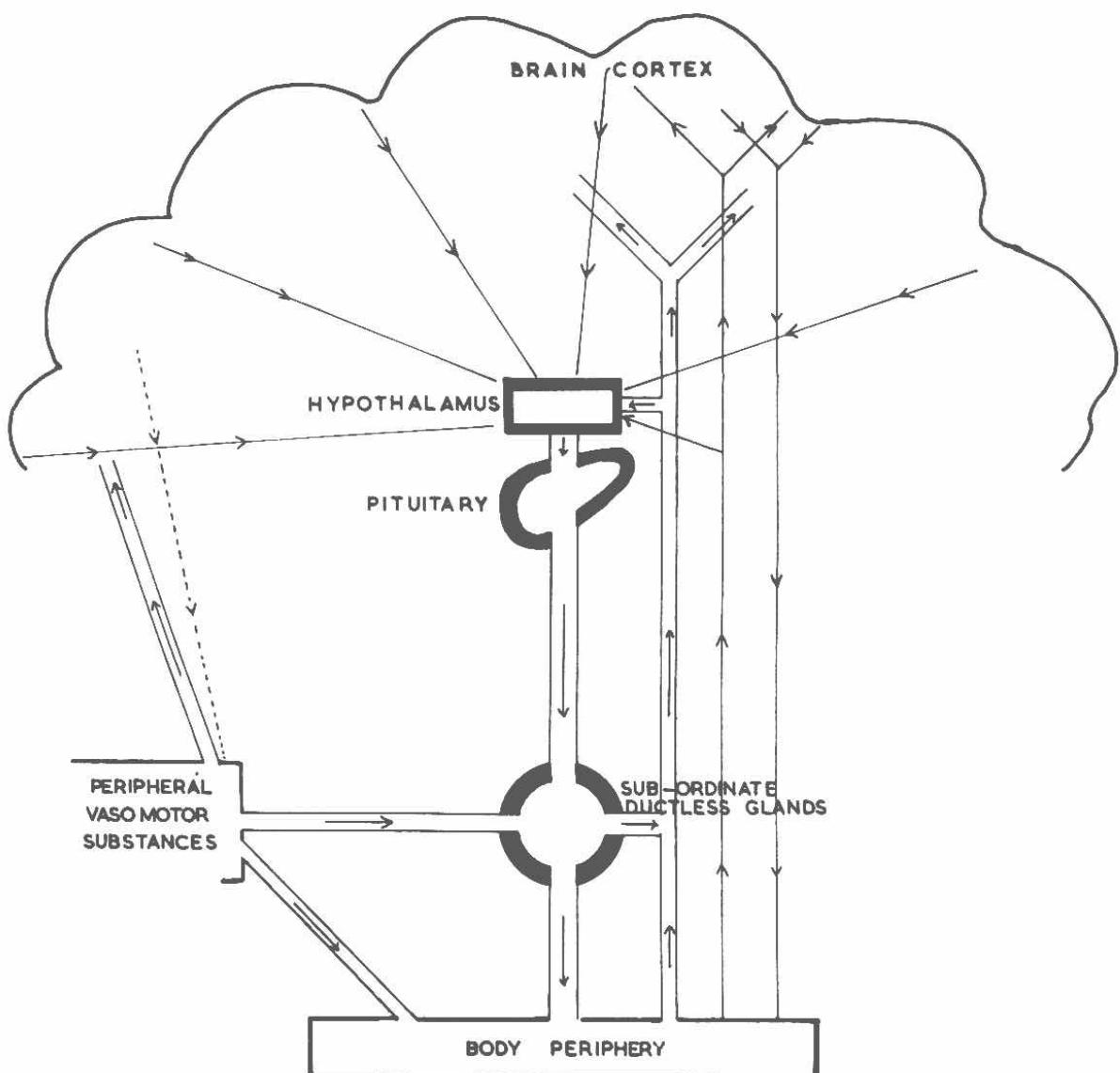
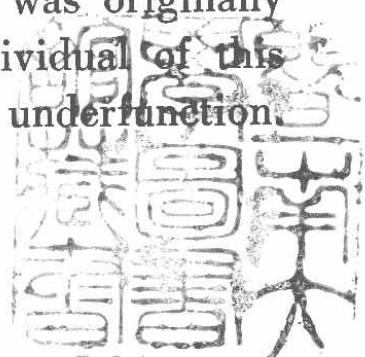


Figure 3

Figure 3 illustrates the various components essential in psycho- and neuroendocrine interrelation.

Normal neuroendocrine interrelation is necessary for the pursuit of normal everyday life. The process, of waking up, for instance, produces for some time an increased stimulation of the pituitary resulting, as far as we were able to investigate, in the highest 17-ketosteroid excretion rate during the 24-hour cycle, while during sleep the lowest 17-ketosteroid excretion rate can be observed. It would be useful to remember that not only emotions and other stress conditions are influencing the neuroendocrine regulation, but also all demands of daily normal life.

A realization of the neuroendocrine interaction can give us some indication of the developments to be expected in psychoendocrinology for the future. Since it is well known that any emotional stress can trigger off endocrine changes that must also be true in the case of any psychopathological disturbance. It is only a matter of time until the various endocrine investigation methods are improved to such a degree that it will be possible to recognize the endocrine concomitants in any psychiatric condition. It can safely be foreseen that a viewpoint developed tentatively by M. Bleuler at the 1957 Symposium in Freiburg, according to which one should separate endocrine psychosis from genuine psychosis, would not be tenable. A clear realization of the development of the vicious circle on the basis of the neuroendocrine interrelation will also help to remove us still further from the unproductive trend to thought consisting of cause and effect as pointed out above. One can understand why, when confronted with a mental patient, and dealing with his endocrinology, it is futile to analyze him according to the pattern of primary cause and secondary effect. The logical interpretation of the neuroendocrine interrelation is that we are dealing with a vicious circle and it is extremely difficult to find out where it has started. Should one succeed in improving psychopathological symptoms by substitutional treatment of an endocrine underfunction observed simultaneously; one still could not say that the mental disturbance was due "primarily" to the underfunction of the gland in question. It is possible that this reduced glandular function was originally caused by a severe mental trauma that in an individual of this constitutional background had led to a glandular underfunction.



The latter disturbance then had an influence on the brain, deteriorating its function, already impaired by the trauma, still further. Thus, the circle is closed leading to a continuous further deterioration of the brain and the glandular function. To be successful, any therapy given to such patients must start with a break in the pathogenetic sequence of such a vicious circle.

THE PATHOGENESIS OF MENTAL DISEASE IN THE LIGHT OF A PSYCHOENDOCRINE CONCEPT

The Hormone Equilibrium during Mental Breakdown and the Acute Disease

One of the drawbacks to present clinical endocrinology is the extreme scarcity of studies and descriptions of developmental phases in the various clinically recognizable major endocrine disorders. A few facts, mainly worked out by Shehan, are known about the conditions that can, sometimes after years, lead to various anterior pituitary lobe disturbances, particularly excessive blood loss during a confinement. We ourselves made some observations about the early development of adiposity, hirsutes, and increased blood pressure during the adrenarche in girls who suffered from a severe infectious disease, particularly scarlet fever, in their early youth.

Comparatively more is known about the symptomatology of thyroid disease. It seems that the time of the development of clinically manifest hypothyroidism, which can sometimes last 6 to 8 years, is particularly interesting in psychoendocrine studies. During these years clinicians can rarely guess the progressively deteriorating state of the thyroid of the patient. Only a few very experienced doctors can, sometimes, on the basis of some clinical symptoms connected with gastric dysfunction, changes in temperature sensitivity, or menstrual disturbances, draw some tentative conclusions which prompt them to ask for laboratory investigation of the thyroid function. The introduction of the radioactive tracer methods using I^{131} enables us nowadays to diagnose the actual thyroid activity of such intermediate states at an early stage (see paper of Bullmore, Kay, Smith and Stott in this symposium).

We believe that it might be extremely useful in some cases of acute mental disorder if the thyroid activity were investigated more often. Such investigation is, at the moment, still a quite difficult thing to ask since the psychopathological disorder, in which the psychiatrist is obviously mainly interested, often overshadows the endocrine disorder. In our experience, even major endocrine disorders such as myxedema, Graves disease, Cushing's or Addison's disease, are too often disregarded should they occur during the state of acute schizophrenia which was the cause for the patient's admission to a mental hospital. Of course, psychiatrists alone cannot be blamed for such an oversight. Had the patient been admitted to a medical ward it is highly probable that the endocrinologist would have dealt with the endocrinological picture only; for him the physical disturbance would have naturally overshadowed the very important psychological concomitants. Yet, many errors involving inappropriate psychiatric treatment procedures could be prevented if thyroid activity were measured in more of the newly admitted acute cases. It is even possible that once the significance of thyroid activity in the vicious circle leading to acute mental breakdown is sufficiently well known, investigation of this activity will become part of the routine investigation undertaken in every new admission; regardless of whether one is dealing with a 60 year old involutional depressive, or a 16 year old hebephrenic, and such investigations will be made as a matter of course along with investigations of blood, urine, etc. Once such a routine is established one will see that it is by no means always correct to assume retardation of mental processes and sleepiness in thyroid underfunction as it is so regularly described in the textbooks of clinical endocrinology. Among the first symptoms encountered in many patients in the initial states of hypothyroidism is diminution of receptor sensitivity. The threshold rises for hearing, seeing, tasting and smelling, and consequently the reaction time is also prolonged. The intelligence index, however, does not change at the same time, and the patients become aware of the fact that they are unable to make full use of their mental capacities. They feel that they are now less able to do their jobs—consequently

conflict and mental stress situations are unavoidable. The three pathogenic factors mentioned above are then present, also the emergency situation and the disturbed hormone equilibrium which, according to the premorbid personality of the patient, can lead to a multitude of psychopathologic phenomena.

It is interesting to look through the window of an admission ward at these psychoendocrine developments.

A young man, 18 years of age, has done well while he lived at home. He completes his grammar school education successfully, but now must study hard for examinations. He suddenly cannot concentrate or even read a book, he daydreams and occasionally hears voices. He breaks down in despair about his inability to go on with his chosen career, and when he is examined a very low thyroid activity is discovered. This had never been suspected before. Actually the possibility is rarely investigated in similar cases since the psychopathological symptoms completely overshadow the physical disturbance. This boy could have gone on living quite normally for some time had the additional environmental demand of sitting for an examination not occurred. Owing to his disturbed thyroid activity, however, he cannot adjust himself to the increased demands, and breaks down mentally in accordance with his premorbid personality pattern.

The same pathogenetic history can also be observed, for instance, in a 24 year old greengrocer, who lived happily and contentedly, until he had to join the army, when he broke down mentally. Or one could see it in a particularly interesting hospital porter who for a long time confused the control series of the Bristol Tracer Department by showing a very low 24 hour I^{131} uptake, and yet, although his personality was always considered "odd," he was, to all intents and purposes, normal. However, he showed a most dramatic schizophrenic breakdown when his fiancee let him down.

All these patients reacted to treatment of the thyroid disturbance which will be discussed later on (see paper of Bullmore, Kay, Smith and Stott in this symposium).

Another man, 25 years old, who did well during the war, seeing action with a combatant unit, comes back but cannot settle for longer than two months in any job; his readaptation to civilian life is impossible, he starts having hallucinations, and in response to them he becomes aggressive and is admitted to a mental hospital. He, too, shows a very low thyroid activity, improves after treatment with thyroid, and twice relapses because his physician refuses to prescribe further thyroid tablets, since he has improved. He needs thyroid tablets exactly as a diabetic needs insulin.

Acute female patients more often show hyper than hypothyrotic disturbances. The former are, of course, easily diagnosed by laboratory methods, but also occasionally show clinical symptoms.

Take, for instance, the case of a 17 year old girl who, while studying for her teacher's training certificate, has an unfortunate disappointment in love. She suddenly becomes very religious, cannot concentrate on her work and hates her father, whom she accuses of behaving like a scoundrel to her mother, and finally she hears a voice commanding her to interfere with his bad activities. She has lost 28 pounds in the two months preceding her admission to the hospital, has a fine tremor and a very high I^{131} metabolism, and B.M.R. considerably increased even when measured under Thiopentone. It is interesting that the mother of this girl also had a thyroid disturbance some years ago. She improves following antithyroid treatment, but relapses a few months after leaving the hospital when her antithyroid treatment is stopped, because her doctor considers the gland now in order. The situation is soon repaired when the antithyroid treatment is begun again.

In such a case the pathogenesis can easily be traced: there is in the first instance a mental trauma, which disturbs the hormone equilibrium in the described manner, and the patient is therefore unable to make a sufficient mental adjustment owing to her faulty homeostasis. On the contrary, the increased amount of thyroid hormone produced disturbs the brain function further, and this feedback starts a very dangerous and deteriorating vicious circle. It would be too late to start this patient on psychotherapy directed

towards repair of the psychic trauma, since it would not succeed in interrupting the circle. Psychotherapy is more promising in the lower plane of thyroid disturbance.

Quite identical endocrine disequilibriums can be seen occasionally in severe acute anxiety or phobic states, and in depressive states in older patients. That is the best illustration of the fact that the quality of the acute mental disturbance depends mainly on the preformed personality pattern of the patients. Very similar case histories containing almost identical psychiatric disturbances can be reported in patients who show completely normal thyroid activity, and where the predominant endocrine disturbance lies in another region. There is, for instance, the well cared for son of a loving family who lives comfortably with his parents. He is a shy but well liked boy of 16½ years, his body is rather plump and the clinical endocrinologist would describe him as a late developer, but otherwise quite normal. He would give him a good prognosis for development to full manhood. The boy is in many subjects, one of the best in his class, and is therefore encouraged to study for a rather difficult scholarship. In about two months' time, however, after intensifying his studying, we meet him in the admission ward under the diagnosis of simple schizophrenia. The psychoendocrinologist at first sight agrees with the situation as it has just been described. He investigates the thyroid activity finding it completely normal, but on determining the boy's 24 hour 17-ketosteroid excretion rate finds only 1.5 mg./24 hrs. This amount is definitely too little since a normal boy this age should excrete at least 6 mg.; and he finds further that the inguinal canals of the boy are wide open so that the testicles slip back into the abdomen under the slightest pressure. The responsibility of the psychoendocrinologist in such a case has become very grave indeed during the last years. He knows, for instance, that this kind of patient is most likely to become a permanent invalid if he undergoes a course of deep insulin coma (see paper of Kay in this symposium). He also knows that treatment with Chlorpromazine is not indicated (see paper of Reiss in this symposium). He knows, on the other hand, what therapeutic results can be

achieved if one tries to stimulate maturation of the definitely immature patient by suitable means (see paper of Bullmore, Reiss and Smith in this symposium).

One of the most interesting groups of psychoendocrine disturbances is to be found during adolescence where retarded genital maturity or prematurity, and a discrepancy between the developmental state of the brain and the gonads, can lead to a multitude of behavior disturbances and to psychotic manifestations (see Bullmore et al.).

Other young men slightly older than the patient we have just discussed, and being of military age, may have quite normal genitalia, but have the same psychiatric diagnosis when admitted to hospital. They are, however, in an exhausted state after a period of prolonged exercise and routine to which they are not accustomed, or they are unhappy and frustrated after leaving the parental home for the first time in their lives. They also show a very low 17-ketosteroid excretion rate with a normal or sometimes an increased thyroid function. They, too, are bad bets for insulin coma therapy (see paper of Kay in this symposium), and left alone, improve spontaneously more often than not (see discussion of spontaneous improvement). Should they not improve small doses of testosterone stimulate their adrenal cortex into the production of more ketosteroids and corticoids, a process which is often accompanied by mental improvement.

There are the periods of physiological endocrine changes taking place during the life span of the individual when the width of the adaptability is considerably narrowed. Precipitating causes, emergencies occurring at such junctures, always lead to some functional disturbance. In a person with a suitable personality pattern, the total spectrum of possible psychopathological disturbances can be observed. The quality depending entirely on the preformed personality pattern, the mental breakdown consisting mainly of an exacerbation of previously existing personality traits.

Such periods of physiological change particularly abound in deviations in the time factor and quantity of hormonal production rate. Such developments narrow the width of adaptation to a



definitely pathological size, and mental breakdown becomes more probable.

The event of menstruation should not only be regarded as an occasion when the equilibrium of the sex hormones changes, and in connection with all the metabolic sequels of these changes, but also as a regularly repeated stress condition. This stress condition can, in predisposed persons, (with an intermediate thyroid disturbance) lead to a monthly recurring psychotic phase. Realization of this pathogenesis (that can, however, only be achieved by regular thyroid investigation) will lead to a correct assessment of the case and prevent the physician from erroneous treatment procedures. Suitable treatment from the thyroid angle, in such cases, very soon leads to complete relief.

Great progress has been made in recent years in the understanding of premenstrual tension syndrome. One can, of course, see that the further we progress in its investigation the more complex this syndrome becomes (see papers by L. Rees and G. Mall in this symposium).

Treatment of this condition is usually based on substitutional principles, using various corpus luteum preparations. We (Batt and Reiss) are of the opinion that it might be better to get, one might say, the ovary trained to produce its own corpus luteum hormone. We have therefore started to treat some of these patients with chorionic gonadotrophin. In some clinics chlorpromazine is used to combat the premenstrual syndrome. Any improvement, however, with this treatment is likely to be only temporary, as our own experience has taught us. The basic condition is deteriorated, and this can be understood considering the action of chlorpromazine on the ductless glands of animals. A very short time after the commencement of chlorpromazine treatment, the ovary weight is significantly reduced (see paper of Reiss in this symposium).

One of the greatest upheavals in the interplay of the ductless glands of a woman takes place during and immediately after confinement. Confinement and the changed environmental demands arising from the presence of the baby are also a stress condition

which in women with a suitable personality makeup can precipitate various forms of psychosis, if they are unable to adjust themselves, owing to the delay in the repair of their hormone equilibrium.

It would be a grave error to assume that the endocrine disturbance in postpuerperal mental breakdown is restricted to the ovarian function only. There is practically no endocrine disturbance which we have not seen in this illness. There can be such diverse disturbances as thyroid underfunction or overfunction (even at times accompanied by exophthalmus), adrenal cortex underfunction with a very low ketosteroid excretion rate or adrenal cortex overfunction with a very high ketosteroid excretion rate. Of particular interest is the adrenal cortex overfunction accompanied by high ketosteroids but no hypertrichosis owing to a lack of time after the stress for this morphogenetic syndrome to develop.

In the majority of these patients the recovery is spontaneous. Improvement is always accompanied by normalization of the 17-ketosteroid excretion rate and thyroid activity as determined by laboratory methods. Sometimes the normalization of the hormone equilibrium precedes the mental improvement and it is very useful if the laboratory investigations can predict recovery before it is clinically obvious, since treatment which might interfere with the spontaneous regulation of the hormone equilibrium can be withheld.

If spontaneous improvement does not occur and cannot be predicted from the laboratory investigations, treatment should be started as soon as possible to prevent fixation of a pathological thought content.

Investigation of the mental breakdown occurring during menopause supplies us with one of the clearest examples of the multi-dimensional psychoendocrine concept. A woman, whose mother died in a mental hospital, marries at the age of 19 and her husband dies suddenly when she is 25. He leaves her with three children but without subsistence. She becomes a washerwoman, successfully brings up her children, and is well esteemed in the neighborhood. At the age of 49 her periods stop, she has hot flushes, but she

goes on with her accustomed work. One day she has one of her usual misunderstandings with an employer, which she had previously solved in a jocular way. This time, however, she goes home, makes an unsuccessful suicide attempt and afterwards deteriorates so much that her admission to a mental hospital becomes necessary. The loss of her ovarian activity was the essential factor in the disturbance of her hormone equilibrium. Her adaptability was dangerously reduced.

The endocrine concomitants of the menopause, and the psychopathic features occurring at this time, are considerably more complicated than usually assumed and described in the textbooks. Lack of realization of this fact is the cause for frequent failure to improve the state by the usual treatment with estrogens. The usual description quotes just a decrease of ovarian activity, and owing to this failure of a peripheral ductless gland an increased effort is made by the anterior pituitary lobe to regulate by increased production of gonadotrophic hormone. It is, however, by no means the only activity of the anterior pituitary lobe that is changed, the accessory changes being entirely dependent on the endocrine constitution of the individual. There is, for instance in some, a simultaneously increased production of growth hormone which finds its outward expression in the so-called "witch's face." There can also occur a considerable underfunction of the thyroid. This apparently is secondary since the main effort of the pituitary anterior lobe is directed towards more production of gonadotrophic hormone, while thyrotrophic hormone is produced in a reduced quantity. The contrary state can also be seen, and that is an increased thyroid activity owing to an increased production of thyrotrophic hormone. Patients with low ketosteroid production (1 to 2 mg./24 hrs) during this climacteric condition are no rarity. They are effected by a decreased ACTH production of the pituitary anterior lobe. The whole picture of this endocrine imbalance during the menopause does not gain in clarity if one considers the disturbances that can occur in the endocrine function as a sequel to the changed mentation. We see here one of the best examples of how, once an endocrine vicious circle has started,

it is near to impossible to decide which is the primary change. Hyperthyroidism in the menopause can be initially caused by the spontaneous increased production of thyrotrophic hormone parallel the gonadotrophic hormone, or it may be just a sequel to psychic trauma that some women encounter when they see the most important phase of sex life is finished.

This complexity in endocrine deviations during climacteric conditions demands more thorough investigation and treatment than has been carried out hitherto. Women with menopausal difficulties are usually treated by the general practitioner, who is quite satisfied when the main symptoms such as headaches and hot flushes improve, and who leaves the psychological difficulties for nature to heal. The case that reaches the busy psychiatrist is not much better off since the psychiatrist is usually satisfied to see some improvement in the main symptoms. He might have tried, at the beginning, some E.C.T., but usually with little success as is often the case in menopausal depression. He then tries treatment with estrogens and is satisfied with a small amount of improvement. The psychopathological deviations, however, remaining during the menopause may become fixed and deteriorate, any of the known treatments being unsuccessful. It will therefore be necessary to pay much more attention to the endocrinology and psychology during and after the menopause.

The introduction of electroplexy and the great success of this treatment in involutional melancholia has cut short the endocrine evaluation of this state. Systematic investigation of the endocrines during this illness could be quite productive; particularly if the state is accompanied by underfunction of the thyroid or the adrenal cortex in which case supporting therapy on the basis of the endocrine disturbance found can prove very useful. Control of the endocrinological status during E.C.T. should in some cases also prove helpful, particularly where improvement is seen after 1 to 2 E.C.T.'s, and disappears when E.C.T. is continued in the orthodox way. What has happened can be seen by investigation of the 17-ketosteroid level, which when originally very low rises after the first two E.C.T.'s, then falls again, sometimes to even below the

normal range when E.C.T. is continued. It is assumed that this change in the 17-ketosteroid excretion rate indicates a stimulation of the adrenal cortex by the first and second E.C.T.'s, which is connected with mental improvement. Continuation of the E.C.T. leads to overstimulation and in consequence to exhaustion of the adrenal cortex.

The existence of the virile climacteric syndrome is at present sadly neglected, especially in mental hospitals too well equipped with E.C.T. machines. The condition can easily be diagnosed since the patients always have a very low 24-hour 17-ketosteroid excretion rate (below 3.0 mg./24 hr.) and very often an increased prolan excretion. The most unusual psychopathological features can accompany changes in the hormone equilibrium in accordance with the personality make up. There is, however, one always recurring symptom, the patient feels unable to deal adequately with his often very responsible job and develops, on the basis of this conflict situation, paranoid but mainly depressive features. There is a lack of confidence, self reproach and inability to concentrate often leading to suicidal tendencies. Often, although not always, this state is accompanied by impotence. Tearfulness is, in our experience, a most salient feature. This state, which occurs more frequently than is generally assumed, is rarely differentiated by the psychiatrist from involutional depression; but it can, unlike the latter, be treated very successfully with testosterone, which in suitable cases brings about a most astonishingly quick improvement in the symptoms.

The study of the immaturity of the adolescent (see Halkerston et al. [1957] and Bullmore, Reiss and Smith in this symposium) has resulted in better understanding of the immaturity found in the later life of men. The clinical endocrinologist accustomed to dealing only with a fully developed endocrine entity usually pays attention only to eunuchs and castrates, missing entirely the intermediate states. Clinically an interesting syndrome could be defined by us in men who had, like the immature adolescent, wide open inguinal canals with the testicles usually high in the scrotum. The testicles would, with slight manual pressure, slip back into the inguinal canal

or even into the abdomen. In some of them it could be observed that when they sat on a chair sideways and bent the trunk backwards the testicles retracted into the abdomen. Such a tendency on the part of the testicles to move into the abdomen means that this will most probably occur spontaneously under various conditions, such as sleep or contraction of the scrotum when cold. It is well known that for proper development and function the testicles need a temperature well below the normal body temperature and it can be appreciated that functional disturbances of various degrees can occur in men with open inguinal canals. Some of these people showed, even at the age of 19 to 23 years, no beard growth at all, while others had only a very scanty beard growth. None of them had any hair on the chest—all had a female pubic hair border (see J. Bradley's paper in this symposium).

It is most interesting to see how these individual patients always look much younger than their age would warrant. It would perhaps do to emphasize at this juncture that this form of immaturity in adult life is comparatively frequent. It can by no means be regarded as a pathological symptom. On the contrary, the immature person retains the capacity to learn much longer than the man who is fully developed at twenty-four, and is very often a much more interesting and amusing personality. No doubt people like Tamerlane, the brilliant Mongol conquerer of Western Asia, who had undescended testicles, and many others have seemed brilliant just because they were psychoendocrinologically not completely mature, and therefore more accessible to new impressions and situations. The hormone equilibrium of the immature person is, however, much more easily disturbed than that of the mature person and therefore, provided that his personality pattern is psychopathologically prone, precipitating causes produce mental breakdowns easily.

The Hormone Equilibrium after One Year of the Disease Process and in Chronic Patients

Some forms of disturbed hormone equilibrium are not repaired even after one year particularly if various physical treatments

were applied which deteriorated the hormone equilibrium. If one tries, at this time, to restore the disturbed equilibrium, one more often than not sees little change in the psychopathology. The patient has learned his mental disease exactly as other people learn a foreign language. He has memorized it, he has become conditioned to it, he is chronic. We are dealing here with a problem beyond psychoendocrinology, but one that should be tackled in a systematic way. It is obvious that whichever way is finally found, a preliminary repair of the hormone equilibrium will be helpful; since the patient will be able to adjust himself normally once the subject of the pathological thought content has been removed.

Only a few experiences are at our disposal in this direction. Sometimes when a patient has not improved after repair of the hormone equilibrium, one single E.C.T. can produce an almost miraculous improvement. Something similar can be seen occasionally when chronic patients react unsatisfactorily to deep insulin therapy (D.I.T.), and one single E.C.T. which, at the beginning of the treatment would have been completely useless, has a very beneficial influence. It seems that one of the functions of E.C.T. consists in the interruption of various newly acquired patterns of transmission in the brain which develop during long lasting mental disease. But all this is purely hypothesis and still awaits physiopathological explanation.

We have, however, also seen chronic patients in whom the hormone equilibrium has become normalized spontaneously during the long lasting disease. This normalization has no effect on the fixed psychopathology. There too we face a problem of reconditioning which, however, should be carried out in a way that does not disturb the hormone equilibrium again.

HORMONE EQUILIBRIUM DURING RECOVERY FROM MENTAL DISEASE

The Hormone Equilibrium during Spontaneous Improvement

When looking back at Figure 2 schematizing the elements concerned in a mental breakdown, we can see there only two variables since one can assume that the inherent genetic factors and the

basic personality pattern are unchangeable: (1) the precipitating emergency situation, (2) the hormone equilibrium. Accordingly, it should be possible that an acute psychopathologic condition improves, even if a previously disturbed hormone equilibrium remains unchanged, if only the immediate cause of severe stress, the emergency situation, is dealt with successfully. Indeed, many patients can be relieved just by sending them to the hospital and so freeing them from environmental stress. The unchanged disturbed hormone equilibrium, however, indicates the disturbed adaptability and forces us to give a bad prognosis toward recurrence of the breakdown, which is very often confirmed. If the patient leaves the hospital while still in this state of a disturbed hormone equilibrium, he very often returns in a comparatively short time.

We had occasion to observe another group of patients who arrived in the hospitals with a normal hormone equilibrium. These were either army cases who had their mental breakdown abroad and were sent back to the base hospital (Royal Victoria Hospital, Netley), or civilians who had been investigated in an observation ward for some time before they were transferred to St. Ebba's Hospital in Epsom. Their original diagnosis was usually a serious one (simple schizophrenia) but the great majority remitted a few weeks after admission to the hospitals. This observation enabled us to postpone any treatment in such cases as were admitted with a normal hormone equilibrium, and to wait for spontaneous improvement, without interfering with the already normalized equilibrium by conventional treatment procedures. It was assumed that these patients, during the time of their acute mental breakdown, had a disturbed hormone equilibrium which, however, improved spontaneously during the time it took to admit them to the other hospital.

The existence of a normal hormone equilibrium in patients admitted on the day of, or only three to four days after, their "mental breakdown" gave the psychiatrist the opportunity to see whether the patients' symptoms indicated a real pathological mental disturbance, or whether they were just an unusually temperamental

reaction form to an unpleasant situation. It may occur that some psychiatrically nontrained physicians send an individual to the mental hospital for observation as soon as his mental conduct threatens to get him into conflict with the conditions of his environment. There is, of course, the case of the malingerer to be considered. It is difficult to imagine that somebody who shows severe psychopathological symptoms and who becomes a real psychiatric problem, should maintain a completely undisturbed hormone equilibrium.

The most productive way of inquiring was the longitudinal investigation of individual patients, and coordination of their biochemical and mental changes. One of the most interesting results of this coordination was originally found in some cases where the psychiatrist withheld any specific treatment in order to see what change in environment, and ordinary hospital care and attention, could do for the patient. Some of these patients indeed showed a spontaneous remission and it was most interesting to see how the sometimes very disturbed hormone equilibrium came completely in order, sometimes before the mental improvement was finally established. Such investigations later led to a very useful procedure. The biochemists who had started to follow up the spontaneous endocrine changes in a newly admitted acute patient, whenever they saw a normalizing tendency in the changes of the ketosteroid excretion rate or of the thyroid, or where a normal hormone equilibrium was found, were able to tell the psychiatrist to withhold any physical treatment as the patient might recover spontaneously.

Examples of such longitudinal investigations and coordinations between biochemical and mental change were published by Reiss (1952), Sands (1956), and Batt et al. (1957).

The Hormone Equilibrium during and after Treatment with Conventional Routine Methods

By following up changes taking place during various psychiatric treatment procedures, and coordinating them with the simultaneously occurring mental changes, we were able to get much information about the biochemical and endocrinological changes which

are typical of recovery from a mental disorder or failure of the applied treatment. It seems that various empirical treatments are only successful in their course if the hormone equilibrium is improved. A statistically significant correlation between normalization of thyroid activity and mental improvement after various forms of treatment was found in a series of several hundred patients (Reiss, 1954). Thyroid activity alone was taken in this series as an index for the hormone equilibrium.

ELECTROPLEXY

In addition to a number of relevant activities particularly in the memory function, E.C.T. exerts an intensive action on the function of the ductless glands. E.C.T. acts, of course, as a general stress producing changes similar to various other stress agents.

By the way of the hyothalamus and the pituitary, which are stimulated, there is a marked interference with the function of the peripheral ductless glands. The quality of this interference is by no means uniform, and depends to a great extent on the initial state of the gland. Thus in a number of cases where the thyroid shows increased activity due to overproduction of thyrotrophic hormone, E.C.T. can undoubtedly lower the former into the normal range. This process is usually accompanied by mental improvement. The mechanism of the endocrine action in this case is not yet fully clarified, but it seems that the decrease in the thyroid activity occurs as a sequel to the increased mobilization of A.C.T.H. and other trophic hormones, which are antagonistic to thyrotrophic hormone. Occasionally in hypothyrotic patients the thyroid activity increases after E.C.T. up to the normal range. Such changes, however, have been seen only in cases where there is too little thyrotrophic hormone originally produced, and where a general pituitary underfunction was in existence. We have also seen, under the influence of E.C.T., considerable deterioration of hyperthyrotic and hypothyrotic states. The hyperthyrotic patients become, as assessed by the I^{131} tracer method, more hyperthyrotic, and hypothyrotic cases showed a still further decrease in their function. Both these changes were not accompanied by psychiatric improvement. Thus

the action of E.C.T. is rather unpredictable, but the situation might improve when better methods of thyroid investigation, particularly in regard to the assay of circulating thyrotrophic hormone, are available. Therefore, E.C.T. will certainly not be used as a method of choice in cases of thyroid disturbance which may be treated profitably by more specific methods.

E.C.T. stimulates the adrenal cortex by way of increased A.C.T.H. output. The most easily measured outward expression of this is an increase in the excretion rate of the 17-ketosteroids and the corticoids. This increase, however, is sometimes of short duration, reaching its maximum after 2 to 3 E.C.T.'s, and falling again sometimes below the normal range, indicating a considerable reduction of adrenal cortex and pituitary anterior lobe activity, due apparently to overstimulation.

We are still engaged in correlating changes in ketosteroid levels with changes in the mental state, but such longitudinal investigations take a very long time and often go wrong owing to a lack of coordination. The only fact we have seen so far is that the considerable mental improvement one sometimes sees after one or two E.C.T.'s is usually accompanied by a rise in the 17-ketosteroid excretion rate, in patients whose 17-ketosteroid levels were originally below the normal range.

DEEP INSULIN COMA THERAPY

Some members of our group have, during the last years in St. Ebba's Hospital, Epsom, (Batt, Bullmore, Kay, Reiss and Smith), and in the Royal Victoria Hospital in Netley (Brig. Robinson, Col. McGhie, Maj. Stewart, and Reiss), investigated the endocrine concomitants of deep insulin therapy and are still engaged in this interesting study. A number of important facts became apparent. Insulin coma therapy, like electroplexy, acts differently on patients showing different stages of hormone equilibrium. However, only those patients improve who show a normalization at the completion of the treatment. It seems that patients with a high adrenal cortex activity before treatment have a much better chance for recovery than those with the low or exhausted adrenal cortex function.

Sexual immaturity is always connected with a bad prognosis for insulin therapy. The present results of our investigations into the endocrinology of deep coma insulin therapy are reported by Dr. Kay in this symposium.

PHARMACOTHERAPY

There is a fundamental difference between treatment with drugs and hormone therapy. The drugs are not produced in the body as are the hormones. Drugs are given for their specific or empirical effects, and the duration of their effect is limited; while hormone therapy is an attempt to restore an endocrine equilibrium when this has been disturbed. Various drugs have, besides their actions on nervous activity and transmission, great influence on the hormone equilibrium, and it is possible that the latter action is the basis for their sometimes long-lasting beneficiary effects on disturbed mental activity.

That seems to be particularly the case during chlorpromazine therapy. The action of this tranquilizing drug is not only restricted to a reduction in the transmission of stress, but animal experiments have shown that it acts, according to the symptoms observed in the endocrine system, similar to a stressor agent. It has, apart from that, also a toxic action on the gonads, particularly on the ovary—the ovarian weight being significantly decreased one day after the start of chlorpromazine treatment.

In clinical practice arrest of the menstrual cycle is well known, as is occasional impotence in men. It will therefore be understood that one has to consider carefully to which patients chlorpromazine should be administered. It would, for instance, not be indicated in immature patients even if the momentary psychological effects were satisfactory, since the basic disturbance would be enhanced and no lasting effect could be reached (see paper of Reiss in this symposium).

PSYCHOTHERAPY

Since we know that emotional traumas can influence the hormone equilibrium it would only be logical that psychotherapy should be

able to influence a disturbed endocrine balance favorably. Indeed many of the improvements in the hormone equilibrium, with mental improvement following as observed after "routine hospital care and attention," could be ascribed to the success of psychotherapy and the attention given by the ward nurses and ward doctor. For the clinical endocrinologist it is also nothing new that particularly hyperthyrotic patients often improve without any treatment except hospitalization and rest, since hyperthyroidism has, in the majority of cases, a neurogenic pathogenesis. Indeed, twenty years ago rest cures were still the treatment of choice for hyperthyroidism.

Frequently patients arrive at the hospital in a very acute phase of mental disorder, showing simultaneously an extremely high index of thyroid activity. After about two weeks they are reported "settling down nicely" and are mentally improved, while the index of the thyroid activity also shows a tendency to fall, sometimes even to within the normal range.

We have, however, failed to see that psychotherapy, of whatever form, applied systematically has ever improved a disturbed hormone balance completely. This is most probably due to the fact that no psychotherapeutic procedure is ever free from the production of various mental stress conditions, even if only mild. Thus, in this case we face a similar condition, although on a smaller scale, as is found in certain other routine treatments, for instance, insulin coma therapy with its production of stress. Where the adrenal cortex activity is already reduced or exhausted, application of further stress cannot be beneficial; where, however, the adrenal cortex activity is increased, these psychological stresses are not strong enough to reduce it. Further, in immature persons, no stress condition whatsoever is beneficial. We have seen patients who received psychotherapy for many months without any success, and who after admission to the hospital, were treated on the basis of an intermediate thyroid underfunction with thyroid medication, and improved within a few weeks. It seems advisable to investigate the endocrine balance before embarking upon psychotherapeutic procedures of any kind. Improvement of the endocrine equilibrium makes patients much more accessible to psychotherapeutic adjust-

ment. As a matter of fact, there is practically not one member of our group who does believe that an independent hormone therapy is possible in psychiatry. Endocrine treatment can only bring the patient into a state where he is accessible to psychotherapeutic adjustment and reeducation dealing with the necessities for the adjustment of his life after leaving hospital. The situation can best be likened to one from another field of medicine, namely how after the amputation of a leg the orthopedist can supply a prosthesis. However, after receiving the prosthesis the patient still cannot walk. Some intelligent patients can do so, of course, with plenty of will power; the majority, however, must be taught to do so by the physiotherapist.

Freud foresaw the part endocrinology would play in psychiatry, but, as the classical worker he was, he himself, refrained from following up this way of inquiry, since it is something one cannot "flirt" with but which must be investigated very thoroughly. He used to insist that one should explore psychology to its limits while waiting patiently for the suitable advance in the biochemical analytical technique.

It might be worthwhile at this juncture to discuss the psychosomatic approach to mental disease in its relation to our psychoendocrine concept. The psychosomatic approach is based on the unquestionable observation that psychological illness and stress can produce a great number of physical symptoms (e. g.: indigestion, palpitation, headaches, giddiness, frequently of micturition, diarrhea, etc.) without presenting any psychological symptoms at all. In another group of patients there is peptic ulcer, ulcerative colitis, hypertension, neurodermatitis, and various forms of rheumatic disease, which develop as a result of primary psychological disturbances and are in their course definitely aggravated by emotional factors. Minski, for instance, pointed out quite correctly that the pain and discomfort of the ulcer patient is made worse not so much by dietary indiscretions as by emotional upsets and disturbances, and he also described the high percentage of ulcer patients in his series who presented obsessional or anxiety symptoms. However, he does not pay enough attention to the fact

that the important role cortisone plays in the development of ulcer is already well known. Further, there is no attention paid to the fact that psychic emotions stimulate the adrenal cortex to produce more cortisone. In analyzing the other psychosomatic diseases mentioned, one would always find that the endocrine function is wedged between the psychological stimulus and the finally developed organic disease. It is not sufficiently realized that we have to deal here with a psycho-neuroendocrine vicious circle as described above. The psychological stimulus acts through the known pathways on the peripheral glands. The increased function of the latter is responsible for the various physical illnesses (peptic ulcer, etc.). The hormonal and neurogenic feedback from the gland and the affected peripheral organ system influences again the cerebral condition, closing the circle of deterioration in a complex disease. Psychotherapy alone would only rarely be able to break through such a circle. One will have to consider whether attempts to deal with the endocrine links in this vicious circle before, or simultaneously with the psychotherapeutic procedures does not bring one much further in one's therapeutic attempts. Since, in the various psychogenic illnesses overactivity of the adrenal cortex seems to play a rather dominant role, it might be possible that sometimes treatment with hormones antagonistic to the adrenal cortex might have some beneficial effect. It might be relevant to mention in this connection that, acting on the basis of this consideration, Mr. Peacock at the Bristol Surgical Clinic saw some very encouraging results with the effect of Triiodothyronine on ulcer patients.

THE SCOPE OF HORMONE THERAPY

It appears that some endocrine deviations such as thyroid under- or overfunction can be treated much more easily on a rational endocrine basis than by some empirical treatment such as electroplexy, whose effect is still uncertain as far as endocrine changes are concerned. It must, of course, be clear that in this case the same hormone therapy cannot be used in groups of patients suffering under similar mental disturbances, but only on patients who

show similar endocrine deviations. Since the individual members of a homogenous mentally disturbed group can show a great variety of accompanying endocrine deviations, one can, at present, certainly rule out any hope of ever finding a special hormone therapy for depression, schizophrenia, etc. It must be clear that all the older therapeutic attempts, in which special hormone treatments were recommended for a whole psychiatric disease entity, (as for instance with thyroid hormone), and carried out on a large scale were bound to discredit hormone therapy in psychiatry.

The other danger in the introduction of a rational hormone therapy is the tendency to ask what per cent improvements were achieved. Taking the psychiatric disease entity as a basis for the calculation, such questions are completely unsuitable in the light of the facts explained above. It will never be possible to say, for instance, what per cent of acute female schizophrenic patients were cured with a particular treatment, but at the best only what per cent of those members of this patient group who showed, say, increased thyroid activity were cured by normalizing the latter. At the moment a description of a hormone treatment of even a very small number of patients, who were successfully (or unsuccessfully) treated, after careful hormone analysis is of much more value than a great statistical table about the success of some treatment based on a group containing members who are not physiologically homogeneous. Any hormone treatment in psychiatry can only be attempted on the basis of a preceding definition of the endocrine status of the patient.

The whole future of any therapy based on the psychoendocrine concept depends on further elaboration and refinement of the investigation methods at our disposal. Further progress in the investigation methods will permit us to recognize borderline disturbances more easily. It seems that many more mental disturbances are accompanying the various intermediate endocrine disturbances than the fully developed symptom. Some practical examples of hormone therapy in psychiatric patients are to be found in the first papers of this symposium.

CONCLUSION

It is the author's belief that the approach of psychoendocrinology to mental disease is based on some undeniable facts. The total sum of these facts is still very small. There appear on the horizon many quite formidable questions which will demand great efforts from the research worker. However, the situation is promising and the psychoendocrine approach, as a method, appears quite heuristic. One of its great advantages is that it has little space for pure speculation, contrary to many other research efforts at present in use in psychiatry. One at least tries to see soberly the many problems awaiting a solution, and not to take refuge in the Mephistophelian recommendation to mask a lack of understanding by the use of words. An apposite quotation is in Bayard Taylor's excellent translation of Goethe's Faust:

"Mephistopheles: On words let your attention center!

Then through the safest gate you'll enter
the temple halls of certainty.

"Student: Yet in the word must some idea be.

"Mephistopheles: Of course. But only shun too sharp a tension,
for just where fails the comprehension
a word steps promptly in as deputy.
With words 'tis excellent disputing;
systems to words 'tis easy suiting:
on words 'tis excellent believing;
no word can ever lose a jot from thieving."

In this connection it is worthwhile to remember that not only words but also figures can be deceptive. After some bitter experiences it was found that it was unwise to accept, uncritically, statements which appear exact and final only because they were based on an impressive array of statistics. It has been shown repeatedly that such statistics can sometimes be dangerously misleading if they are based on physiologically nonhomogenous groups.

It has been pointed out that from a research angle it is more economical to first circumscribe the endocrine disturbance before entering into the investigations of special biochemical disturbances,

the occurrence of which are a secondary result of the primary disturbance in the total hormone equilibrium. It is from this angle that one should view the efforts of a great number of biochemists who just cannot stop hoping that one day they will discover a "schizophrenia toxin" for example. They are still quite numerous, but it is time to realize that even the most beautiful piece of biochemical research can sometimes be just a red herring in our efforts to elucidate the development of psychopathological symptoms in humans. Such phases in a research effort are well known to the endocrinologist. He can remember too well the old days when tetany was first believed to be ergotoxin poisoning, then intoxication with guanidines, until finally parathormone was isolated and its physiological mechanism established. Similarly thyroid deficiency and adrenal cortex deficiency were also originally considered intoxications.

At present it does not appear very probable that special biochemical substances will ever be isolated which can, in spite of the existence of preformed personality patterns, produce specific disturbances of mentation, and elucidate the pathogenesis of psychiatric disease entities.

The approach to psychiatric disease, on the basis of principles evolved in psychoendocrinology, is at present necessarily slow and cumbersome.

The results achieved are rarely dramatic, and improvement of the patient sometimes takes considerable time. In some cases a straight therapeutic effect is produced by repair of the hormone equilibrium, but there remain cases in which such a repair can be best likened to the giving of an artificial limb. The patient must still be taught how to use it, and in the same way skilled psychological treatment is needed to adjust the patient mentally, once the hormone equilibrium is restored.

All this is disappointing to the psychiatrist, who is used to dramatic results, to quick changes, as after E.C.T. or leucotomy, to decisive treatments leading to cures, or complete failure. Also, psychiatrists in general still believe in the primary importance of

their personal relation with, or effect upon, the patient.

It is natural that considering all this many psychiatrists are often loath to learn the new and complicated facts concerning the physiology and endocrinology of mental disease—that they should prefer to rely upon time honored methods of treatment rather than embark upon investigations which take time, money and very much thought, for a result which remains uncertain.

It is, however, only along this hard road that any progress will be made in the knowledge of psychiatric diseases and their cures. Those who do not wish to accept this fact have only to look at the figures for the chronically ill mental patients in all countries, to know that not only is this cumbersome research important, but essential if there is to be any further advance in this young and immature branch of medicine.

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II

The Changing Concepts of the Role of Endocrine Function and Treatment in Psychiatry*

J. C. BATT AND M. REISS†

OUR CONCEPT of the significance of the interrelation of endocrinology and psychiatry has undergone such fundamental changes that a discussion of the relative facts, both of the theory and practice, would seem indicated.

In the past it had been customary to assign to any particular hormone, upon its discovery, the effects of either its over or under production with specific clinical psychopathological entities. We had to discard this approach because identical endocrine disturbances may be found in a number of various and dissimilar clinical groups, and a large number of patients showing variations in their endocrine make-up had no accompanying significant mental changes. This variation could only be demonstrated when the methods of investigation were sufficiently sensitive and reliable, and in consequence we were forced to the conclusion that the quality of the psychiatric symptomatology was most probably determined by the preformed personality of the patient rather than the accompanying specific psychological action of any hormone imbalance that was present.

The second important point was the discovery that the activity of the pituitary is related to the functions of the hypothalamus, and thus an obvious neuroendocrine interacting system is established. Since emotional or other stresses can exert their influence via this mechanism, and thus produce changes in the peripheral ductless glands, there is the effect of the feed back to be considered, and so a vicious circle can be initiated. In this way a further

*Read as introductory paper at the Symposium.

†St. Ebba's Hospital, Epsom, Surrey, England.

deterioration in the mental make-up of a suitable patient may occur. A realization of the neuroendocrine interaction gives us some indication of the developments to be expected in psychoendocrinology in the future. It is well known that any emotional stress can trigger endocrine changes, and it is only a matter of time before the endocrine concomitants to be expected in any psychiatric condition will become recognizable.

From the above it follows that we are not concerned with the action of one hormone producing a specific reaction, but that the feed back will produce changes in other peripheral glands through the effect on the pituitary and hypothalamus, and obviously mental stress may thus not influence only one but several of the ductless glands. In as much as the hormone equilibrium is an essential to the well being of any particular individual, it would seem important to investigate this fully in the future, and to realize that as the total metabolism of the body, including mineral and vitamin utilization, are dependent upon the interaction of the various hormones, these endocrine changes will be the basic elements for our consideration.

Hormone equilibrium is a contributory factor in the process of adaptation of the individual to his environment, and a disturbance of it, or an inability of it to cope with the various demands made upon it, will obviously be one of the main factors to be considered during the course of a mental illness. The multiplicity of these essential factors has led us to consider them under the main heading of psychoendocrinology, and we may summarize the various factors concerned in the production and continuation of a mental illness under the following headings:

- (1) The genetic and personality factors.
- (2) The precipitating cause.
- (3) The hormone equilibrium.

It will of course be realized that (3) and (1) are interrelated, and that under (3) we are concerned with the ways in which the endocrine system may react to any type of stress.

In approaching the concepts of therapy, based upon our ideas,

it is perhaps wise to note that the fundamental difference between hormone and other pharmacological substances is that the latter are given for their specific or empirical effects, but hormone therapy is an attempt to produce an endocrine equilibrium when this has been disturbed. Originally substitution therapy, as for instance thyroid in myxedema, or the inhibition of an overactive gland by its partial or complete removal, were the main methods at our disposal, but with the realization that the exhibition of one hormone may have far-reaching effects on other ductless glands the principle of simple substitution makes the similarity between this type of therapy and other pharmacological methods inapplicable; and in administering this type of therapy one must always be aware of the feed back principle to the controlling pituitary which makes it necessary for a careful survey of the clinical material at frequent intervals. Thus the principle of hormone therapy which we have adopted is that of the interplay of a number of factors, the balance between which is the desired goal, and when we find that there is a hormone disequilibrium present in the vicious circle of stress, personality pattern and neuroendocrinology, we feel that it is not unreasonable to attack this circle at the point of known weakness, irrespective of the type of psychiatric syndrome that may be present; and we feel that when a normal endocrine balance is established the patient is in a better position to withstand any increased environmental demand than he was previously exposed to, although he may still need some assistance from other therapists.

Realizing that this concept has not been widely held in the past we can now understand why it is useless, in the light of our present knowledge, to administer some particular hormone in a particular specific psychiatric syndrome and expect some significant success to occur; and in fact it is a disadvantage if it does occur, since on repetition by other workers the chances of failure increase, and eventually a statistical analysis will often point to the insignificance of the original findings because no consideration had been given to the state of the endocrine balance before the experiment, but merely to the similarity of the symptomatological pattern.

DISTURBANCES OF THE THYROID FUNCTION

For the purposes of this discussion we are discarding those cases of thyroid abnormal function in which the physical signs of either under- or overactivity are obvious. Since although these may be connected with certain psychological manifestations, the diagnosis is at once apparent, and presents no difficulty either to the physician or the psychiatrist but would rather turn attention to any psychiatric condition in which, on testing, an intermediate functional thyroid dyscrasia is found, irrespective of the type of psychiatric symptomatology present. This idea in fact is one of the main elements of our whole outlook, for we realize that the development of, for example, a myxedema may take several years, but at the beginning of the process the physical signs of this condition may be sufficiently insignificant to be overlooked or may even be undetectable to the trained observer, but if the patient so handicapped by his endocrinological imbalance be insulted by some environmental demand, and he is of a suitable personality pattern, he may well find himself the subject of psychiatric illness, the quality of which will depend upon his previous make-up.

It will of course be obvious that should this present as a schizophrenia then the underlying incipient failure of the thyroid may be undetectable to the trained observer, but if the patient so handicapped by his endocrinological imbalance be insulted by some environmental demand, and he is of a suitable personality pattern, such possibilities the patient may well be hastened into a regimen of deep insulin therapy quite unnecessarily. It is just these cases in which the psychiatric picture overshadows the underlying physical concomitant that present the greatest pitfalls in diagnosis. An excellent example of such illogical therapy is well illustrated by the casual giving of thyroid to schizophrenics, following the work of Hoskins and Sleeper when they reported some success with this hormone, and when their imitators gave no consideration as to the need for this therapy based upon a previous investigation of the function of this gland, and it is not surprising under these circumstances to find that this practice fell into disuse because of the apparently poor therapeutic results.

One of the first indications of the interrelation of body functions

with hormone therapy was demonstrated by Gjessing, when he limited his thyroid therapy to those cases where he considered a suitable change in nitrogen metabolism indicated it.

Our own practice, based on a more direct approach, is to investigate the various parameters of thyroid activity and other endocrine factors at the same time, and we have concluded that although some cases might benefit by the exhibition of this hormone, in other cases a suppression of an over acting gland will produce more promising results. Of course an investigation of the thyroid alone would be useless, since this would not take into account those examples in which the over- or underactivity was of primary origin or secondary to a pituitary dysfunction, and the third group of rarer cases in which the sensitivity of the tissues of the body is altered, and the whole of these factors must be taken into account in any individual case. After this enumeration of the principles involved we can leave this subject and await the later paper of Drs. Bullmore, Kay, Smith and Stott to give us in greater detail some of the findings that we have observed at St. Ebba's Hospital.

DISTURBANCES OF THE ADRENAL CORTEX

In relation to schizophrenia our particular interest has been directed towards those cases which, on admission to the hospital, have shown a low ketosteroid output. We have noted clinically that the histories often show factors that may be deduced as long-acting stress conditions, and we have wondered if this has not resulted in some exhaustion of the adrenal cortex. The response, however, to an injection of A.C.T.H. will often produce a positive increase in the ketosteroid output which, however, cannot be repeated the next day, and therefore the deduction seems not unreasonable. Without at once having any concept of the significance of these findings we analyzed a series of these patients who had been given insulin coma therapy, and found that their prognosis was bad as compared with those schizophrenics whose original 17-ketosteroid output was above or at the upper limits of normal, and it was interesting to observe that a number of this second group

showed a reduction in the 17-ketosteroid levels with a fall into or just below the normal range, but stabilizing themselves at a figure below the normal. Dr. Kay, however, who has investigated these ketosteroid curves fully, will be giving us his findings in a later paper. It might, now be useful to summarize some of the known facts about adrenal cortical activity established to date.

- (1) Adrenal cortex tumors may be accompanied by schizoid symptoms, particularly of the paranoid type.
- (2) These symptoms improve when the adenomata are successfully removed.
- (3) The effect of insulin coma therapy seems to be more successful when an originally increased adrenal cortex activity has been reduced and maintained inside the normal range.
- (4) It is well known that the administration of cortisone produces, in a certain number of patients, a psychiatric symptomatology.
- (5) It has been shown that dehydro-androsterone can induce aggressive and paranoid features when given therapeutically.
- (6) The importance of the onset of puberty, a period when a large amount of ketosteroids are released into the circulation, holds a time-honored position for the onset of schizophrenia.

We are of course only too well aware that our knowledge of the role of the adrenal cortex in psychiatric states is only elementary, and that the major part is yet to be elucidated, and have from time to time been confronted with paradoxical findings when investigating patients biochemically. For instance we have seen patients with a high 17-ketosteroid output but a low corticoid excretion rate who apparently improved on small doses of cortisone.

Perhaps sufficient has been said to show how impossible it is to give a substance such as cortisone or hydrocortisone to psychiatric patients without first assessing, as far as our present laboratory methods will allow, the need of the body for this particular substance, and we wonder what would have happened had the physicians used insulin in diabetic cases without the protection of

using the blood sugar levels as a basis for dosage, as we fear some experimenters have used new hormones on unselected groups of cases, with no knowledge of the body needs beforehand.

DISTURBANCES OF THE MALE GONADAL FUNCTION

In our previous paragraph a reference was made to puberty and its significance in relation to the onset of schizophrenia, and from this it would seem a logical step to investigate maturation in the male particularly. In as much as the later paper by Drs. Bullmore and Smith will give details of our researches in this field, together with discussion of the incidence, psychopathological significance and treatment of both sexual immaturity and prematurity, we propose here only to outline the principles involved.

We have thought this was one of our most rewarding investigations, since the rectification of the endocrine abnormality has been accompanied by unexpected improvement in the behaviour of our subjects. That immaturity in the adolescent has given us a better understanding of immaturity in the adult naturally follows, and we are again ignoring those cases of the fully developed eunuchs and castrates so dear to the clinical endocrinologist, and concentrating on the intermediate states on the principles discussed in our previous paragraphs.

Clinically immaturity in the male is accompanied by patent inguinal canals and an ability for the testes to retract into them or even into the abdomen, a sign that may be either demonstrated by slight manual pressure or even occur spontaneously when the patient lies down, or arches the back, or makes some similar movement; and since it may be presumed that such occurrences happen spontaneously, it naturally follows that when this physical sign is present the required lower external temperature, so essential for natural maturation, is denied these organs. Such men usually show an accompanying deficiency of the beard (if not its complete absence), a lack of hair on the chest and a female pubic hair distribution. We understand that Dr. Bradley is to enlarge upon this condition later. We do not suggest that this is of necessity a pathological state, nor do we suggest that immaturity of the intellect

accompanies immaturity of the gonads. However, should such a person have a premorbid personality vulnerable to such precipitating causes as he may be subjected to, the chances of his developing a psychiatric illness are increased, and it has been our experience that when this illness is a schizophrenia insulin coma has produced no improvement while the inguinal canals are still patent.

Impotence

The only remark here that we would like to make about this significant symptom is that it should not be considered solely from the point of view of psychopathology, nor from the point of view of sex hormones, for we have seen it as an early symptom of thyroid underfunction, and mention it here merely to show the impossibility of dealing with such a condition unless a full endocrine picture is obtained.

Homosexuality

The two factors which have attracted our attention in this condition are the force of the sex drive and its direction. The force may be increased by giving male hormones or reduced by giving estrogens, but the direction is unaltered. It is therefore illogical to use either as a therapeutic measure. Our interest in this subject has been the observed presence of homosexual tendencies amongst schizophrenics, which disappear on their recovery.

DISTURBANCES OF THE FEMALE GONADAL FUNCTION

This problem is considerably more complex than that of the males, since normal ranges for estrogens and pregnandiol are not known, but where an immaturity is present we would again emphasize the necessity for the complete examination of the patients, since amenorrhea may accompany a thyroid underfunction, and not require estrogen therapy at all.

Prematurity is perhaps entirely a clinical problem, and in this respect it should be remembered that a high 17-ketosteroid excretion rate may occur some time before maturation is complete. Thus the adrenarche precedes the menarche by two to three years. We freely admit, however, that so far we have been unable to find

any therapeutic line of attack in these cases, and are fully conscious of those contradictory examples where there is no increased keto-steroid excretion rate but a premature development of the secondary sex characteristics.

Premenstrual Tension

It would be presumptuous of us to refer to this in any detail when such authorities as Dr. Linford Rees and Professor Mall are following. We should therefore only like to say that in the treatment of this condition the symptomatic removal of the tension by tranquillizers should not be indulged without due consideration to their effect on the ductless glands. One of us will be discussing this in greater detail later.

Puerperal Psychosis

No time is perhaps more suitable for the precipitation of a psychosis, whose quality will depend upon the previous personality, than that of the arrival of a new baby immediately after the confinement. Whatever the symptomatology, we have found almost any peripheral gland may bear the brunt of the stress, and we have also observed that it is usual for a spontaneous normalization of the endocrine balance to occur, often preceding the clinical one, thus giving us a laboratory means of assessing the prognosis. If, however, this does not occur, it is only then that we consider it justifiable to interfere endocrinologically.

The Menopause

Both the male and female climacteric we are not discussing, since this Congress is devoted to schizophrenia. It may therefore be left to some other occasion.

DISTURBANCES OF THE PITUITARY ANTERIOR LOBE

While realizing the difficulties in assessing this accurately, we think it is fair to assume that, when a combination of peripheral glands is involved, the central control must be blamed. The clearest clinical picture of underfunction is seen in adolescents with retarded growth and emaciation, immature gonads and slight or

absent pubic hair, accompanied by a low thyroid activity and diminished ketosteroid excretion rate. No mention is made of the psychiatric symptoms because these are usually of a heterogeneous group, mainly psychopathic, hysterical or schizoid in type.

Our problem in these cases is to find some means by which the anterior pituitary can be stimulated, and the method which we have found most suitable is to give small doses of testosterone as the enanthate, as this is absorbed quite slowly, thus necessitating a dose of 50-100 mg. once in two weeks only. There follows not only an improvement in the biochemical findings, but also a satisfactory weight increase, accompanied by a disappearance of the mental symptomatology.

In the adult the same criteria are used in the diagnosis of this state, but since the secondary sex characteristics have already developed the falling out of pubic and axillary hair is often noted, and here we have observed the main symptomatology to be a complaint of gross anergia accompanied by loss of interest, but without marked depression. Bleuler has described similar cases. Our treatment is the same as in the adolescents.

States of pituitary overactivity with secondary thyroid hyperactivity and their treatment are being described later, but it may be mentioned that the giving of 50,000 units of estrogen daily can reduce an increased 17-ketosteroid excretion rate if it is due to an overproduction of A.C.T.H., and it is also the treatment that has been used by one of us in acromegalic cases.

CONCLUSION

We have endeavored in our review of the various psychoendocrinological problems to indicate the principles that we have adopted in deciding therapy in any particular case, and in doing so have shown the contraindications, basing our ideas on the concept that we do not look upon our findings as cause and effect, but merely at one point at which the vicious circle may be broken. The whole principle may be summarized by the suggestion that unless a demonstrable abnormality is present we have withheld any endocrine

approach to a particular case, but at the same time suggest that the frequency at which endocrine abnormality may be demonstrated indicates that a further investigation into the interrelation between psychiatry and endocrinology is more than warranted. The endocrinological approach does not clash with other forms of therapy but can act simultaneously with them, for once the balance in this field is restored the patient is more able to withstand stresses in his environment, either external or internal, and therefore other types of treatment stand a greater chance of success once this fault has been rectified. We have also suggested that it is wise not to submit random groups of psychiatric conditions to hormone therapy, and so provide inevitable disappointments for the observer. We feel that when considerations of the type we have suggested are applied to psychiatric treatment there is the possibility that this will give another weapon in the war against conditions which at the present day cause a larger amount of social incapacity than any other single factor.

III

Investigations of Thyroid Function of Mental Patients, and the Possible Use of Some Results for Rational Treatment Procedure

G. H. L. BULLMORE, W. W. KAY, D. W. SMITH AND
H. J. STOTT*

AMONG ENDOCRINE disturbances occurring with mental illness, disturbances of thyroid function have long been recognized. Our experience, gained by the systematic examination of the endocrine balance in mental patients, has revealed that there are many cases in which there is endocrine imbalance that does not manifest itself clinically, and which is only recognizable by special laboratory methods. In the fringe zone between the accepted normal and the clinically recognizable abnormal, there are many cases with endocrine imbalance or abnormality which may be described as "mild" or "border line" whose physical or mental life is disturbed and who do not recover until their endocrine imperfection is, or becomes corrected. There are patients whose psychiatric illness overshadows their endocrine imbalance. In others, the evidence of endocrine abnormality is contradictory and reliance on simple clinical observation alone might lead to wrong conclusions about the endocrine status. All this is especially true of patients with thyroid dysfunction.

In this paper a scheme is presented for the systematic investigation of patients with a view to detecting and assessing abnormalities of thyroid function and so obtaining a basis for rational therapy. The differentiation of thyroid abnormalities into primary and secondary types and the recognition and reconciliation of

**St. Ebba's Hospital and Mental Hospitals' Group Laboratory at Westpark Hospital at Epsom, Surrey, England.*

apparent contradictions and incongruities are discussed. Therapeutic procedures are detailed and illustrative cases are presented.

METHODS

The establishment of a diagnosis of thyroid dysfunction, or for that matter any endocrine dysfunction, of the "fringe" type cannot be made by any single test, clinical or laboratory. The application of a battery of tests is necessary. The single application of the battery of tests is not always to be relied on and repeat tests and longitudinal studies may be necessary in some cases. The close interrelationship of the thyroid with other endocrine glands necessitates an investigation of general endocrine function as an integral part of the thyroid studies.

Our full scheme of investigation is as follows:

I¹³¹ Tracer Test: The methods described by Haigh, Reiss and Reiss (1954) and Reiss et al. (1952) are used. No single parameter is relied on, but an overall assessment is made on the basis of the following parameters:

- (1) The I¹³¹ uptake slope measured over the thyroid during the first hour after the intravenous injection of 28 μ c I¹³¹.
- (2) The percentage of the injected I¹³¹ dose in the thyroid at 24 hours after the injection measured with a circular Geiger counter placed round the neck (Ring Count RC). This gives a count unaffected by the position of the thyroid in relation to the counter.
- (3) The I¹³¹ excretion rate in 24 and 48 hours (E₂₄ and E₄₈).

From these measurements various factors, whose normal ranges are known, are calculated. First, from the gradient of uptake of I¹³¹ in the first hour, a factor K is calculated. Then from this, using either the 24-hour uptake ("ring count") or the excretion rate in 48 hours, an index of thyroid function, I_T is calculated. Normally, the sum of RC and E₄₈ lies between 80 and 100 per cent of the dose injected. This affords a check on these measurements. In this way, even when RC is not at the peak value at 24 hours, a satisfactory index of thyroid function is obtained.

Basal metabolism rate is measured in the usual way on a closed circuit apparatus. In restless patients, the sleep technique described by Bartels (1949) and Fraser and Nordin (1955) is used.

Plasma protein bound iodine (PBI) is determined by the technique of Grossman and Grossman (1955).

Serum Cholesterol is determined by the method of Schoenheimer and Sperry (1934). Blood for both PBI and cholesterol determinations is collected by venepuncture from patients fasted overnight. Little weight is placed on the cholesterol determinations as they are of little use in border line cases.

Urinary 17-ketosteroids and 17-ketogenic steroids are estimated by the technique of Norymberski et al. (1955 and 1956) on 24-hour specimens of urine collected for the tracer test and at other times as necessary.

Careful clinical observations are made in all cases.

DIFFERENTIATION OF VARIOUS TYPES OF THYROID DISTURBANCE AS BASIS FOR THERAPEUTIC PROCEDURES

The application of laboratory investigation methods has enabled us to distinguish various forms of hypothyroidism which are at present not yet sufficiently recognized. This is a serious drawback in treatment, e.g. dried thyroid or thyroxine alone is not always suitable for the treatment of hypothyrotic cases even if they are manifest clinically.

Hypothyroidism can be either primary or secondary to pituitary underfunction. In the latter case it is more often than not accompanied by underfunction of other glands, particularly the gonads and sometimes the adrenals. The differential diagnosis between primary and secondary hypothyroidism can be made in the laboratory by giving thyrotrophic hormone for a few days. If the thyroid responds to this treatment, as shown by an increase in K and RC, the existence of a secondary hypothyroidism can be assumed.

We have frequently seen patients who, at the tracer investigation, show normal or even increased thyroid activity, but whose B.M.R. is below normal. Some of these patients can even show clinically

recognizable signs of hypothyroidism. The B.M.R. of such patients cannot be increased by administration of large amounts of thyroid. Their body tissues are insensitive to thyroid hormone.

This state has long been recognized. In 1885, Charcot described the Formes Frustes of hyperthyroidism. In such cases, many of the classic signs and symptoms of hyperthyroidism may be absent or the patient may show a mixed picture of hyper- and hypothyroidism. Thus, there may be thyroid enlargement and tachycardia, but a dry skin and a history of increase in weight. Such patients show a peripheral insensitivity to thyroid hormone. Cases of this type occur frequently in psychiatric patients.

In some cases of peripheral insensitivity to thyroid hormone, Triiodothyronine provokes an increase in oxygen consumption while thyroxine and thyroid extract are without effect. As a result of this observation it has been argued that the basic cause of the condition is a defect of the enzyme systems responsible for the liberation of the ultimate form of the hormone—Triiodothyronine or some similar substance—which is the effective agent within the cell. Some cases, however, respond to treatment with nicotinic acid or other vasodilators; during treatment with these drugs, the patient reacts normally to thyroid hormone. This suggests that the state of the peripheral circulation is a probable factor in determining the use of available thyroid hormone.

Peripheral insensitivity to steroid hormone also occurs. In patients with normal levels of 17-ketosteroid excretion and normal gonadal development there may be a complete absence of sexually determined hair and other steroid dependent sex characteristics (Robinson et al. 1956). This condition may be accompanied by insensitivity to thyroid hormones. Multiple insensitivity of this type is coming to be regarded by some workers as being related to pituitary underfunction. (Gordan 1954-55)

Another group of patients shows a symptom called by Reiss and Haigh (1954) "pseudo-hypothyroidism." In the tracer test, during the first hour after injection of I^{131} , these patients show a flat uptake slope identical with that of severely hypothyroitic patients. Their 24-hour I^{131} uptake rate, however, can be normal or even increased.

There is, thus, incongruity between the K and RC values. Such incongruity is usually associated with anxiety or excitement, and on prolonging the first observations beyond thirty minutes, an increase in the rate of uptake can often be obtained by simple reassurance of the patient.

Incongruity of this type is thought to be due to a generalized vasoconstriction affecting the thyroid vessels. This view is supported by the fact that when a tracer test showing the anomaly is repeated after the administration of ergotamine tartrate, the incongruity is decreased or abolished. Further, incongruity can be produced in the rat by carrying out tracer tests after the administration of adrenalin or after a variety of stress conditions, all of which are able to cause high adrenalin levels in the circulation (Badrick et al. 1954).

The various forms of hypothyroidism and hypothyroid-like states are summarized in Table 1.

Table 1
DIFFERENTIATION OF HYPOTHYROID-LIKE STATES

	K	RC	PBI	BMR	SENSITIVITY TO	
					THYROXINE	TSH
Primary Hypothyroidism	Low	Low	Low	Low	+	Nil
Secondary Hypothyroidism	Low	Low	Low	Low	+	+
Peripheral Insensitivity	Normal to high	Normal to high	Normal to high	Low to normal	Nil	K RC PBI } + BMR: Nil
Incongruity between K & RC	Low to zero	Normal to high	Normal to high	Normal to high	+	RC PBI BMR } + K: Nil

Treatment is necessarily based on this analysis of the type of underfunction.

In most cases of primary hypothyroidism the form of treatment adopted is the administration of thyroid in small doses at first, slowly increasing in amount. The dosage is controlled by the clinical state of the patient, with the aid of B.M.R. and the serum cholesterol determinations. Tracer tests are useless during treatment because it is known that thyroid medication reduces still further the I¹³¹ uptake. It is of the greatest importance that when the patient leaves the hospital arrangements be made for continuation of the treatment, which the patient needs as the diabetic needs insulin. If the treatment is interrupted relapse occurs.

As it is now considered that adequate amounts of circulating cortical hormones are necessary for the normal response of peripheral tissue to thyroxine, thyroid alone is used if the 24-hour output of 17-ketosteroids and corticoids is normal. If the output of 17-ketosteroids and corticoids is below normal, small doses of cortisone are given in addition.

For secondary hypothyroidism the logical treatment is the use of T.S.H. Cases of this type are usually complicated by failure of other endocrine glands consequent on pituitary dysfunction. Each case should be treated in accordance with an overall endocrine assessment. Where underfunction of several glands is established, total stimulation of the anterior pituitary lobe can be achieved with very low doses of testosterone. We use for this purpose testosterone oenanthate which has a very slow absorption rate and is, therefore, used as a depot preparation.

Where peripheral undersensitivity is found it is necessary to increase the access of circulating thyroid hormone to the peripheral tissues. This is achieved by the administration of vasodilators, e.g. nicotinic acid in doses of 100 mg. t.d.s. In some cases this may need to be supplemented by graded doses of Triiodothyronine.

When hyperthyroid activity is primary the manifestations of the hyperthyrotic state may occur accompanied or unaccompanied by signs of sub-normal function of other endocrine glands (especially the adrenals). On the other hand, increased outflow of thyrotrophic

hormone, giving increased stimulation of the thyroid, will cause increased output of thyroid hormone, if the thyroid is capable of responding to the increased stimulus, and produce the manifestations of hyperthyroidism. The hyperthyrotic state will then be secondary to overactivity of the anterior hypophysis and may be associated with other evidence of endocrine overactivity.

If hyperthyroidism is associated with increased excretion of 17-ketosteroids or corticoids or with exophthalmos or ophthalmoplegia, it is always secondary to hyperfunction of the anterior lobe of the pituitary. Treatment must be directed to reducing pituitary activity; antithyroid drugs are often contraindicated.

In cases of primary hyperthyroidism antithyroid drugs were used. It should, however, be emphasized that drugs of the Thioruacil group do not permanently prevent the uptake of iodine by the thyroid; they merely prevent the conversion of inorganic iodine to organic compounds such as di-iodotyrosine and thyroxine. In many cases the gland enlarges and becomes more vascular. I^{131} tracer tests subsequent to the administration of propylthiouracil may thus, after several months' treatment, show a normal or high uptake of the iodine, yet this may be accompanied by a fall of the B.M.R. This dissociation between the I^{131} tracer uptake and the B.M.R. and P.B.I. in longstanding use of antithyroid drugs will be discussed elsewhere.

In cases of secondary hyperthyroidism thyroxine or Triiodothyronine was employed to suppress T.S.H. production, often in conjunction with cortisone to guard against the precipitation of a thyrotoxic crisis. In severe cases propylthiouracil was given in addition to Triiodothyronine. In one case where there had been excessive loss of weight and the 24-hour 17-ketosteroid excretion rate was low, testosterone propionate was given in addition for its known anabolic effect.

When there was evidence that the hyperfunction of the pituitary was not limited to stimulation of the thyroid alone and that other endocrine glands were being stimulated to over production of hormones, estrogens were used in doses of 20,000-50,000 units by I.M.I. daily over a period of at least three weeks. In these cases

the 24-hour excretion of 17-ketosteroids and corticoids was measured twice weekly to estimate the effect of treatment. The fall of the output pointed to successful suppression of the anterior pituitary.

The various treatment procedures and their control by laboratory investigations are summarized in Table 2.

Table 2
TREATMENT AND CONTROL OF THYROID DISTURBANCES

STATE OF THYROID	TREATMENT	TREATMENT CONTROLLED BY
Hyperthyroidism:		
Primary	Anti-thyroid drugs	I^{131} tracer BMR PBI
Secondary	Estrogens Triiodothyronine Antithyroid drugs	I^{131} tracer BMR PBI 17-Ketosteroids
Hypothyroidism:		
Primary	Thyroid preparations	BMR Cholesterol
Secondary	Substitution: TSH Stimulation: Depot Testosterone	I^{131} tracer BMR PBI 17-Ketosteroids
Peripheral Undersensitivity	Nicotinic acid or other vasodilator Triiodothyronine	I^{131} tracer BMR

RESULTS OF TREATMENT

Examples of treatment based on and controlled by the laboratory investigation of the thyroid activity were published by Reiss et al. (1953) and Robinson et al. (1956). Statistical evaluations showing a significant correlation between the normalization of the thyroid activity and mental improvement were reported by Reiss (1954).

Some typical examples of our treatments are described.

A case of Primary Hypothyroidism

This man had been well till he was 19; but after an attack of "gastric 'flu'" during army service he had never regained full health. He had been in and out of mental hospitals, and had been considered probably schizophrenic on account of his general slowness and lack of activity. He had been unsuccessfully treated with E.C.T. On admission his illness had lasted ten years.

His I^{131} Tracer test showed considerable underactivity. No uptake could be detected in the first hour; the 24-hour uptake was 6%. The 17-ketosteroids were normal (11.8 mg./24 hours). He was treated with dry thyroid and became stabilized on 4 gr. daily.

He made slow but steady improvement over a year; eventually he reached such a good level of briskness and worked so well in the hospital that it was thought he should obtain a job outside. This, however, proved just beyond him.

Cases of Primary Hyperthyroidism

This man, in his late twenties, had an ineffective schizoid personality. He had been under treatment for three years for depression, alcoholism and homosexuality. On admission the diagnosis of schizophrenia was considered, and not long afterwards he was undoubtedly psychotic for a time. He was often awkward to handle and indulged in alcoholic and homosexual escapades.

Investigations showed a high thyroid activity. The 24-hour I^{131} uptake was 73% (later 80%). P.B.I. was 7.3 $\mu g./100ml.$ B.M.R. +13%.

He was treated with "neomercazole" (20 mg. daily). Three months later the 24-hour uptake was 30% and the P.B.I. 5.3 $\mu g./100 ml.$ Clinically there was an all 'round improvement. He lost his depression and gave up alcohol. He became more practical and his personal relationships improved. Schizoid features were virtually absent; his homosexual urges were lost and he became mildly and immaturely heterosexual. He departed from hospital very much improved and obtained a job which he held for some months.

A fifteen-year-old girl who was orphaned nine months before admission when her mother died of cancer. Her performance at school had deteriorated. She had started behaving oddly—sitting around in the rain during school hours and drinking ink. She showed thought blocking prior to admission. She had not lost any weight and appeared quite plump.

Initial investigations: Sleeping pulse 82/92 per min. Resting B.M.R. +39% I^{131} Tracer Test: K too steep to register, RC 69% (above normal).

Repeat Investigations one month later: there was only little change in results of laboratory investigations. B.M.R. +25% I^{131} Tracer Test:

K, 15.3 (well above normal) RC 62% (above normal) 17-ketosteroids varied from low to normal.

Treatment: Propylthiouracil 200 mg. daily.

Result: She gained weight. The B.M.R. fell to +2% and -6%. She had become normal mentally and was discharged to a hostel. When seen nine months after discharge she was still well and working.

Single Female aged 38. She was suffering from recurring phobic illness, marked panic attacks and fears. She had psychotherapy at a "neurosis center" without effect. She attempted suicide, showed hysterical behaviour, and was very emotional, agitated, talkative, depressed and generally very difficult in the ward.

Family History: Her mother had goitre.

Investigations: Warm skin, tremor of hands, loss of weight. Eyes bright and moist, no exophthalmos or lid retraction. Tachycardia (sleeping pulse 80-100/min.). I^{131} Tracer test showed marked increase in thyroid activity (K 29, RC 75%). Ketosteroids in low normal range. B.M.R. +100%, P.B.I. 9.8 $\mu g/100$ ml. (considerably increased).

Treatment: Propylthiouracil 200 mg. daily, later reduced to 100 mg. daily.

Result: Left hospital three months after treatment, virtually symptom free except for some loss of confidence.

A seventeen-year-old girl who was unable to go out or to travel because she had attacks of panic and fears that she would faint or die outside her home. She was difficult, rude, cheeky and abusive at home. She said that she developed sudden sweats and feelings that she might faint. She had lost weight. Her behaviour towards her parents was so trying that she was sent to live with an aunt at the seaside, but to no avail. There was no overt evidence of hyperthyroidism, but investigation was thought worth doing.

Investigations: B.M.R. +24% and +25%. I^{131} Tracer Test: RC 66% (which is considerably above the upper normal limit). 17-Ketosteroids fluctuating just below normal range.

Treatment: Standard on propylthiouracil 200 mg. daily.

Result: After approximately one month B.M.R. +1%. I^{131} Tracer Test: RC 53% (almost normal). Became symptom-free and was discharged home with the intention of finding employment. She has gained 7 lbs. in weight.

A Case of Secondary Hyperthyroidism

A married woman, aged 45, with children.

Previous history: Depressive illness seven years before, treated with E.C.T. and recovered.

Present Illness: Pneumonia four months before admission, and "never felt well since." One month before admission became very

depressed, with poor appetite and sleep, was tearful, agitated and felt she had "let her family down." Restless and wringing her hands. She was seen at home and admitted to hospital as an agitated depression four days later. She had lost weight.

On admission she had a tremor of the hands, warm moist skin, high pulse pressure, slight exophthalmos with some lid retraction and impaired ability to gaze upwards (i.e. exophthalmic ophthalmoplegia).

Investigations: B.M.R. +85% P.B.I. 10.3 $\mu\text{g}/100 \text{ ml}$. (well above normal). P.B.I. (repeat) 6.8 $\mu\text{g}/100 \text{ ml}$. (above normal). Serum Cholesterol 145 mg.% (below normal). I¹³¹ Tracer Test: (Dose given orally) RC 59%.

Treatment: Triiodothyronine 80 μg . daily. Cortisone 50 mg. daily. Later she was given propylthiouracil 200 mg. daily and testosterone mg. 10 daily by I.M.I.

Result: The thyroid activity returned to normal and all symptoms except the mild ophthalmoplegia cleared. Became mentally symptom free and was discharged to go home.

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IV

Endocrine Investigations in a Juvenile Psychiatric Unit

G. H. L. BULLMORE, M. REISS, and D. W. SMITH*

THE MALE Juvenile Unit at St. Ebba's Hospital accommodates about 40 boys, with very few exceptions, between 12 and 16½ years. The mental disturbances dealt with cover a wide range, from behavior disorders to schizophrenia.

An increasing use of endocrine investigations has been made in the Unit since 1954, and as a result certain lines of treatment have been developed as an important adjuvant to the previous methods of in-patient care, which included benevolent discipline, schooling and psychotherapy.

The division of adolescent psychiatric disease into homogeneous groupings is a matter of great difficulty, and, if achieved, correlates but very partially with the type of endocrine imbalance found. Likewise, a wide range of psychotic or neurotic reactions may be associated with the same endocrine picture. On this account we have not yet been able to make a statistical assessment of our therapies.

This paper outlines the nature of the methods of investigation, the clinical and laboratory findings, etc., and the nature of treatments given.

METHODS OF INVESTIGATION

Clinical endocrinological investigations were coordinated with laboratory investigations, psychiatric interviews, school and ward reports. Psychological tests were done before, during and after treatment.

The thyroid activity was assessed by a battery of tests (I^{131} tracer test, P.B.I. and B.M.R.) as described in the paper of Bullmore, Kay, and Stott (page 52).

**St. Ebba's Hospital, Epsom, Surrey, England.*

The total 17-ketosteroids were determined by the method of Callow, Callow and Emmens (1938), and later by the 17-ketosteroid method of Noryberski, which gave values in reasonable agreement with the original method. The values given by Talbot and Butler and co-workers were taken as the normal range for 17-ketosteroids in various age groups. They are in agreement with the experience of one of us gained a few years ago by investigation of boys in a public school (Reiss 1954).

The β 17-ketosteroids were determined either by digitonin precipitation or by total absorption chromatography on alumina according to the method of Pond (1951). This method enabled us to determine the androsterone and etiocholanolone fractions of the urinary 17-ketosteroids, which seem, particularly in immaturity, more important than the total 24-hour 17-ketosteroid excretion rate.

Corticoids were determined mainly as ketogenic steroids by the method of Norymberski.

RESULTS

103 boys were investigated. Table 1 shows the distribution of the cases in four groups, depending on the predominant endocrine features found. In only 14 per cent of the boys could no endocrine deviation be found, either clinically or by laboratory investigations. Most of them improved as a result of routine hospital care and attention, education in the school attached to the Unit, and psychotherapy where it was needed.

Disturbances of thyroid activity were found in about 16 per cent of the cases. Their treatment followed the lines described in the paper of Bullmore et al. (page 52). One case of especial interest will be described:

Table 1

Normal hormone equilibrium	14	14%
Immature	48	46%
Premature	25	24%
Thyroid disturbances	16	16%
Total	103	100%

A boy of 14 from an unstable home, who developed fits when two years old, grew up unruly, boastful and aggressive. From the age of seven he was in institutions of many kinds—an epileptic colony, three mental hospitals, and various day and residential schools. When admitted, he had taken to wandering and singing in the streets for money. He had had no fits for 4 years, but had very violent tempers. At first hospital regimen, psychotherapy and adjustments of anticonvulsants produced no worthwhile effects. His impulsive outbursts included throwing plates with intent to harm. At this stage it was found that his thyroid activity was very high. Treated with Carbimazole he gradually settled down and made good use of the hospital facilities. The charge nurse, the former target of the plates, reported him as "willing to do anything for you" and "works like a bloody horse." He got outside work in a garage, and on being discharged home he got a first class testimonial from his employers.

The occurrence of epilepsy in hyperthyrotic juveniles is one which is at present engaging our attention. We do not yet know whether the hyperthyroidism is a sequel of the epileptic hyper-excitability or vice versa, since it is known, from the work of Woodbury and others (1952), that following the exhibition of thyroid hormone the threshold of the brain to electrical stimuli is reduced. A decision is not made easier by the occasional observation that increased thyroid activity can be reduced by Epanutin, while on the other hand, the frequency of epileptic seizures is reduced by treatment with antithyroid drugs. This is a field which urgently demands systematic investigation.

By far the greatest number of cases investigated showed disturbances in maturation, as can be seen in Table 1. There is a wide variation in the normal development during the ages 12 to 16½ years. To define the borderline is very difficult, but it can be safely said that our patients were, at both ends of the scale, either at the extreme limits of normal or beyond it.

Figure 1 illustrates the range between two cases lying near the means of the two groups of delayed and premature development. These are the genitals of two boys of exactly the same age (13½).

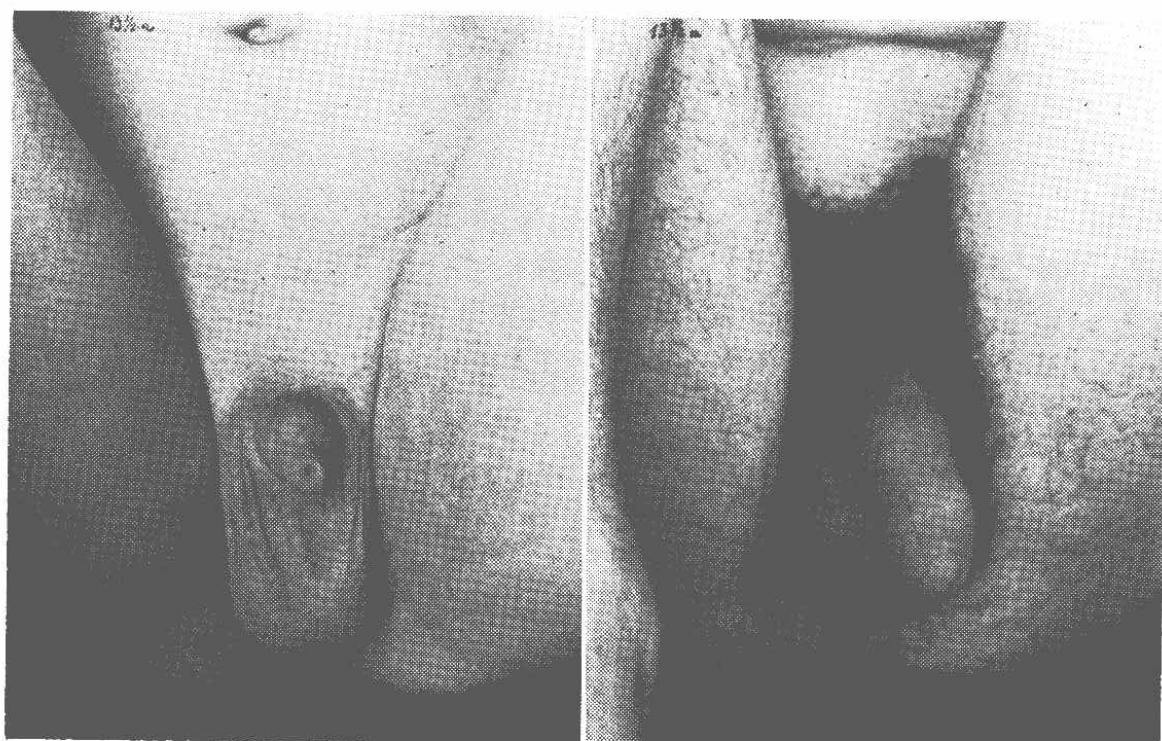


Figure 1

In the first case, the testicles are no larger than beans and the penis is infantile. There is no trace of pubic hair. While the other boy has the genitalia of a fully grown man, pubic and body hair is well developed, and his voice is broken.

Table 2

IMMATURE	PREMATURE
Shy, inferiority feelings.	Self-confident.
Asocial, bad mixers.	Social and good mixers.
No friends.	Many friends.
Poor at games.	Very good at games.
Always led and bossed in a gang.	Mainly leaders.
If criminal offenders always persuaded by others.	Primary criminals.
When schizophrenic mainly of insidious onset, inability to concentrate, retarded, few hallucinations.	If schizophrenic, sudden onset, dramatic symptoms, vivid hallucinations, aggressive.

The two groups show contrasting psychological pictures which are shown in Table 2, although the psychological mechanism of "compensation" is but one fact that tends to obscure the picture in the immature group.

IMMATURITY

Primary Pituitary Underfunction

There is one form of immaturity which must be regarded as due to primary pituitary underfunction. Several peripheral functions are disturbed, such as growth, gonads, adrenals and thyroid function. There is no sign of axillary or pubic hair, the boys are usually emaciated. Psychologically they often show anorexia, in addition to the varied psychopathology which may occur in immaturity.

The 24-hour 17-ketosteroid excretion rate of these boys is always low, sometimes less than 1 mg., while the thyroid activity may be low but can also be increased, owing to the lack of gonadal and adrenocortical antagonism. One of us (M. R.) had an opportunity of observing such boys for years at a time when the present endocrine treatment was not available, and where attempts at substitution therapy were undertaken without success. We believe that substitution therapy is useless in such boys. The best growth hormone for instance will not produce growth when the thyroid is disturbed; and if it does produce growth when the thyroid is normal the gonads will be unaffected. In those cases having marked anorexia and emaciation on admission, treatment was a matter of urgency, and even a life saving procedure. In the other cases, it was useless to await spontaneous maturation. The only therapeutic procedure at the moment is based on an attempt to stimulate the total function of the anterior lobe of the pituitary. This can be done with very small doses of testosterone in the form of a depot preparation which permits the absorption of about 1.0 m.g. testosterone daily. Criteria for success in stimulating the pituitary were the considerable rise in the ketosteroid excretion rate (which was greater than could be accounted for by the testosterone absorbed from the depot), and a rise in the originally depressed thyroid activity. Apart from that, increase in the body length by one inch in about six weeks, and in body weight by 14 pounds in the same period, were considered criteria for successful endocrine treatment. Success in the physical treatment was accompanied by mental improvement, sometimes remarkable.

The following are histories of one neurotic and one psychotic boy, and illustrate this treatment:

A boy of 12, described as "an accomplished juvenile hypochondriac of bird-like appearance," was shy, solitary and indifferent to games. Of recent months he had complained of feelings of suffocation, a lump in the throat and abdominal pains. He refused to attend school, where he was much teased and flew into rages.

His height was 4 feet 7 inches; weight 68 pounds; his genitals and pubic hair were poorly developed. Thyroid activity and ketosteroid excretion rate were very low.

He was treated with testosterone enanthate 100 mg. weekly. He gained 14 pounds in weight and an inch in height; the genitals increased in size. About a week after starting treatment he claimed to feel better, being able to run about and not be worried by teasing. The thyroid activity rose to normal levels. When the patient departed 11 weeks after admission he said he had no bodily symptoms, and that he had lost his anxiety and his tempers. His educational ability improved, and he expressed a desire to return to his school.

An Irish boy of 13, referred as a case of schizophrenia, who for some months had displayed disturbed behavior, had broken windows, torn up his clothes in rage, laughed and talked to himself, and would not wash or go to bed. On admission he was found to be a tiny under-weight boy with a marked Irish accent and elfin-like appearance. He looked bewildered and was considered aurally hallucinated; he was preoccupied with talk about his conscience and his sins. His weight was 77 pounds, and his height 4 feet 9 inches. The excretion of steroid hormones was low, but his thyroid activity was within normal range. He settled well in hospital, and showed in the first weeks some slight improvement. He was treated with small doses of testosterone depot. Three weeks after the first injection he was well enough to go on weekend leave; he began to work off his aggressive ideas by punching a pillow; he became less anxious, mixed better, and claimed to have settled down well in hospital and not to be worried any longer by sins and conscience. His pixy-like appearance had given way to that of a normal youth, and he strode about like a young man. In 3½ months he had gained 1¼ inches and 19 lbs. After three injections his mother demanded his discharge at a time when he was on leave, although not fully well. She claimed he was so much better it would upset him to return.

In parenthesis it may be remarked that the same treatment has also proved successful in girls of the female Juvenile Unit, who were admitted with symptoms similar to those described above. Sands (1956) has already published one of these cases which we were able to observe.

Sexual immaturity

The failure of maturation in these boys is restricted to the gonads. Physically the boy looks less than his years, height is usually below normal, although we have recently seen a boy of 16 who looked eunuchoidal and was already 5 feet 6 inches. The span is usually less than the height, and the ground pubic ratio of height is below the normal range for the relevant age. The voice is never broken, even in boys of 16 years.

The testicles are situated high up in the scrotum and commonly, with slight manual pressure, may be pushed up into the inguinal canal or even into the abdomen. In a few of these patients it was found that if the boy sat sideways on a chair and bent his trunk backwards, the testicles retracted into the abdomen of their own accord. In a few patients the testicles could only be seen when the patient was sitting; as soon as he started to walk one or other of the testicles slipped back into the abdomen.

The pathophysiological significance of this condition depends on the ease with which the testicles may return to the abdomen spontaneously, as for instance during sleep or when the scrotum contracts with cold. Impaired testicular development resulting from the effect of the higher intraabdominal temperature follows as a consequence of this behavior, and tends to perpetuate the immature state of these boys. In such cases spontaneous improvement is unlikely.

The 17-ketosteroid excretion in the majority of these immature boys was below the normal range, but could be normal or occasionally even above it. This is easily understood when one considers that the gonadal contribution to the total 17-ketosteroids is comparatively small, and that various stress factors connected with the mental breakdown, or the preceding environmental conditions, were likely to mobilize various amounts of ketosteroids from the adrenal cortex.

Substitution therapy with large amounts of testosterone is contraindicated in such boys, since it tends to depress the pituitary

activity. Our present approach, therefore, is to stimulate the gonadal development with chorionic gonadotrophin (1500-3000 int. units daily). Maturation of gonadal function is usually achieved in 4-6 weeks without danger of androgen overdosage. Successful treatment at a physical level shows increase in size of all sexual organs, narrowing or closure of the inguinal canals, and growth of sexually determined hair.

The main characteristic change in the excretion of steroid hormones during this treatment is a rise in the androsterone and etiocholanolone fractions of the 17-ketosteroids. The total ketosteroids excretion rate also rises, but mainly in those cases where it was low before treatment. Where it was high, owing to increased stress conditions as already discussed, it need not change, and

Table 3

Case No.:	Duration of treatment (days).	Number of determinations.	Total 17-ketosteroids (mg./24 hrs.)	Ketosteroid fractions mg./24 hr.				
				Artifacts.	Dehydroepiandrosterone (D.H.A.).	Androsterone.	Etioclanolone.	11-oxy-17-ketosteroids.
1 13 yrs. 1500 i.u. Chor: Gon: daily.	—	6	6.2	0.4	0.6	2.2	1.6	0.9
	14	1	8.4	0.5	0.5	4.1	2.3	0.7
	20	1	11.1	1.1	0.4	3.2	4.8	1.1
	27	1	10.4	0.7	0.9	4.8	2.3	1.4
2 15 yrs. 1000 i.u. Chor: Gon: daily.	—	3	3.1	0.4	0.5	1.0	1.0	0.7
	7	1	3.1	0.3	0.3	0.7	1.2	0.3
	12	1	2.6	0.2	0.2	1.1	0.8	0.3
	27	1	10.0	0.7	0.4	5.3	2.3	1.0
3 14 yrs. 1000 i.u. Chor: Gon: daily.	—	1	11.3	1.4	2.2	1.9	3.0	1.3
	2	1	17.9	2.2	2.4	5.3	3.8	1.4
	6	1	15.7	1.7	1.7	5.7	4.8	1.2
	14	1	12.9	0.7	1.5	6.1	2.1	0.6
	27	1	19.9	2.6	2.1	8.6	3.9	2.1

can even fall below the original level when, with mental improvement, the patient's emotional stress is reduced, and with it the increased activity of the adrenal cortex. This assumption is made more probable since cases were observed where an increased thyroid activity was reduced to normal after a few weeks' treatment with chorionic gonadotrophin, which is apparently also due to the reduction of the emotional stress.

Some examples of the typical change in the ketosteroid excretion rate after treatment with chorionic gonadotrophin are shown in Table 3.

Two typical case summaries of patients treated with chorionic gonadotrophin will now be given, one again being "neurotic" and the other "psychotic":

An illegitimate boy of 14½, torn in his attachments to his mother and two foster homes, was at some disadvantage compared with a more intelligent and less rejected illegitimate half-brother. On admission he was described as a solitary, dejected, enuretic boy, small in stature, and underdeveloped intellectually, socially and emotionally. He had a pleasing but pathetic smile.

For almost a year he was treated with routine methods, and made only the most modest improvement. At 15½ he showed no real evidence of puberty and had added only 3 pounds to his admission weight of 77 lbs. His height, however, had increased from 4 feet 9¼ inches to 4 feet 11 inches. The 17-ketosteroid output was low; the thyroid activity slightly increased.

Two months after treatment with chorionic gonadotrophin 1000 units daily he had developed puberty, his height had increased by one inch and his weight by 16 pounds. His enuresis was greatly reduced in frequency, and he was able fully to take his place with the biggest boys. His I.Q. measured on the Wechsler Scale had risen from 84 to 94. The ketosteroid excretion rate had risen, and the thyroid activity was in the normal range.

At a formal interview he remained diffident, but met outside the ward he was normal enough and could be heard bellowing at his friends with gusto. He is now 16 years old and has just left the hospital and started work.

The second case, a boy of 13, the fourth child of six, was the eldest son of an ineffective but affectionate family. He was a poor scholar, inclined to show off or be truant when upset. After an operation for hare lip at the age of 11, he had become preoccupied with his bodily health. When he was eventually taken to a psychiatrist, he was de-

scribed as in a depressed panic state and judged to be auditorily hallucinated. On admission he was anxious almost to the point of panic, and talked in a sad, complaining way on the verge of tears. He showed some pressure of talk with flight of ideas; he also had ideas of persecution and influence and fears of harming or being harmed by his fellows. Some of his ideas were sufficiently bizarre to warrant the label schizophrenic. His thyroid activity on admission was increased, as shown by a high I¹³¹ tracer test, high plasma protein bound iodine, and a raised B.M.R. His admission weight was 98 pounds and height 5 feet 2 inches. His testicles were small, his inguinal canals open; he had no pubic or axillary hair.

Treatment with chorionic gonadotrophin 1500 units daily was started, and he improved fast physically and rather more slowly mentally; while on this treatment he put on 22 pounds and some 2 inches. Formal psychological testing showed the disappearance of psychosis; clinically, after going through a phase of overactive cheekiness, he emerged confident and in good spirits, with only faint traces remaining of his morbid symptoms. He was recently discharged weighing 135 pounds, height 5 feet 4 $\frac{3}{4}$ inches, after a stay of eight months.

In concluding our description of immaturity, we would like to draw attention to a small group of patients who excreted low amounts of β -ketosteroids and were, therefore, treated by Sands, Strauss and other workers with dehydroandrosterone, sometimes with good results. It is not yet clear how much of this substance exerts a specific action, or to what extent it was transformed to α ketosteroids and exerted a stimulating action on the anterior pituitary lobe after this transformation. Our experience with chorionic gonadotrophin has led us recently to abandon this approach and to prefer the considerably shorter treatment with gonadotrophic hormone, which apparently mobilizes all the steroid hormones the body needs. This form of therapy has the advantage that having initiated maturation the process apparently continues without further treatment.

The physical signs of the premature group have already been described, together with some of the psychological and psychopathological qualities associated with this condition. The configuration, genitals, body hair, and voice are those of a grown man.

The 24-hour 17-ketosteroid excretion rate is mainly above the normal range of the age group, owing to their increased production by the testicles and adrenals.

In five of the cases the thyroid activity was also raised, indicating the existence of a primary pituitary hyperfunction. This may be a sequel of internal and environmental stress conditions.

Some of these boys recovered spontaneously by hospital care and attention, while their 17-ketosteroids excretion rate also fell.

In others we tried to suppress the activity of the pituitary anterior lobe with estrogens. The therapeutic problem for this group is still in a state of flux: no absolutely reliable therapeutic agent leading to a depression of the anterior pituitary activity is known.

A boy of 14½, who had got on fairly well at school until the age of 13, when he became difficult and believed everyone was against him, truanted from school and became uncooperative and demanding at home. He refused to wash and had outbursts of violent and odd behavior, breaking windows and china. On one occasion he dug up the lawn and buried his shoes under it. He was keen on football and other games, and had been interested in girls. He was said to have had a girl friend since the age of 11, and had been having sex relations with her for six months.

On admission he was cooperative and agreeable but slow in speech, giving a sensible account of himself, and showed no psychotic features. He tended to cause trouble in the ward, leading other boys into mischief.

His genitals were very well developed, and he had prematurely developed hair on chest, pubis and thighs, a strong beard and moderate acne. He masturbated every day.

His 24-hour 17-ketosteroid excretion rate was around 9.0 mg. The I¹³¹ tracer test showed increased activity. His E.E.G. was within normal limits. He was treated with stilboestrol mg. ii daily. Masturbation stopped. His behavior in the ward improved. He made satisfactory progress at school, worked consistently in the tailor's shop, and was discharged to his home, and has now been at work for a year.

DISCUSSION

It appears that endocrine disturbances can be detected rather frequently in juvenile psychiatric patients. Disturbances of maturation form the major group of deviations in this age range, and attempts to correct these deviations are associated with mental improvement.

The psychological characteristics associated with the immature and premature groups correspond to those which have been observed in late and early developers among populations of normal boys, as described by Tanner for instance. But in the case of

juvenile psychiatric patients, these characteristics may be overshadowed by over compensation or by the symptoms of their illness.

It is reasonable to assume that, in some cases at least, the disturbance of maturation impairs the boy's ability to adjust himself to his environment and predisposes to a mental breakdown.

Many of our cases come from bad homes and are subject to severe environmental stress of one sort or another. The further a boy deviates from the developmental norm for his age, the more he will feel isolated from the group with which he has grown up. This is a more important factor when the boy lags behind the group. Both his physical appearance and his awareness of his sexual inadequacy would give rise to inferiority feelings.

In addition, the immature boy is not equipped to complete his emotional development, and, therefore, he is less able than his more mature fellows to adjust to the increasing responsibilities which he has to face. (Breaking away from the home, chasing girls, social contact, preparation for earning a living, etc.)

The premature boy, on the other hand, may be subjected to drives for which he is not emotionally or intellectually prepared. These drives may find an outlet in sexual malpractices, in criminal activities, or may lead to a schizophrenic breakdown. The premature boy who is also premature in emotional and intellectual development may not indeed come to a mental hospital, but come in conflict with the law, since the activities appropriate for his physiological age attract social disapproval.

Of course, given a good home background and understanding parents and teachers, both the immature and the premature boy may develop at their own pace without an overt mental breakdown, and such understanding is fortunately by no means rare.

When somatic retardation accompanies gonadal immaturity the boy remains a child. He may be less aware of his physical inadequacy, and development is delayed but not out of step. The cases we have treated have done well.

A discrepancy between chronological age and mental and physical maturity often seems a significant factor in the development of psychiatric disturbances. This discrepancy can, according to

personality pattern and cultural background, trigger off a wide range of psychopathological manifestations. The fact that therapeutic interference with the endocrine component of this discrepancy produces psychiatric results, confirms our view that increasing attention must be paid to the endocrine aspects of immaturity and prematurity.

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V

Clinical Observations on the Action of Chorionic Gonadotrophin in Adult Male Psychiatric Patients

J. J. BRADLEY*

IT HAS been observed that a number of patients showing evidence of physical immaturity show a greater tendency to break down under stress: the pattern of their illness being determined by their basic personality structure and genetically determined predisposition to various forms of neurotic or psychotic illness.

The physical criteria we have observed as evidence of immaturity are as follows:

- (1) The patient looks younger than his years.
- (2) Beard, body and pubic hair (often with a female border) are sparse, but the hair on the head is usually dense.
- (3) Wide open inguinal canals into which the testicle can pass freely, the patient often making the spontaneous comment that he "loses" them—an extreme case observed recently complained that he would lose his testicles for "days at a time."

This syndrome of immaturity as detailed is independent of age, the oldest case observed by us was a man of 62 who looked no more than 40.

Biochemical findings common to members of this group were found as follows: Total ketosteroid excretion rate is rarely below normal range, but it must be realized that the total ketosteroid excretion rate is a resultant of adrenal cortex and testicular activity and that the gonadal contribution is, at a maximum, only 30 per cent of the total. The increase of tension before or during a mental breakdown can be regarded as a stress condition, which accounts

**St. Ebba's Hospital, Epsom, Surrey, England.*

for increased adrenal cortex activity, and hence even if the gonadal contribution is comparatively small the total will still be normal or raised. In view of this the ketosteroids in some of our patients were fractionated and it was found that the ketosteroids androsterone and etiocholanolone which are largely of gonadal origin were originally decreased.

Some of these patients showed increased thyroid activity which was presumably a result of stress, and returned to normal range on mental improvement. Similarly originally raised total 17-ketosteroid excretion rate fell when the patient improved clinically. No regular pattern in estrogen excretion rate could be found, in some it was of normal range, in others considerably raised.

Psychological Concomitants

It has been difficult to correlate premorbid personality and physical and biochemical findings into a unitary concept of psychological and physical immaturity. It has been observed that in any mental illness there will be a tendency towards regression to a more infantile level of functioning, but the past histories of these patients suffering from widely differing psychiatric syndromes have had some features in common:

- (1) Lack of overt aggression, timidity, complaints of inferiority feelings, hence a difficulty in making friends, with little interest in competitive sport or success in jobs.
- (2) A tendency towards dependence on the mother or mother figure.
- (3) Poor or perverted sex drive.

Objects of Therapy

Observation of four patients in the hospital under the usual beneficial conditions with consequent relief from environmental stresses resulted in some moderate spontaneous improvement which soon became static; and it was obvious that they were still unfit to adjust outside of the hospital. It was considered whether physical maturation of the patient by stimulation of the underdeveloped and

underfunctioning gonads could contribute to his mental maturation enabling him to deal with his internal and external environmental problems.

The patients were, therefore, treated with chorionic gonadotrophin in order to stimulate the endocrine function of the testicles. This way was chosen in preference to any substitution therapy with steroid hormones since the latter in high doses only suppress the anterior pituitary, and the treatment once started must continue practically indefinitely. Treatment with a trophic hormone stimulates the endogenous production of these hormones in physiological quantities, and it can be hoped that once increased activity of a peripheral gland is initiated it can go on later spontaneously without the need for further treatment.

CASE HISTORIES

A single laborer of 23 was admitted to hospital because of increasing solitariness for six months, and a refusal to go to work because he could hear a voice saying "get on with it." He had always been shy and backward, and was found to have an I.Q. (Wechsler) of 60. On examination he was tense, awkward and inaccessible, suspicious and replies to questions were evasive. He had shown no interest in sex, and denied any sexual feelings.

Family history suggested that his parents and five unmarried elder brothers were all of low intelligence. Physically he looked about 17, slightly built with scanty beard—needing a shave once weekly, sparse pubic and axillary hair. Genitalia were small with widely patent inguinal canals, the testicles sliding into the abdomen when he leaned backwards.

Total 17-ketosteroid excretion rate was within normal range, but androsterone and etiocholanolone excretion rates were low. The estrogen excretion was $24.2 \mu\text{g}$ 24/hrs, which was the highest value found so far in a man of his age.

Thyroid activity was initially raised but was normal in one month after starting treatment. He was treated with 1,000 i. u. of chorionic gonadotrophin, daily.

One month after this psychiatric examination revealed that his behavior was more assertive. He was able to hold his own with other patients. At interview he would assume the dominant role. Enquiries into his sexual activity met with positive hostility suggesting that there had in fact been some awakening of interest. Physical examination showed increased growth of hair on his chin (needing a shave twice weekly), and increased pubic hair. His testicles would no longer retract

into the abdomen on leaning backwards, suggesting narrowing of the canal. He had also gained 11 lbs. in weight.

The clinical changes coincided with a rise of total ketosteroids and fractionation showed that this was largely in the α fraction, indicating increased gonadal function.

After twelve weeks treatment was discontinued, but he rapidly relapsed into his mental state on admission and lost 6 lbs. in three weeks. He was then treated with 3,000 units of chorionic gonadotrophin daily and improvement was noted as soon as 48 hours after injection. This was continued for three months and was then replaced by small doses of depot testosterone (250 mg. weekly) which acts by stimulation of the anterior pituitary—this having virtually the same effect as an injection of gonadotrophin. Mental improvement has been maintained for three months.

An obese man of 40 was admitted to hospital suffering from a chronic anxiety state in response to domestic stress. Although of high intelligence from a socially superior family, with a private income of 2000 pounds p.a. he worked as a postman. His personality had a schoolboyish quality, he was anxious to please and would begin an interview by making a weak joke. He was married with two children (both under child psychiatrists) his wife regarding him as another problem child, but his sexual life was meagre, he preferred his wife to masturbate him than to have intercourse. He had fantasies of changing his sex. He did not make friends easily, but had female pen friends in all parts of the world. He would write overtly sexual letters to an aged aunt, but prefacing each with "Darling Mummy." Past history revealed that he has a stammer since the age of 6.

Physically he was obese with a high pitched voice and boyish face and a female pubic hair border. Genitalia were average but the testicles retracted into the abdomen on eliciting the cremasteric reflex.

Thyroid activity was found to be increased by I¹³¹ Tracer and B.M.R. and total ketosteroid excretion rate was within normal limits. He was treated with 6,000 i. u. of chorionic gonadotrophin daily for six weeks.

Physical examination after this time showed some change; he had regrettably gained 14 pounds in weight, but his voice had deepened considerably. Androsterone and especially etiocholanolone fractions increased during treatment, and it was interesting to note that the total 17-ketogenic steroids (corticoids) also rose from 9.2 to 23.2 mg./24 hours. After the same time the total oestrogen level rose from 8.6 μ g to 24.2 μ g.

He remained rather like an overgrown schoolboy in many ways, but on discharge was playing a more dominant role with his wife and no longer complained of anxiety symptoms. His wife reported that six weeks after discontinuing treatment he seemed more "grown up" and was taking more interest in the children, taking them out which was quite a new development, and was calmer and patient.

For the last six months he has received supportive psychotherapy and has remained well adjusted to his job and home situation. His relatives have spontaneously confirmed this improvement.

A man of 30 gave a history of obsessional rituals since the age of 12. He had an unsettled and unhappy childhood because of unstable parents, and had always been timid and dependent on his mother, with difficulty in making relationships with girls. In 1953 he became more anxious and was unduly sensitive to criticism, feeling that people were talking about him, and was treated with deep insulin therapy with some improvement, although he still indulged in hand washing rituals. The illness has necessitated treatment in hospital for about six months in every year since 1953. His chief complaints before his present treatment were obsessional rituals connected with toilet and dressing, depression, difficulty in making relationships and he expressed spontaneously that he felt his symptoms were "tied up with his mother."

On examination he looked younger than his years, shaved every other day (although dark haired), and had small testicles and widely patent inguinal canals.

Thyroid activity was within the normal range. Only total 17-ketosteroid excretion was determined and this was found to be within the normal range, and remained so with few fluctuations during the following treatment.

He was treated with 3,000 i. u. of chronic gonadotrophin daily and six weeks after this his beard was found to be stronger (needing a daily shave), testicles were larger and inguinal canal became narrowed.

Psychologically he is more outgoing, says he "feels free from his mother" and is more able to make relationships with women.

Obsessional rituals have decreased, and he is able to get through his toilet much more rapidly.

A heavily built youth of 19 was admitted to hospital complaining of "lack of blood" and "mental pains in the head." He had a vacant expressionless face, retarded thought processes and incongruity between thought content and mood. He was aurally hallucinated and claimed to be the second Christ.

Physically he was found to have sparse facial hair—none on chest or axillae, female distribution of pubic hair, small testicles and wide open inguinal canals.

Total 17-ketosteroids were in the low normal range, but the β -fraction was found to be above normal range, suggesting low α or gonadal steroid. Thyroid activity was normal.

He was treated with 3,000 μ of chorionic gonadotrophin daily and made a steady improvement over a period of six weeks, although previously no spontaneous improvement had occurred after two months' hospital care without specific treatment. This improvement coincided with a rise in the androsterone fraction.

He lost his delusions and hallucinations, was more sociable, but

remained quiet and affectively shallow. On discharge his parents considered he was his normal self.*

The foregoing cases showing widely different psychiatric syndromes have been treated with chorionic gonadotrophin on the basis of physical and biochemical findings.

All these patients have shown some improvement and it is noted that in three cases in which fractionations have been carried out it coincided with a rise in the α or gonadal steroids.

In 1945 Hemphill and Reiss treated 18 male schizophrenics on the basis of histological evidence of atrophy of the testicles with pregnant mares serum gonadotrophins. This has mainly an action like that of follicular stimulating hormone, but also contains small amounts of luteinising hormone which would be analogous to the chorionic gonadotrophin which we have used in the foregoing cases. Of the 18 cases treated, two recovered completely and six showed some degree of improvement. The eight cases showing improvement showed a greater degree of testicular regeneration than those who did not improve. It is questionable whether the testicular histology used as a basis for the treatment with a gonadotrophic extract can be regarded as a predominant feature in the cases described by Hemphill and Reiss since it is known that many endocrine conditions can lead to disturbances of the testicular histology. We regarded it at present safer to be guided by the clinical signs of immaturity already detailed as a basis for the use of gonadotrophic hormone. More intensive application of laboratory methods, particularly the determination of gonadal steroids would give further help in making such a therapeutic decision. It has, however, to be emphasized that such treatment can never be restricted to schizophrenia but will be useful on the wider plane of immature patients suffering from a variety of psychiatric disturbances ranging from behavior disorders to psychotic illness.

The appropriate endocrine treatment of the neurotic patient, particularly, should facilitate considerably subsequent psychotherapeutic measures.

*I am indebted to Drs. Reiss and Robinson for permission to quote the case of this patient who was under their care.

VI

The Premenstrual Tension Syndrome in Relation to Personality, Neurosis, Certain Psychosomatic Disorders and Psychotic States

LINFORD REES*

PREMENSTRUAL TENSION is a syndrome occurring during the second half of the menstrual cycle and consisting of a number of mental and physical signs and symptoms.

The syndrome consists of marked emotional instability, tension and irritability, together with one or more of the following manifestations: anxiety, depression, headache, bloated abdominal feelings, swelling of the subcutaneous tissues, increase in weight, tightness and itching of the skin, painful swelling of the breasts, dizziness, palpitations, and fatigue. In some women, lassitude, inertia, lack of initiative, and difficulty in carrying out intellectual tasks are prominent symptoms, and in some hypersomnia, excessive thirst and appetite and increased sex desire.

The symptoms usually appear during the week prior to the onset of the menses and reach their greatest intensity during the last day or two of the cycle. Some patients have an onset of symptoms from 10 to 14 days before menstruation and in a minority of patients the syndrome continues during the first few days or even throughout the period of menstrual flow.

The etiology of the premenstrual tension syndrome remains controversial. A number of theories have been postulated implicating physiogenic and psychogenic processes. The physiogenic theories of causation include the hormonal, physiological and biochemical changes. The psychogenic theories implicate emotional factors, instability of the nervous system and personality instability. Hoffman

**The Bethlem Royal and the Maudsley Hospitals and St. Bartholomew's Hospital, London, England.*

(1944), in a review of the literature, came to the conclusion that an unstable nervous system may be the primary factor and it is often suggested that the syndrome is primarily a neurotic manifestation predominantly occurring in unstable people. The incidence and prevalence of the premenstrual tension syndrome is difficult to assess as there is no sharp dividing line between mild and insignificant premenstrual changes and the clearly defined premenstrual tension syndrome. There is, in fact, a continuous gradation in intensity from the physiological changes occurring, in the latter half of the menstrual cycle, to the extreme degrees of the premenstrual tension syndrome. Thus, it is not surprising that different authors give different figures regarding the incidence of syndrome. Figures range from 25 to 100 per cent and Fluhmann (1956) gives a figure of 60 per cent. Freed (1945) states that 40 per cent of normal women suffer from considerable distress. It is impossible to compare figures given by different workers as one cannot be certain that the criteria used were identical, or that the groups were true random samples of the normal population.

The syndrome should not be confused with the premenstrual discomfort experienced by many women without significant disability. The premenstrual tension syndrome may severely interfere with well-being, work and social activities and can be incapacitating.

The present communication gives a brief account of investigations designed to obtain information regarding the following questions:

(1) Is the premenstrual tension syndrome primarily psychogenic and/or primarily a manifestation of neurosis or personality instability?

(2) What is the incidence of the syndrome in normal, well-adjusted women and women suffering from varying degrees of neurosis and personality instability?

(3) What is the interrelationship between the premenstrual tension syndrome and neurosis, when they coexist?

(4) What are the etiological determinants of attacks of asthma, urticaria and vasomotor rhinitis occurring premenstrually?

(5) What is the relationship between the premenstrual tension

syndrome and certain psychotic states which recur at the premenstrual phase?

GROUPS STUDIED

The following groups of patients were investigated. They were all women of reproductive age, that is aged between menarche and menopause.

(1) 51 normal women and 84 patients attending outpatient psychiatric and psychosomatic clinics. These groups were studied to ascertain the relationship between the premenstrual tension syndrome, personality instability, neurosis and predisposition to neurosis. Such a group was considered likely to provide the widest variation in intensity of neurosis and emotional instability, ranging from the normal stable person to the severely neurotic and maladjusted patient.

(2) Groups of patients suffering from asthma, urticaria angioneurotic edema or vasomotor rhinitis were studied to ascertain the etiological determinants of the premenstrual incidence of attacks of these disorders. They consisted of (a) 27 patients suffering from premenstrual incidence of asthmatic attack, and a control group of 27 asthma patients of similar age distribution, who showed no evidence of a tendency to develop attacks premenstrually; (b) a group of 12 patients suffering from premenstrual attacks of urticaria/angioneurotic edema, and a control group of 12 urticaria patients, without premenstrual incidence of attacks; and (c) 17 vasomotor rhinitis patients, with premenstrual incidence of attacks, and a control group of 17 vasomotor rhinitis patients, without premenstrual incidence of attacks.

(3) (a) 10 patients suffering from recurrent schizophrenia following postpartum schizophrenic illness; and (b) 15 patients suffering from recurrent severe depressive or other psychotic states.

METHODOLOGY

The following methods of investigation were used:

(1) Clinical interviews with patients and relatives. Information was obtained relating to menstrual history and symptomatology; family history; childhood neurosis; adjustment to school, work and marriage; personality, assessed both in terms of clinical type

and with regard to various traits and in terms of general stability.

(2) In the normal group, the Maudsley Medical Questionnaire and the word connection test (Eysenck 1947) were used as additional methods of detecting and assessing neurosis.

(3) Outpatients were given a special chart for daily recording of a series of premenstrual manifestations and related items. A number of items were also included in order to assess the patient's reliability in recording data. Each patient was given detailed instructions, with regard to the criteria for recording data, in order that the records should be scored in as standardized a manner as possible.

(4) Inpatients included the recurrent premenstrual attacks of schizophrenia, depression etc. They were investigated in the hospital and daily records were completed by the nursing and medical staff.

(5) Daily records made over a number of menstrual cycles enabled assessment of the presence and intensity of the premenstrual tension syndrome to be made and also the tendency in affected patients for attacks of asthma, urticaria, and vasomotor rhinitis to be associated with the premenstrual phase of the cycle and the relationship between psychotic attacks and the menstrual cycle. The information obtained was entered on a special item sheet containing some 200 items for each patient. Important features were rated according to severity, either on a seven point scale, which was used for the degree of premenstrual tension, severity of neurosis, general adjustment and personality stability, or a three point scale, by which various symptoms and signs were also graded according to severity. The information on the item sheet was eventually transferred to Hollerith Punch Cards and analyses carried out by Hollerith Counter Sorting machines.

RESULTS

Premenstrual Tension Syndrome in Relationship to Personality and Neurosis; Incidence of Premenstrual Tension in Normal and Neurotic Groups

The normal group had 78.7 per cent with no premenstrual tension symptoms compared with 38 per cent in psychiatric and

psychosomatic patients. The incidence of moderate degrees of premenstrual tension were 16.4 per cent in the normal and 30 per cent in the psychiatric and psychosomatic patients; severe premenstrual tension occurred in 5 per cent of the normal and in 32 per cent of psychiatric and psychosomatic patients. These differences are statistically significant. If the groups can be regarded as random samples, there appears to be a higher incidence of premenstrual tension in psychiatric and psychosomatic patients than in normal women. As there is no sharp dividing line between neurosis and normality, and as neurotic symptoms are often an exaggeration of normal personality traits or attributes, it is desirable to attempt an assessment of the stability and degree of neurosis in the normal group. This was carried out by clinical interview and by means of the Maudsley Medical Questionnaire and the word connection test. Comparison within the normal group of individuals with premenstrual tension with those free from premenstrual tension symptoms revealed no significant differences in the incidence of personality instability or neurosis. The following findings were obtained:

- (a) Premenstrual tension syndrome can exist in women who have little or no evidence of personality instability, maladjustments or neurosis, or of evidence indicating a probable predisposition to neurosis.
- (b) Many women with severe neurosis do not suffer from premenstrual tension symptoms. For example, in a group of 82 patients who were free from premenstrual tension syndrome, 20 per cent had severe neurosis, 23 per cent showed clear evidence of predisposition to neurotic illnesses and 18 per cent had very unstable personalities. Thus neurosis or emotional instability in itself is not sufficient to account for the development and occurrence of the premenstrual tension syndrome. This is also borne out by the fact that in patients with severe premenstrual tension and who also suffered from neurosis, the onset of premenstrual tension antedated the onset of neurosis in all patients except one. A number of patients with neurotic disorders responded to psychiatric therapy, with marked improvement in their neurosis, without significant im-

provement in their premenstrual tension state. Conversely, it was possible to eliminate the premenstrual tension syndrome by pharmacological and hormonal methods of treatment, to be described, without significantly affecting the coexisting neurosis.

An attempt was then made to compare the degree of severity of the premenstrual tension syndrome with the degree of severity of neurosis, of personality instability and with the degree of predisposition to neurotic illness by features described by Slater (1942). It was found that there was a positive correlation between the rating of neurotic constitution and predisposition to neurotic breakdown and the rating of premenstrual tension. The greater the predisposition to neurotic breakdown the greater the intensity of the premenstrual tension symptoms. Similarly there was a positive correlation between the severity of neurosis and the intensity of premenstrual tension symptoms. Furthermore, patients with severe degree of premenstrual tension were found to have a significantly higher incidence of moderate and severe degrees of maladjustment than patients with no premenstrual tension.

Thus, while it is possible to get premenstrual tension syndrome occurring in normal well-adjusted women, with the evidence being against it being primarily a neurotic manifestation, there is a positive correlation between the intensity of the premenstrual tension syndrome and the degree of assessed predisposition to neurosis, the severity of coexisting neurosis and the degree of personality instability and degree of maladjustment.

Rees (1951-1953) concluded from the available evidence that changes in the internal environment were primarily responsible for the occurrence of the premenstrual tension syndrome and also for the majority of its physical and psychological manifestations. There is considerable individual variation in reaction to such changes in the internal environment and it was considered that the patient's reaction will be influenced by (1) constitutional factors, for example: (a) stability of the autonomic nervous system and homeostatic mechanisms, (b) personality type, (2) degree of general stability, that is ability to cope and adjust to changes in the internal environment and stresses in the external environment. Stability

will be reflected in general adjustment during life to family, school, work and marriage and in personality reactions and in interpersonal relationships. (3) The coexistence and severity of neurosis. The intensity of the premenstrual tension syndrome will be dependent on two main factors: (a) the degree of change in the internal environment, including the endocrine and biochemical changes to be described and (b) the person's reaction to such changes.

If the characteristic changes in the internal environment are marked enough, it is possible to get premenstrual tension syndrome in women who are otherwise quite stable. In unstable and neurotic women the intensity of the symptoms and the degree of disability will be influenced by psychogenic factors as well as the above-mentioned physiogenic factors. Psychogenic factors will include constitutional predisposition, degree of neurosis, general stability and certain attitudes, and environmental stresses which may also serve to accentuate the intensity of the premenstrual tension symptoms. It is particularly striking that inpatients suffering from neurosis, the type of neurotic disorder and the significant conflicts and psychodynamic processes underlying the neurosis, tend to be made manifest during premenstrual periods frequently dormant at other times.

Premenstrual Incidence of Attacks of Asthma, Urticaria and Vasomotor Rhinitis

Random samples of women of reproductive age attending an Asthma Allergy Clinic were studied by special daily records, as already described. It was found that approximately one third of these patients showed a marked tendency for attacks to develop during the week before the onset of the menses, with a peak incidence one or two days before the onset of the menstrual flow. The patients who had a demonstrable tendency for attacks to occur premenstrually were compared with control groups of female patients suffering from the same disorders, who showed no tendency for premenstrual precipitation of attacks. The groups were accurately matched for age, marital status and parity. The premenstrual group was compared with control groups with regard to the following features:

MENSTRUAL DATA

No significant differences were found in menarchial age, length of the cycle, emotional reaction to menarche. Patients with premenstrual attacks of asthma were found to have a significantly longer duration of menstrual flow than the control asthmatic group.

INCIDENCE AND SEVERITY OF PHYSICAL AND PSYCHOLOGICAL MANIFESTATIONS OF THE PREMENSTRUAL TENSION SYNDROME

Comparison of the premenstrual asthmatic, urticaria and vasomotor rhinitis patients with the corresponding control groups revealed that the premenstrual incidence of attacks had a statistically significant correlation with the presence of various physical, emotional and psychological manifestations of the premenstrual tension syndrome—there being a statistically significantly higher incidence of the severe and moderate grades of severity in the premenstrual tension syndrome.

ETIOLOGICAL FACTORS

Investigation as to the relative importance of psychological, allergic, infective and other causative agents was made in all patients. It was found that while multiple causation is the general rule, plurality of etiological factors was particularly evident in patients who showed premenstrual incidence of attacks. This indicates that the pathogenetic mechanisms responsible for the attacks are evoked by a wide variety of causal agents. There is clinical and experimental evidence that premenstrual factors can exert summative effects with allergic, psychogenic, infective and other causative agents in precipitating attacks of these disorders. (Rees 1958).

Premenstrual Recurrence of Psychotic States

It is well-known that severe psychotic reactions in some women may be associated with premenstrual and menstrual phases of the cycle. There is evidence that suicide, criminal acts of violence and serious or fatal airplane accidents in women pilots are associated with the premenstrual and menstrual periods (Peller 1935), Morton et al. (1953), Rubin and Winston (1953).

Rees (1953) drew attention to the fact that in some women the premenstrual syndrome developed or became worse after childbirth. In a series of 12 patients with premenstrual recurrent depressive states following childbirth, it was found that they had developed various manifestations of the premenstrual tension syndrome for the first time after childbirth. In a detailed clinical, endocrinological and metabolic longitudinal study of 31 patients suffering from postpartum schizophrenia, Rees (1957) found that in 10 of these patients, following the recovery from the initial postpartum illness, there was a tendency for schizophrenic symptoms, qualitatively similar but usually quantitatively less marked to occur before menstrual bleeding. The recurrence of schizophrenic symptoms was found both with a pseudomenstrual or anovulatory type of bleeding and also with the resumption of true menstrual periods. Evidence from vaginal smear examinations, endometrial biopsies, indicated evidence of progesterone activity at the time of recurrence of psychotic disorders. There was also a tendency for an alteration in the relationship between acid stable formaldehydogenic steroids (A.S.F.S.) and 17-ketosteroids at the time of exacerbation or recurrence of psychotic state before menstrual bleeding. In most instances there was a marked tendency for A.S.F.S. excretion to be higher just before and during the disturbed period.

A patient who had marked agitation, confusion and depression recurring premenstrually was intensively studied over a period of 7 months by means of daily vaginal smears, serial electroencephalographic recordings, water balance, sodium and potassium excretion and adrenal cortical functions. It was found that the occurrence of premenstrual disturbed behavior was associated with a high level of estrogen with deficient progesterone, increase in weight due to salt and water retention, and increased urinary excretion of A.S.F.S.

It is interesting to note that a follow-up investigation of postpartum schizophrenic patients with a subsequent premenstrual recurrence of schizophrenia, usually showed a tendency for the premenstrual recurrence of psychotic symptoms to become progres-

sively less marked, with the passage of time until full recovery took place.

Bodily Changes Associated with Premenstrual Tension Syndrome

A number of biochemical changes have been found associated with the premenstrual phase of the cycle and with premenstrual tension syndrome. We have noticed a tendency to water retention in a proportion of our patients as already described. Thorn (1938) found the retention of sodium and water premenstrually and regarded it as being due to the action of ovarian steroids. Greenhill and Freed (1941) considered that sodium and water retention was the immediate cause of premenstrual tension symptoms. Morton (1950) also found a hydration to be a feature of the premenstrual phase.

Hydration would account for the swelling of subcutaneous tissue of the body, also for the increase in weight, tight feelings in the skin, heavy feelings in the head, bloated feelings in the abdomen and pruritis. Rees (1953) found that dehydration therapy relieved such symptoms, but did not always relieve the emotional instability, anxiety, irritability and depression. He considered that hydration was not responsible for all the symptoms of the syndrome.

Endocrine factors have been postulated by a number of authors. Frank (1931), who introduced the term "premenstrual tension," considered the manifestations to be due to a high level of circulating estrogen, brought about by a high renal estrogen threshold. Israel (1938) thought that the syndrome was due to the action of unantagonized estrogens and that the primary fault was lack of progesterone secretion, due to faulty luteinization. Gillman (1942) and Hamblin (1945) adopt the opposite view and consider progesterone to be the hormone responsible for the syndrome. Morton (1950) produces strong evidence in support of the theory that the syndrome is attributable to the action of unantagonized estrogen resulting from lack of progesterone.

Zuckerman (1955) showed that estrogens in adult females controlled water metabolism, produced changes in the function of the anterior pituitary and the adrenal cortex, and stimulated the

growth of epithelia of the reproductive organs. He found that estrogens in rabbits and ferrets induced hydration and that in monkeys edema was most marked in the sexual skin, even when this was denervated or even transplanted to the chest wall. He found that neither progesterone, testosterone or adrenocortical hormones were able to retain in the sex skin, water and salt retained by the action of estrogens. He considered that similar changes occur in other parts of the body and in other organs including the brain.

Chauchard (1943) from chronaximetric studies, found that the central reflex time was altered by estrogens and that the excitability of the nervous system was modified. He considered that this effect was produced by the influence of enzymes or redistribution of electrolytes resulting from the action of estrogens. Selye (1950) considered that estrogens have stressor action and produce the typical manifestations of the general adaptation syndrome, in experimental animals. Rees (1953) drew attention to the close similarity between phase of shock of the alarm reaction described by Selye (1950) and the manifestations and changes occurring in the premenstrual tension syndrome. Selye (1950) pointed out that while estrogens have water retaining properties, progesterone and testosterone have diuretic properties.

Torda and Wolf (1944) found that estrogens increase synthesis of acetylcholine, whereas androgens and progesterone decrease its synthesis. It is possible that this action may be one of the factors accounting for the autonomic lability occurring in the premenstrual tension syndrome.

In conclusion we may say that our investigations are in keeping with the hypothesis that the syndrome is associated with lack of progesterone, which permits the action of unantagonized estrogens, giving rise to salt and water retention and various other physiological and biochemical effects on the body, including the changes in central nervous system and autonomic nervous system, and adreno-cortical functions. The physiological and biochemical changes occurring with the premenstrual tension syndrome provide a possible explanation for the premenstrual incidence of asthma,

urticaria and vasomotor rhinitis and their association with physical and mental manifestations of the syndrome and also for the summative effects observed between premenstrual, psychological, allergic and infective factors in these disorders. In keeping with our findings are the observations of Mohun (1943) who found that the manifestations of vasomotor rhinitis, during pregnancy paralleled the level of estrogens in the blood and Mortimer et al. (1936) who demonstrated that estrogens produced, in the monkey, reddening and swelling of the nasal mucosa.

THERAPEUTIC IMPLICATIONS

Taking into account the various aspects and components of the premenstrual tension syndrome, as described, it follows that treatment may be directed at different aetiological levels, e.g.

- (1) Psychotherapy, including explanation and reeducation to improve attitudes, relieve symptoms and minimize the degree of incapacity.
- (2) Dehydration, to relieve symptoms due to hydration.
- (3) Administration of progestogens to compensate for any lack of progesterone and to antagonize the action of estrogens.
- (4) Administration of androgens to antagonize action of estrogens, as suggested by Greenblatt (1940), Geist (1941) and Freed (1945).
- (5) Chorionic gonadotrophic hormone to stimulate follicle growth and luteinization.

Psychotherapy was considered by Rees (1953) to have an important but limited role in the treatment of the premenstrual tension syndrome. The syndrome was not found to be amenable to psychotherapy alone, but psychotherapy of a simple kind could help the patient in the understanding of the condition and help to improve her attitude and reaction to it. The anxious, striving, overconscientious obsessional woman may feel intensely frustrated by the interference with physical, mental and social well-being caused by the premenstrual tension state. She may tend to force herself to keep up the tempo of work and life in spite of her symp-

toms. This often leads to greater frustration and increasing tension. This type of patient often benefits from the knowledge that her emotional changes have a physical basis particularly if she modifies the demands she makes on herself in relation to her premenstrual symptoms. Similarly the person who is hypochondriacal, very dependent or hysterical, may allow premenstrual tension to interfere unnecessarily with her work and social activities. Again explanation and reeducation with the aim of producing a more salutary attitude to her symptoms, can be helpful in minimizing the degree of incapacity.

Dehydration therapy, by means of diuretics, together with restriction of salt and water intake, were found to be helpful in removing some of the manifestations of the premenstrual tension syndrome, but did not provide complete relief.

Progestogens, such as progesterone by injection or ethisterone by mouth, given during the second half of the cycle, were found to be more effective, as also were androgens, such as methyl testosterone (Rees 1953).

A trial is being made with chorionic gonadotrophine in the treatment of recurrent premenstrual schizophrenic, affective and other psychotic disorders. It was given in doses of 1500 units twice weekly during the last two weeks of the menstrual cycle. In order to prevent undue postponement of the onset of menstruation the last injection was not given later than 3 days before the expected menstrual period. The preliminary results with chorionic gonadotrophine are promising.

Not all patients benefit from treatment with the endocrine therapies described above, even when applied in combination with dehydration measures and psychotherapy. Further research is needed to discover effective therapeutic measures in these patients.

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VII

On the Hormonal Treatment of Pre- and Postmenstrual Ovarian Psychoses

G. MALL*

THE PRESENT paper represents an attempt to cast light on a sector of the field of endogenous psychoses in women. The sector in question is that of the cyclical, periodically recurring psychoses, a problem which may be definitely clarified in the near future by endocrinological methods.

When the dates of admission of women suffering from acute mental disorders requiring immediate hospitalization are analyzed with a view to their relationship to the beginning of the next menstrual cycle, one obtains the distribution graph shown in Figure 1. The graph shows, on the one hand, the time of the start of menstruation as determined in our clinic and, on the other hand, the time of admission to the clinic, both exactly known. As a rule the objective case histories further reveal that in the case of these acute disorders only a very short time had elapsed between the outbreak of the psychotic exacerbation and the commitment to the clinic. With these facts in mind, one may conclude from figure 1 that *the great majority of women suffering from acute psychoses are admitted during the premenstrual phase*. This applies first of all to the various schizophrenic disorders, but evidently also to endogenous depressions (see Figure 2).

If the psychopathological syndromes observed during premenstrual phases of excitement and confusion are compared with the symptoms noted in cases of postmenstrual psychosis, the comparison, based on the evaluation of 50 premenstrual and 43 postmenstrual psychotic phases, yields the picture shown in Table 1.

With all due reserve we are inclined to conclude from this table that during the *premenstrual phase of excitement* the psychosis is pathoplastically characterized by *centrifugal, sthenic, extensive im-*

*Pfälzische Nervenklinik Landeck, Klingenmünster, Germany.

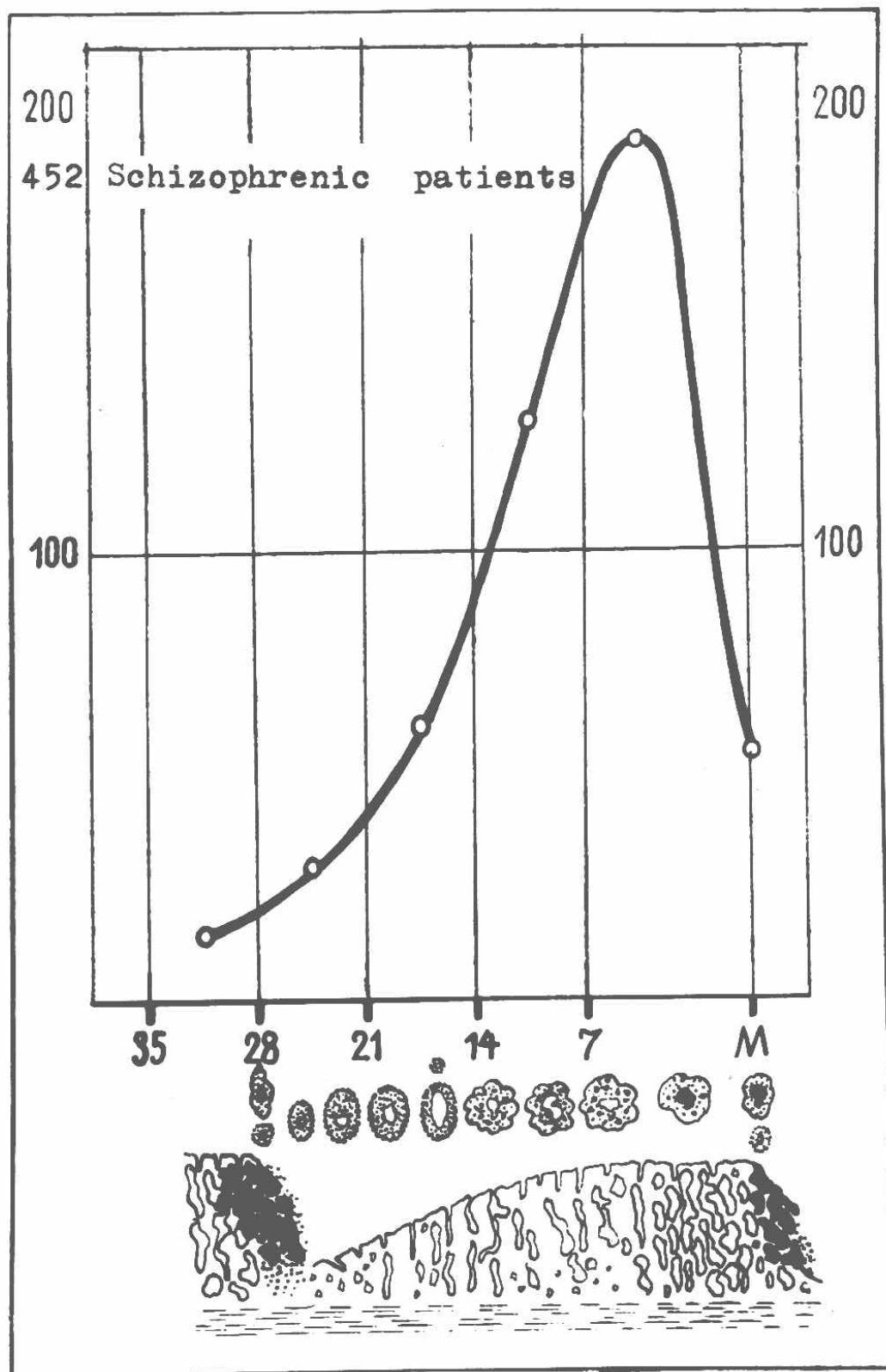


Figure 1

pulses and an explosive craving for motoric and other forms of release, where the postmenstrual clinical pictures are marked by asthenic, adynamic features, sensitive hallucinations, sleep disorders, psychomotor retardation, headaches and impoverishment of impulses.

Table 1

	Premenstrual	Postmenstrual
Great psychomotoric excitement	16 x	3 x
Loud shouting	10 x	2 x
Primary delusions	10 x	9 x
Anxiety	8 x	8 x
Stupor	6 x	1 x
Refusal to eat	5 x	1 x
Inhibitions (Sperrungen)	5 x	0
Hallucinations	4 x	7 x
Incoherent thinking	4 x	3 x
Grimacing	4 x	1 x
Silly behavior	3 x	3 x
Mutism	2 x	0

When one analyzes the intrinsic rhythm of these periodically recurring psychoses by means of detailed case histories, one finds that the course taken by these disorders may be of any of the following six characteristic forms, of which we designate forms A to E as synchronous forms, while the asynchronous form F shows no evidence of any influence of the menstrual cycle on the psychopathological course of events (see figure 3).

Figure 3 shows schematically the phases of excitement in correlation with menstruation. Form A shows regularly recurring premenstrual phases of excitement which fade away again after the start of menstruation. Form B shows a psychotic picture which continues after the beginning of menstruation and fades away after its stopping until the next phase of excitement begins in the second half of the next interval. Form C likewise starts with a premenstrual excitement which persists, however, even during menstruation and gradually fades away only postmenstrually. Form D, on the other hand, shows the very opposite type of intrinsic rhythm. Here we regularly find postmenstrual psychical changes in the first half of the intermenstruum which fade away entirely in the second half of the intermenstruum. Form E is a rare variant which shows a short and transitory phase of excitement roughly at the time of ovulation.

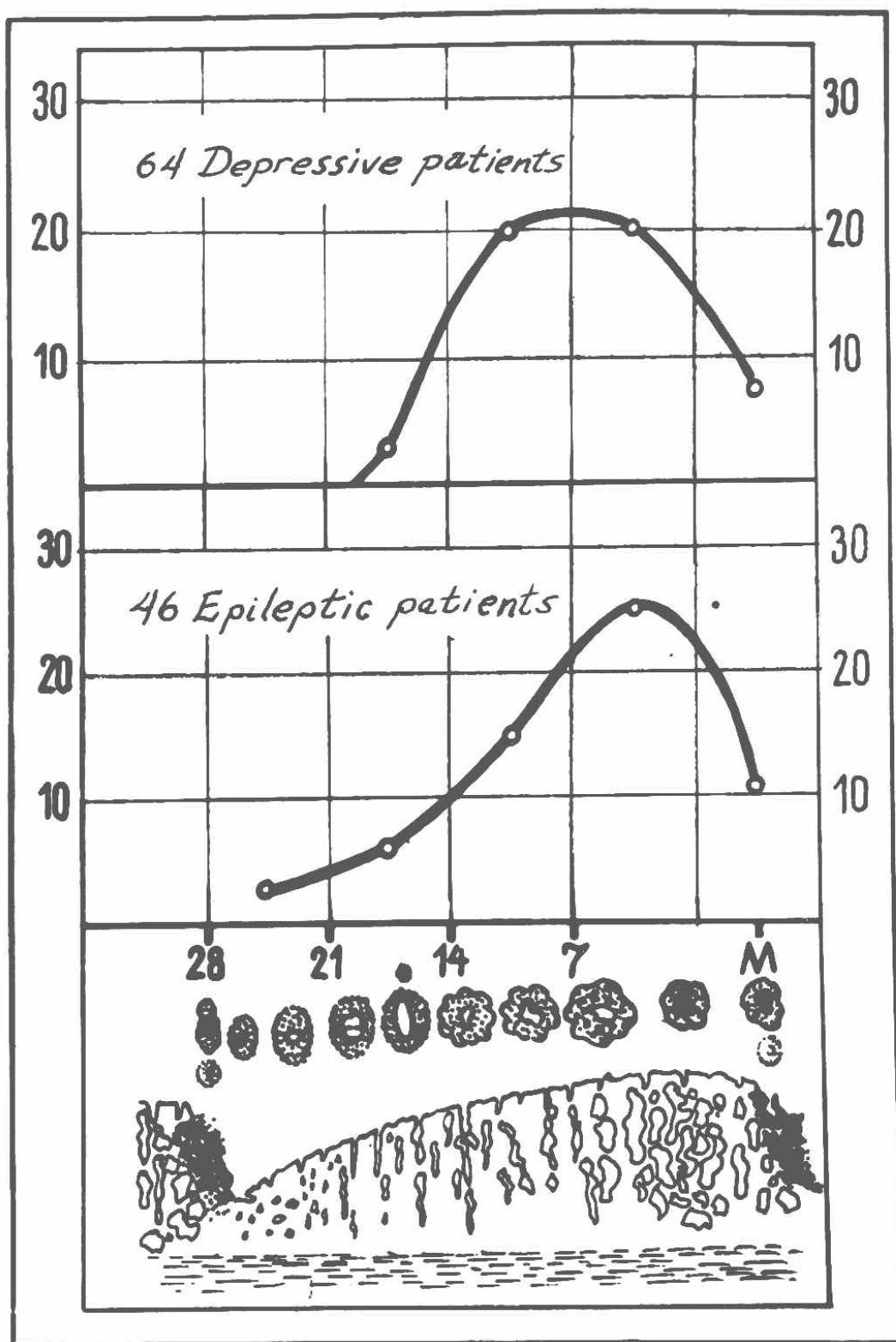


Figure 2

In clinical practice these schematic forms are naturally often masked by the interfering therapy (electric shocks, insuline, chlorpromazine, reserpine, etc.). Nevertheless, careful observation will often reveal the phases in spite of the treatment. To obtain clues on the course of the disorder it often suffices to read from the fever chart the menstruation dates and the electric shocks administered.

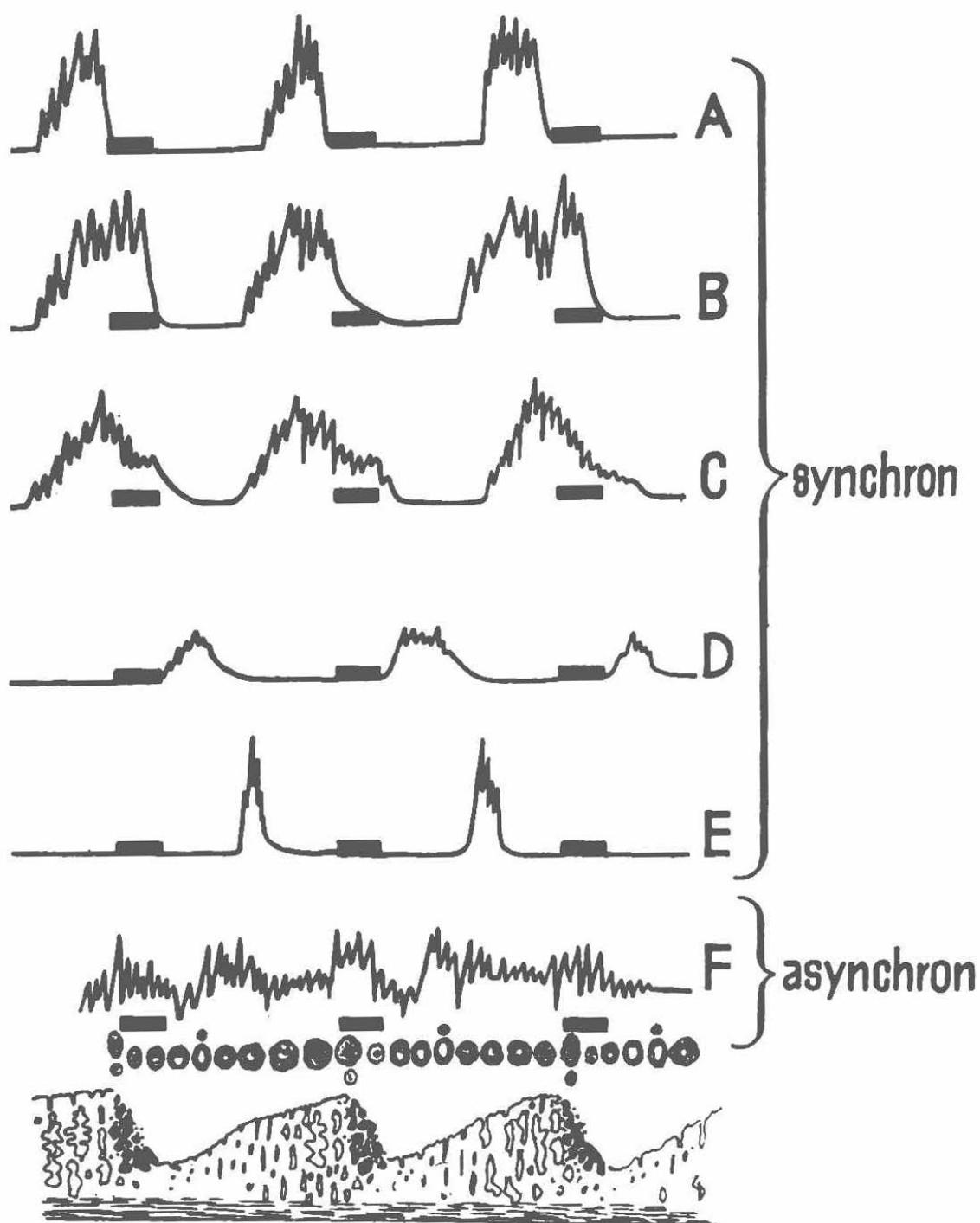


Figure 3

As stated before, the asynchronous form F is not influenced by the menstrual cycle. One encounters this form in the central schizophrenias and their final stages. In the initial stages of the psychoses (i.e. during the first months of the disorder) the pattern of forms A to C, as well as of D and E, seems to remain unchanged; later, however, there may be a transition from form A to B or C. A transition from form A to D should be extremely rare, however.

In this connection the question arises whether lighter forms of periodically recurring troubles corresponding to these psychotic clinical pictures may not occur in some healthy women.

Before turning to our therapeutic attempts, we must make a few remarks on the endocrinological problems presented by the various aforementioned forms of the course of the disorder. In 1933 F. Georgi and E. Fels carried out the first continuous measurements of estrogen in the urine of schizophrenic women. In the case of one amenorrheal schizophrenic, repeated urine examinations failed to reveal any trace of estrogen in the urine. In the case of two schizophrenics with normal menstruation, however, the authors noted a pronounced reduction of estrogen production. From the ranks of the psychiatrists a few fundamental observations regarding periodically recurring psychoses in women were reported recently by Henri Baruk, who divided these psychoses into hypofolliculinary and hyperfolliculinary ones and tried to reproduce them in animals. According to Baruk, the premenstrual phases of excitement correspond to the hyperfolliculinary, the postmenstrual ones to the hypofolliculinary form. In the latter cases he occasionally observed a decline of up to 80 units in the estrogen contents of the urine in a single day.

We ourselves are not in the possession of any continuous data on the estrogen contents of the urine of our patients. The most we have been able to do has been to collect the urine during the corresponding period in cases of characteristic psychopathological symptoms. We are indebted to Prof. H. J. Staudinger for the analysis of this urine. The values obtained so far indicate, however, that extreme upward or downward deviations evidently hardly occur among our patients. At the most one might speak of *relative* hyper- or hypofolliculinuria. The only case of an absolute increase of estrogen (215 gammas in 24-hour urine; method after Bates and Cohen) was that of Miss A., who was committed to our clinic because of a premenstrual state of confusion. Besides a pronounced, impulsive restlessness, the patient showed serious aphrodisia and attempted in an uninhibited way to enter into erotic contact with the attending physicians. Feelings of shame were entirely absent. Intense masturbation had led to extensive pruritus vulvae. But even disregarding this extreme case, we found that the other patients with relative hyperfolliculinuria likewise showed—in addition to their psychotic symptoms—pronounced libidinous-erotic

traits necessitating special psychotherapeutic treatment. Our patients with relatively low estrogen values, on the other hand, rather showed a lack of libido and sexualization, in line with the overall poverty of impulses and the adynamia of this category of patients.

Turning now to the hormonal treatment of these periodically recurring psychoses, we must remark first of all that the states of acute excitement and confusion may, of course, be controlled more or less simply by means of electric shocks, chlorpromazine, reserpine and the like. These are, however, no more than symptomatic *pseudosuccesses* of the therapy, since quite frequently a similar phase of excitement recurs again as early as in the next corresponding phase of the following intermenstruum. In the course of five years of direct study and observation of these cases in our clinic, we tried first of all to exercise a favorable influence on the ovarian insufficiency by means of small doses of Progynon-C and Proluton-C tablets. Experience showed, however, that we had chosen our doses too small. It was only after we had started administering to patients with premenstrual psychoses 65 mg 17 α oxyprogesterone capronate (Proluton-Depot, Schering) in the second half of the intermenstruum, if necessary in combination with 100 mg. testosterone enanthate, that the success of our treatment began to surpass that of all previous therapeutic attempts. It would be desirable, though, also to vary the dosage of this form of hormone treatment according to the biochemical analysis of the daily urine. However, as long as this is not generally possible in routine clinical therapy, the aforementioned treatment seems to us to be the method of choice. An occasional undesired effect of this treatment, with Prolution-Depot is premature or irregular menstruation. aggressive or psychopathic behavior was regarded as contraindicated.

To patients with hypofolliculinary, postmenstrual psychical disorders we have been administering for many years with considerable success 20 α ethinylestradiol (1 tablet Progynon-C) daily during the first half of the intermenstruum, in combination with a single injection of 100 mg. of testosterone enanthate. We continue this treatment for several consecutive months before gradually reducing the testosterone doses.

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VIII

A Note on the Treatment with Diandrone of Eight Women Patients

E. B. STRAUSS and W. A. H. STEVENSON*

IN PRESENTING this paper, may we admit from the start that, in contrast to the other contributions to this Symposium, it violates nearly all the canons of scientific research—the number of patients dealt with is ridiculously small and lends itself to no kind of statistical evaluation. Our results have not been checked against control groups. Our assessment of response to treatment depends on clinical judgment alone and is, therefore, undesirably subjective; and there are many other legitimate objections. Nevertheless, it is our belief that small scale clinical observations still have their part to play in medical research, especially in a field that is as yet so imperfectly explored as psychoendocrinology. This, then, is a small kite sent up a few feet into the air from our back garden and must not be taken more seriously than that.

Following upon our studies of the effect of Epidehydroandrosterone on immature and inadequate male subjects (1955), we decided to investigate the effect of Diandrone, as we shall call it hereafter, on a group of eight similar female patients aged from twenty-five to thirty-five. We chose young women of good intelligence and appearance, who should have passed through the difficulties of adolescence, but who were still in its toils. Many of the symptoms might have been considered normal in teenagers, such as shyness, inability to mix with the opposite sex, black moods, lack of confidence at work and in social contacts, and timidity in dealing with superiors. Many of the selected group exhibited some obsessional features in their makeup. It was often impossible to check our clinical observations and impressions against laboratory tests, owing to lack of facilities.

**St. Bartholomew's Hospital, London, England.*

As in the case of our male patients, treatment was preceded by careful physical examination, with special reference to weight, blood pressure, breast texture, hair distribution, white cell counts, haemoglobin estimations, eosinophile counts, sedimentation rate and menstrual history. The physical examination and white cell counts were repeated at regular intervals. A history of anti-social, aggressive or psychopathic behavior was regarded as contraindication to treatment. Diandrone was given orally in tablet form, the initial daily dose being 2.5 mg. It was always given in divided doses, with periods of rest every few months to assess progress.

With one exception (patient No. 6), all the patients had had previous psychiatric treatment of one kind or another, with doubtful improvement. All were emotionally immature and looked younger than their years.

Each patient was seen approximately once a week; and interviews were limited to a few minutes superficial talk except in the case of patients 4, 7, and 8, who had half-hour psychotherapeutic sessions once a week.

CASE 1. A married woman aged thirty-four, who complained of shyness, depression, inability to concentrate, obsessional rumination on her past experiences, and fears of the future. She dreaded coitus and was unable to achieve orgasm. She was unable to work. Her heredity was bad and her childhood extremely unhappy. Her father had deserted her mother, who died in a mental hospital when the patient was aged five. Thereafter, she had at times lived with relatives and at other times in institutions. Her maternal grandfather committed suicide when the patient was aged eight; her grandmother made a suicidal attempt two years later; and an uncle committed suicide when she was in her early twenties. She had a poor record at school and subsequently at work. She felt that a mental cloud had been enveloping her; had blunted her emotions and had interfered with her efficiency from the age of fourteen onwards. She, herself, had contemplated suicide, and was taking six Dexedrine tablets a day. She had had eighteen months analytical treatment under inpatient conditions, followed by a course at a training center; and she was next given a course of electroplexy as an outpatient. The general opinion was that an encapsulated schizophrenia underlay her neurotic symptom picture. She had married at the age of thirty; the marriage was unhappy, mainly owing to her sexual inhibitions.

Her 24-hour neutral 17-Ketosteroid output was 6.2 mg., with a negligible beta fraction. She started Diandrone with the usual initial dose. Four days later she made sexual advances to her husband, and enjoyed orgasm twice running. Dosage was gradually increased to 10 mg. daily. The improvement in her sexual life was maintained; and she was, after forty-seven days treatment, able to hold down a job, and reduce her daily dose of Dexedrine to one tablet. She became careful about her appearance, more composed and even developed a sense of humor. She was able to enjoy gardening, and felt that she had more physical stamina. Marital relations improved in other than sexual ways. Treatment was stopped on the seventy-eighth day; she began to relapse six days later, with a return of her depression, inertia, and unreality feelings. She improved rapidly again once treatment was resumed.

CASE 2. An unmarried woman aged twenty-six, who had been treated for anorexia nervosa three years previously. This condition had followed severe trauma. In spite of her intensive treatment, she had not made a complete recovery. All her life she had been lonely, timid, easily depressed, and fatigued; she was frightened of men, and her sexual outlook was prudish. Her 24-hour neutral 17-Ketosteroid output was 2.7 mg. per day, of which the beta fraction was 14 per cent. Treatment with Diandrone started in the usual way with 2.5 mg. daily by mouth; and the dose was gradually increased. By the fourteenth day, she had gained 1½ lbs. in weight. On the twenty-first day she said that she was starting to long for "cigarettes, whisky and wild, wild men." By the forty-ninth day, on a dose of 15 mg. daily, she had gained more weight, was able to discuss her sexual worries, and had lost the downy hair on her back. Treatment was stopped on the ninetieth day; and, on the one hundred and twelfth day, she still felt well, had developed an aggressive sense of humor and had a total gain of 5 lbs. in weight. She began to deteriorate again, however, and lost 2 lbs. in weight. On the one hundred and thirty fourth day, treatment began again with a gradual increase of dosage up to 30 mg. daily. By the one hundred and sixty seventh day, she had stood up to her employer and was abusive to one of us. Dosage was then reduced to 20 mg. She shortly afterwards had an attack of pneumonia from which she made a good recovery. Treatment was stopped again on the two hundred and forty fifth day. By the two hundred and seventy second day, her weight had increased, but the downy hair on her back had returned; she started to become uncooperative, lost her Rabelaisian sense of humor and once more became prudish. On the three hundred and sixth day, she was given 1 gr. of thyroid extract in addition to the Diandrone. By the four hundred and twenty sixth day, she was able to discuss the ways in which she had misled her doctors during the acute phase of her anorexia. Her libido returned, and she found a "boy friend." Her 24-

hour neutral 17-Ketosteroid output at this time, while taking 30 mg. of Diandrone daily, was 11 mg., with a beta fraction of 36 per cent. She admitted to a complete difference in outlook as compared with her past. She then became anxious because she found her problems unchanged and dreaded having to deal with them again, though by then she had given up her secretarial job and was becoming a fairly successful short story writer. She felt that she could no longer allow herself to shelter behind her symptoms and decided that she must terminate treatment and face life. This she did on the five hundred and forty first day, at which time her 24-hour neutral 17-Ketosteroid output had dropped to 4 mg. per day, with a beta fraction of 9 per cent. Follow-up, nearly two years later, showed her to be confident, poised, earning a living as a writer, and normal in every respect.

CASE 3. An unmarried woman aged twenty-six. This patient had suffered for the past ten years from fatigue, recurrent amenorrhoea, vertigo, nausea, fainting, shyness, timidity and depression, sometimes with suicidal impulses. She menstruated twice only at the age of sixteen; and the amenorrhoea was treated first with stilboestrol, which was later changed to estradiol benzoate; but her periods never became regular. A failure of pituitary function of unknown origin was suggested as a possible cause. Her uterus was infantile. An E.E.G. showed some abnormality; and it was thought that her vertigo and fainting attacks were probably epileptic, the epilepsy possibly following measles encephalitis at the age of four. She was shortly afterwards admitted into the hospital after a serious attempt at suicide. She had a course of modified electroplexy (ten treatments in all). A second E.E.G. four and a half months later showed increased abnormality, possibly due to the after-effects of electroplexy. She then had a course of psychotherapy from which she benefited. Diandrone was given in the hope that it would help her to respond in a more mature manner to the stresses of life.

Her family background was exceedingly unstable; and the patient reacted to the frequent domestic crises with hysterical and impulsive behavior and exacerbation of all her other symptoms.

On examination: leptosomatic (asthenic) build; blood-pressure 150/80; weight 96½ pounds; 24-hour neutral 17-ketosteroid output 6.9 mg. (alpha fraction 82.6 per cent, beta fraction 17.4 per cent); white cell count 10,000; Hb. 90 per cent; differential count normal.

She was given dummy Diandrone tablets for two weeks; and no change of any sort was noted. She was then given Diandrone proper, which was followed by no change during the first twenty eight days other than a pleasant feeling of tiredness and lassitude. The dose was gradually increased; and, by the seventieth day, she noticed an increase of confidence, and a diminution of shyness. She decided to take driving lessons, stood up to her rather bullying employer, went out dancing,

and finally obtained a better and much more responsible post. A daily dose of 15 mg. gave rise to too much aggression. Treatment was stopped on the one hundred and thirty first day. She fell and injured herself shortly afterwards and promptly relapsed. Diandrone was accordingly given again on the one hundred and seventy third day, and continued until the two hundred and twenty fifth day, during which time she had to contend with severe traumatic and disfiguring surgical illness and family trouble. It was really surprising how well she adjusted to these unfortunate circumstances. Her menses, too, interestingly enough, became normal and regular at the same time. There was a new crop of domestic worries starting five days after Diandrone was stopped for the second time. This gave rise to deep depression and hysterical behavior, reminiscent of her reaction to stress before treatment. On this occasion we were able to help the patient through her crisis by employing firm and forceful methods which would have been of doubtful utility, or positively dangerous, prior to treatment with Diandrone.

Her vertigo and tinnitus could now be viewed without the confusing welter of unrelated symptoms, allowing a firm diagnosis of Meniere's syndrome to be made. This responded extremely well to Dramamine. Since that time, the patient has had to face many troubles, including another surgical operation and a broken love affair; and she has not broken down. In spite of being tempted on one or two occasions to ask to be put back on Diandrone, she refrained from doing so and coped with her difficulties on her own. It is also interesting to record that this once shy, timid, frigid woman, when she found that she could not meet the right type of man through ordinary social contacts, advertised in a paper and interviewed the applicants with great aplomb. Our biochemical colleagues might be interested to know that, when the 24-hour neutral 17-ketosteroids were reestimated halfway through the course of Diandrone, they had fallen to 5.9 mg.—a somewhat paradoxical result.

CASE 4. An unmarried woman aged twenty-seven. She first came under psychiatric care at the age of sixteen, complaining of depression, extreme shyness, and a conviction that she was physically odd and awkward. These symptoms had come on after a move from London to Aldershot following an air raid experience. It was stated that up to the age of eleven or twelve she had been gay and popular but that recently she could not even bring herself to enter a shop. Schizophrenia was suspected. Members of her family had histories of neurosis and glandular trouble. Her menstrual history was normal. From 1946 to 1954 she had various kinds of analytical psychotherapy and other forms of treatment, with only slight improvement.

In 1954, she was still complaining of severe depression, she felt "shut in" emotionally, and was convinced that she was disliked. A Rorschach test confirmed her superior intelligence, but revealed little evidence

of normal emotional outlook or inner creativeness. Her 24-hour neutral 17-ketosteroid output was 6. mg. of which the beta fraction was 6 per cent. After thirty days on Diandrone (2.5 mg. b.d. by mouth) the depression had cleared, and she became so confident that she was almost afraid. By the one hundred and twenty-ninth day, her social contacts had improved; and she had stood up for herself. There was an increase of libido sexualis; and she decided that the time had come for her to break away from home. A daily dose of 20 mg. produced restlessness; and 15 mg. daily turned out to be her optimum dose. On the one hundred and fifty ninth day, after a postinfluenza! depression, made worse by frustration in a love affair, Diadrone was stopped, for unavoidable reasons; and seven days later she began to relapse in every way, and continued to do so in spite of intensive psychotherapy and hypnotherapy, amphetamines and sedation. She became increasingly depressed and withdrawn and developed paranoid ideas; and her periods became irregular for the first time. By the two hundred and eighty first day, the whole picture was one of borderline schizophrenia.

Diandrone was recommenced twelve days later; and eight days afterwards she regained all the ground which she had lost. Approximately thirty days later, she stopped Diandrone for two days and relapsed again. In the ensuing months of treatment, Diandrone was stopped once or twice, when within a few days her original symptoms began to recur; however, she kept very well whilst taking the substance, survived a family upset, and began to look for more responsible work.

Since that time, she has gradually come to accept herself as a normal introvert, and said that she was possibly too content with her life.

CASE 5. An unmarried woman of good education, aged thirty, who at about the age of twenty-four complained of shyness, timidity, nail picking, blushing, sexual frigidity, feelings of inadequacy, and obsessional rituals at work, and, after an emotional upset, muzziness, tension, depression, depersonalization, and panic attacks. There was a history of neurosis in the family. She had had three major attacks with these symptoms. She had been jaundiced at birth and again at the age of seventeen, with some residual liver damage. She had had two years of analytical psychotherapy, with considerable improvement. Her recurrent depression was then treated by electroplexy. She responded up to a point but remained shy, timid and ineffective, with short mood swings on the diathetic scale, and needing occasional supportive psychotherapy. Her 24-hour neutral 17-ketosteroid output was 11.3 mg. with a beta fraction of 42.4 per cent. In spite of this exceedingly high reading, we decided on clinical grounds to treat her with Diandrone. By the eighteenth day, she said she felt really normal for the first time in years, was able to face her problems more calmly and could even be self-assertive if the occasion demanded it. She became somewhat too aggressive when Diandrone was increased beyond 10 mg.

daily. She continued to improve, so much so that by the fifty ninth day she began to have erotic dreams. She said that her depressive phases had become "shorter and deeper", and that her elated moods were now less intense. She felt much less immature ; her blushing and shyness had diminished considerably, and she was able to make contact with men; in fact she needed some guidance in controlling her desires. She stopped treatment on the one hundred and thirty seventh day and passed through a period of stress satisfactorily. She tended to relapse later, so that treatment was recommenced, with immediate improvement, on the one hundred and eighty fifth day, and continued until the two hundred and sixty eighth day. Since that time she has remained well, apart from tension and depression, which responds to three 400-mg. tablets of meprobamate a day. Her shyness, inadequacy, blushing, depersonalization, and sexual frigidity, have become negligible; rejection by a boy friend, which, in the past would have produced an emotional upheaval, now gave rise only to a short lived psychosomatic reaction.

CASE 6. A married woman aged twenty-six, the mother of two children. She complained of inability to mix, extreme shyness, lack of confidence, blushing, a feeling that people were making fun of her (she even heard their muffled voices when nobody was there). She also complained of depression, impaired concentration and memory. She had been in a hospital twice in the previous two years, but had failed to keep her further appointments. There was a history of both neurosis and psychosis in her family.

Past physical illnesses included chronic otitis media and pleurisy, four and two years previously respectively. She was happily married and was still suckling her second child, fourteen-months old. Her physique was of mixed lepto- and athleticosomatic type. Her 24-hour neutral 17-Ketosteroids were 11 mg. per day, the alpha fraction 98.3 per cent, the beta fraction 1.7 per cent (normal 4 to 10 per cent). She was admitted to St. Ebba's Hospital, Epsom; the provisional diagnosis was depressive type of schizophrenia (duration of illness three years, with remissions). In St. Ebba's Hospital, her 24-hour neutral 17-Ketosteroid output was estimated as 4.04 mg. In her case, the initial dose of Diandrone was 20 mg. It was increased to 30 mg. after a fortnight, and to 40 mg. on the forty third day. She improved steadily on Dianдрone and lost her paranoid symptoms. On her discharge from hospital, Diandrone 30 mg. per day was given by mouth for two months, and then stopped. She was seen after two months without medication when she claimed to be symptom free. She became pregnant two months later, and her attendance became irregular. She next attended in an uncared-for condition during the third month of pregnancy with decaying teeth, avitaminosis, phlebitis, and mental anxiety. She attended thirteen months later, after a normal confinement, exhibiting ideas of reference to the extent of having even consulted the police. At this point she broke off treatment, and we have lost sight of her.

CASE 7. A woman of thirty seven, the younger child of an insecure and neurotic family. Her complaints (since puberty) were: inability to go out alone, panic states, depression, shyness, fantasies and violent upsurges of aggression with which she was totally unable to cope, fear of injuring others, e.g. through poison getting into the food that she cooked.) Her sexual outlook was immature. She was treated, with benefit, by several analytical psychotherapists for ten years or more. Though she became better adjusted in many ways and was able to travel short distances, she remained unable to spend a night away from home, even if it meant walking for hours alone in a fog to arrive there. Moreover, she was still subject to panic attacks and lacked confidence. Her 24-hour neutral 17-Ketosteroid output was 8.4 mg., of which the beta fraction was 1 per cent. After eleven days on 2.5 mg. of Diandrone, she became more confident and self-assertive. By the twenty first day on an increased dose she became anxious and complained of migraine. She said that, whereas the smaller doses had made her confident, the bigger doses made her afraid of her new confidence and aggression. She stopped taking Diandrone until the fifty second day, by which time she was having many bizarre and sadistic dreams. She started again on a daily dose of 2.5 mg. After seven days she said that her symptoms were nonsensical and that her fears were the product of her imagination. By the eighteenth day she began to feel an access of healthy aggression. The dose was then increased to 1.25 mg., t.i.d.; on which dose she became too aggressive. After varying the dose, she was taking 5 mg. a day on the hundredth day. On that dose she reported increased confidence, drive and sexual activity.

Diandrone was stopped because she was afraid that it was making her legs hairy, but psychotherapy continued. Three months later, she spent a night alone in an hotel away from home for the first time in eight years, with the help of Amytal gr. $\frac{1}{2}$ t.i.d., but required it only once more during the subsequent two months. She then slowly relapsed, and began Diadrone again two months later with 1.25 mg. twice daily. She experienced a sharp increase of libido and was able to discuss her sexual worries freely. She also began to stay away from home again. She once again stopped taking Diadrone, when her libido returned to normal. Shortly afterwards, she began again with 1.25 mg. daily for two or three weeks because she realized that she was deteriorating once more, and enjoyed an all-round improvement.

She has become more accessible to psychotherapy, and has continued to make steady progress.

CASE 8. A well-built, single woman aged thirty, who complained of periodic attacks of depression and feelings of shyness and inadequacy. She felt her emotions to be blunted and immature, lacked confidence, and was unable to mix well with men. She had a slight degree of pre-

menstrual tension. There was a schizoid element present in her personality structure. She made a slow, steady improvement over some thirty five half-hour psychotherapeutic sessions, but found it very difficult to cooperate. She was then given a course of Diandrone with the object of hastening emotional maturity. She began with 5 mg. by mouth. Her 24-hour neutral 17-ketosteroid output was 7.6 mg.; fractionation was not possible. Fourteen days later, she was much more forthcoming in interviews and relied less on sleeping tablets. By the twenty-eighth day, her friends remarked on her improvement; she was able to stop her sleeping tablets and to discuss her early childhood resentments and the family instability. She, herself, became surprised at her aggressive feelings towards people who thwarted her ambitions; and she was eating and sleeping well. Diandrone was stopped on the fifty sixth day, when she gradually became "run down". Thirty five days later, she was still somewhat depressed, but remained forthcoming in her psychotherapeutic sessions. We thought that Diandrone was a definite aid in psychotherapy in this case, although there was no way of confirming this impression.

RESULTS OF TREATMENT

The results of treatment conveniently lend themselves to classification under two main headings of "subjective" and "objective", although there is bound to be overlapping.

Both subjective and objective improvement, attributable, in our opinion, to Diandrone, was recorded in the case of seven patients; and it is noteworthy that six out of these seven patients had previously received other kinds of treatment over long periods of time.

Subjective

Seven out of the eight patients reported an access of self-confidence and a diminution of their previously timid attitudes at work and on social occasions. Subjectively, this did not resemble the hectic type of euphoria produced by "boost" drugs, of the amphetamine group for example; on the contrary, the kind of self-confidence induced by Diandrone was characterized by calmness and serenity, combined with an increase of legitimate self-assertiveness and an ability to stand up for one's own rights.

An increase of sexual desire occurred in all our patients; but none of them experienced any difficulty in exerting proper control.

Objective

Nearly all the patients became considerably less inhibited in the therapeutic situation, with the result that they could discuss their intimate problems with increased freedom and clearly envisage realistic ways of meeting them.

Endogenous mood swings did not appear to respond to Dianдрone; but reactive anxiety and depression noticeably diminished when the drug was being exhibited in optimum dosage.

Symptoms attributable to schizoid psychopathy or the obsessional temperament also seemed to clear up to a large extent with Diandrone.

Perhaps the most striking objective finding, as already indicated, was the all-round improvement in the therapeutic situation, enabling psychotherapy to proceed smoothly and rapidly.

CONCLUSIONS

It would seem then, that as in the case of our comparable series of immature male patients, Diandrone can bring about a change in behavior and feeling patterns, and that these changes are both subjectively experienced and objectively discernible.

As in the case of the male group, overdosage, an individual matter, was followed by increased irritability and resentment of authority.

Unfortunately, we were not able to establish any clear nexus between the 17-Ketosteroid readings and the clinical picture. It is possible that, until we have more delicate laboratory techniques at our disposal, and until we possess greater knowledge of the effect on the emotional life not only of the other fractions in the 17-Ketosteroid complex, but of the other steroid hormones as well, clinical judgment will remain the most reliable criterion for the selection of case material.

It is our clinical impression that every individual has his own pattern of hormone equilibrium, and that emotional changes may be associated with exceedingly small variations in the 17-Ketosteroid spectrum, all occurring within the range that is at present considered normal.

Two patients, whose case histories are omitted from this paper owing to shortage of space, did not appear to derive any benefit from treatment with Diandrone. This would bring the total number of women patients (in this series) treated with Diandrone up to ten.

Our results are in broad agreement with those of Ferrari and Declichi, Serra, and Subiani and Laricchia.

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IX

Abreaction with the Use of Adrenal Cortex Derivatives

J. C. BATT and P. DALLY*

INTRODUCTION

FOR SOME considerable time it has been a custom in psychiatry to exhibit various substances either of an anesthetic or stimulating nature (e.g. the barbiturates or methedrine) for the purpose of either obtaining a previously unknown factor in a mental illness, or for permitting the patient to get rid of an otherwise undischarged emotional state, and so improve his particular illness. Both methods have certain disadvantages, and psychiatric workers have been searching for an anesthetic drug which would help them to obtain information from patients as to the cause of their illnesses, but avoiding some of the side effects that had been noted in the past.

It is not surprising, therefore, that when the anesthetic use of some of the steroid preparations became known these were used to obtain the same ends. The uses of these substances are, however, as yet not sufficiently frequent to justify us in giving a mathematical analysis of our results. This paper then is presented simply as a description of our experience in cases so far investigated.

SUBSTANCES

The substance used was 21-hydroxy-pregnane-3,20-dione (the empirical formula being $C_{25}H_{35}O_6Na$), and this has been prepared commercially in two forms. It is described as a steroid with anesthetic properties, and seemed to us particularly suitable for psychiatric practice because the anesthetists had stated that not only did it produce anesthesia but a condition indistinguishable from normal sleep, and that on recovery the patient was in a state of mild euphoria. Were this true, then it would seem obvious that it

**St. Ebba's Hospital, Epsom, Surrey, England.*

would act as a compensation to the disclosure of any unpleasant episodes that they might reveal on questioning.

METHOD

This substance may be given in one of two forms. In both cases the substance is given intravenously. About .5 - 1 Gm. are necessary to produce "physiological sleep." In the one case it should be given as a drip or with a 50 c.c. two-way adaptor syringe, but in the other it may be given as a simple intravenous injection dissolved in 10 c.c. of sterile water.

The exhibition of the drug is followed in a matter of some ten minutes by loss of consciousness, and on a single dose a period of sleep lasting from 15 to 20 minutes or less is to be expected. The duration and depth of sleep depends upon the slight variability noted from patient to patient. When the period of sleep has passed the patient is fully conscious and able to discuss his case completely, but there may be a period of lassitude persisting for a variable length of time up to two hours. On recovery the patient is often mildly euphoric, and will sometimes speak spontaneously, but there may be a lag period, before any information can be obtained, of about ten minutes to a quarter of an hour. It is our practice to leave the patient in charge of a nurse until it is found that he is able to talk, before an investigation of his illness is made.

Material

The material was a random sample of patients admitted to a mental hospital, consisting of both psychotics and neurotics, and originally our attention was directed to the effects of the substance rather than to the possibilities of it as a therapeutic measure.

RESULTS

Twenty-four anxiety states have been investigated by this means, and 75 per cent showed a considerable improvement after a single injection, and half of them showed some degree of abreaction when they recounted their conflicts. One of the important points noted in relation to these cases was that they became considerably more amenable to the discussion of their symptoms; thus rapport was more easily established, and cooperation more readily obtained.

In all, some 12 cases of depression have been investigated by this means, of which 7 showed agitation, and it is interesting to note that the response in these cases was characteristic. When agitation is present it would appear that this may be removed, although the depression may persist, and it therefore may be easier to administer E.C.T. for the removal of the depression, and probably diminishes the number of applications required.

In cases without agitation we have observed, in two, a complete recovery on the administration of this derivative of pregnandiol alone. On both occasions the patient referred to material that had been worrying her, although the clinical picture was that of a typical endogenous depression, and we are exploring the possibilities of this in our depressive cases in the future. Some clinical examples of this may be summarized briefly.

A woman of 62 was admitted with a severe agitated depression in which the emotional state improved after 4 E.C.T., though the agitation was still present. Following one injection the agitation disappeared and the case rapidly proceeded to complete recovery. In two other cases this substance was given before E.C.T. in agitated depression, and although the agitation disappeared the depression remained unaffected. After a period of some 5-6 days the agitation recurred, necessitating the intervention of E.C.T.

So far we have been able to explore only 5 marked hysterical neuroses, but a brief history of the type of result that can be obtained when there is an emotional background to the illness can be summarized in the following case histories.

A man aged 38 was seen with an amnesia extending back for 10 years. He had been given sodium amyta, but this had resulted in a massive urticaria, and on interview he could not tell us if he was married, his address or last place of work, but the steroid elicited the story that he had left his wife to live with another woman, and his desire to break his new liaison was the emotional factor responsible for his illness. It was easy to discuss his condition with him, and his memory was regained, and a satisfactory end to his troubles found, since his wife was more than willing for a reconciliation.

Another case was that of a girl of 19, who had recurrent attacks of asthma most frequently on a Friday. Her mother was inter-

viewed, but could give no cause for this at all, but showed concern for her daughter's condition. When questioned on her recovery from her "sleep" following administration of the drug we discovered that she had fears that her mother was having an affair with the lodger, and that each Friday night was the time when her mother went out with him to the films. It was easy to discuss the nature of this girl's illness with her once these facts were elicited, and shortly after she left the hospital the lodger also left her home, and she has remained well ever since. As a side issue on this case it is somewhat amusing to say that after the daughter had given the information as to the cause of her illness the mother made no attempt to see me again, although originally on inquiry into this girl's home conditions no mention had been made of the existence of this lodger in the household.

Such schizophrenic conditions as we have investigated by this means did not give us any hope for its future use in this particular psychosis, and similarly we had no success with obsessional states.

DISCUSSION

The origin of this method of investigation in theory dates back to 1942, when Selye noted that D.O.C.A. and progesterone, and to a lesser extent testosterone, exerted an anesthesia when given to rats, and Woodbury suggested that D.O.C.A. had an anticonvulsive action in relation to E.C.T. On the other hand, Merriman reported that patients on large doses of progesterone tended to fall asleep. It therefore, seemed that sooner or later a steroid without hormonal or salt retaining effects, but with anesthetic properties, would come to light.

As far as our observations go, we have noted only one disturbing side effect, and that is that two of the patients showed Parkinsonian-like features after their injection, but when this substance was given to Parkinsonians with depression there was no increase in their physical signs or symptoms, so that it would seem that these temporary misadventures were possibly unrelated to the exhibition of this substance.

The literature has referred to the possibility of a phlebitis occur-

ring in the vein used for the injection, but it has not been our experience that this is a considerable risk, and when the smaller injection has been used there has been no complaint whatsoever from the patient.

From the point of view of investigating patients physically, we have found it a most valuable substance for obtaining B.M.R. and E.C.G. recordings when the patient has been, for mental reasons, too uncooperative to permit of these investigations being carried out, and where it has not been possible to obtain basal conditions in the ordinary way for B.M.R. recordings. If a psychiatric exploration is needed, this can follow upon the injection given to obtain the recordings noted above.

A side effect which is not serious, and rapidly disappears, and is present usually shortly after the waking of the patient, is the production of a thought block very similar to that seen in schizophrenia. The patient will sometimes say, when describing symptoms, that "a blind has been pulled down over my mind," and this block may persist for a few seconds. As recovery from the injection proceeds, however, this disappears.

The most important asset that this drug possesses, from our point of view, has been the relief of tension combined with the ability of the patients to discuss their symptoms in clear consciousness. This is in contradiction to any other method of which we have heard for narco exploration or abreaction, and gets rid of the disadvantage of the confusion and depression that may follow the use of the barbiturates or other sedative methods, and of the excitement of methedrine or ether. It therefore, places the patient in a position in which he gains insight without undue emotional disturbance, an undoubted advantage in anxiety states, and because of their clear consciousness avoids the risk of a hysterical attributing his remarks to the effects of a drug, and so denying their authenticity. We feel, therefore, that this is a real advance in this method of approach to psychiatric problems, and although there is a slight delay in obtaining material at the time of the injection, there is a saving of time in the duration of the patient's illness, and it is a method remarkably free from undesirable side effects.

X

Investigations on Endocrine Stigmatized Schizophrenics and Their Families

HANS KIND*

THE FOLLOWING is a report about a series of investigations which took place during the last 15 years under the guidance of Prof. Bleuler at the University Clinic Burgholzli. The investigations were about the interrelationship of endocrinological and schizophrenic disturbances.

The Clinic Burgholzli is a purely psychiatric clinic and is not able to perform complicated endocrinological investigations or hormone analysis. Because of this external limitation we were obliged to turn to problems which were accessible to a less complicated or costly method. The reasons which made our clinic turn to family research in the endocrine psychiatric questions were not all negative (such as the absence of other research possibilities), there were positive reasons: the already established comprehensive foundations in that field of research make this particular line of investigation purposeful and logical. The preliminary examinations by Manfred Bleuler comprised the research of the prepsychotic personality, and the research into the course of schizophrenia and the family pattern of schizophrenic patients. The examinations extended over the years 1929—1942 and they were based on 316 schizophrenic patients and 10,000 of their relatives. Over and above all of these, Prof. Bleuler undertook similar investigations on special sub-groups of schizophrenic patients, on the picture of the late schizophrenic state, and on the influence of shock treatment on the spontaneous course of illness. Calculations of the probability of schizophrenic illness and its distribution in the average population completed his investigations. Not till after the lengthy investigations were completed was it possible to predict, with reliability, in the majority of schizophrenic patients, the spontaneous course of the illness, the

**Psychiatrische Universitätsklinik Burgholzli, Zurich, Switzerland.*

relationship of the prepsychotic personality towards the age and onset of the illness, the course of the illness and its last stages, and, finally, the significance of the above factors in the family pattern.

Once the studies of the above basic problems were completed the investigations suggested themselves (within the endocrinopsychiatric framework) of the possible influence of the endocrine deviations on the course of the schizophrenic psychosis in a single patient and his family.

Often the examination of a single patient does not give a decisive answer to the question of whether the simultaneous occurrence of endocrine and mental disturbances stand in a cause and effect relationship to each other. Nor whether one has a pathoplastic influence on the other, or, whether they are unrelated.

With the help of family research technic it became possible, in such cases, to check the relationship of endocrine and mental disturbances in a family and to discover the nonaccidental correlations.

Sometimes, for instance, it could be shown that the mental and the endocrine disturbances occurred independently of each other among members of a family, even when mental illness took the same course in a member of family as in the patient. However, the absence of the endocrine disturbances in some members but not in others would indicate that the combination of endocrinological and mental disturbances, in the patient was probably only accidental. In other cases it was possible to prove that mental disturbances in a patient as well as in his relatives were often associated with endocrinological disturbances. In such a case there were sufficient grounds to suppose that there existed an inner relationship between the endocrinological and mental disturbances. Finally the third possibility rested with the fact that from the combination of endocrinological and mental disturbances in a family a definite illness shaping influence arose by which it was possible to show that a mental disturbance in carriers of endocrinological disturbances, took a different course than in mental patients who were endocrinologically sound.

The large scale family research, until the present, was directed less towards the examination of connections between the schizophrenic psychosis and the known, clearly defined endocrinological illness, than towards the examination of constitutional variations connected with endocrinological stigmatizations. We have here in mind the so-called acromegaloid body constitutions, the special forms of fat displasias, masculine stigmatization of females, infantile body constitution, disturbances of thyroid functions and goiter. In order to avoid misunderstanding we wish to emphasize that we do not mean by the above mentioned constitutions, variations, simply hypo- or hyperfunctions in hormonal states, but we regard that problem from a more modern endocrinological point of view. Hormone analysis in persons of such constitutions have repeatedly shown that there is no more deviation in the hormonal state than in the average normal person. It has not been proven that the acromegaloid constitution is in any way connected with the functions of the hypophysis. There is, on the other hand, little doubt that the characteristics of the acromegaloid constitution do coincide with changes which occur in the acromegaly due to over-production of the growth hormone. The constitutional masculine stigmatization in the female, in some respect, corresponds with the masculinization, which we see in the cases of androgen hyper-function. There are, however, important differences, mainly in the appearance of the genitals. Until it is proven to the contrary, one might accept the participation of the endocrine function in producing such a constitution although the ways and means by which this happens remain, to a large extent, still obscure. The same considerations are probably valid in certain forms of infantile body constitution. It is considered today rather improbable that there is any endocrine participation in fat displasias.

What connections, until now, have resulted from examinations of endocrinological imbalances in schizophrenia, and, what are the conclusions drawn from the results, upon our general knowledge of schizophrenic incidence?

The connections best known today are the relationships between the acromegaloid constitution and schizophrenia. The results have

also the best statistical foundations, but because of the small number of examined cases it is still not possible to regard the theory absolutely proven. All the results here considered were based on research into the families of schizophrenic patients with acromegaloid body constitution. It became apparent that in these families there is a marked correlation between schizophrenia and acromegaloid body constitution, insofar as many more schizophrenics among the members of the family are acromegaloid than are endocrinologically inconspicuous. Because acromegaloid constitution almost always becomes manifest before the schizophrenia, one is justified in drawing the conclusion, that, in these families the acromegaly stimulates a predisposition to schizophrenia. The inner connection between the endocrine disturbances and schizophrenia might gain further support by showing that in the presence of both disturbances in one patient, the schizophrenia, with regard to its course and its final stages, differs from the average schizophrenia in a patient who is endocrinologically inconspicuous. Primarily, the progressive chronic course, which results in gross mental defects or dementia is considerably rarer. The psychosis is more inclined to run a benign course presenting only slight mental defect as a result. When we turn to other dyscrine constitutional variations we find a quite different relationship to schizophrenia than the relationship found in the acromegaloid body constitution. In our families of schizophrenic female patients with fat dysplasia or masculine stigmatization, the correlation between psychosis and endocrine incident was absent. The fat dysplastic as well as the masculine stigmatized relatives of the patients were no more frequently schizophrenic than is dictated by chance. We are forced therefore to accept the conclusion that the combination presented in the patient is no more than a chance relationship. On the other hand, even in those patients the course of schizophrenic illness has been influenced. The female schizophrenic patients with masculine stigmatization present often, in their psychotic states, psychological masculine characteristics. They are often especially negativistic, harsh, aggressive, evasive and tense. On the other hand, in the fat dysplastic schizophrenic the illness takes on the average more

often chronic progressive course and less often a benign cyclic form. As in the acromegaloid constitution body infantilism in its variety of forms appears to accumulate in certain families. Among the relatives of schizophrenic patients with infantile stigmatization, as among acromegaloids with schizophrenia, a positive correlation could be shown between the two conditions. However, it was less marked than in the acromegaloid and statistically, at least at present, less certain. The assumption might be drawn that infantilism and schizophrenic psychosis are not only combined by chances but are internally related.

Is the conclusion justifiable? Like the acromegaloid constitution, does the infantile constitution, as such, produce in certain families a predisposition to schizophrenia?

In the acromegaloids there are sufficient grounds to assume that we are dealing with a genetically determined constitutional variation which has its basis for the disturbance in the hypophysis-midbrain and this in turn creates the predisposition to schizophrenia.

The genetic predisposition in infantilism is rather questionable. Certain important ideas point to the possibility that some given patterns in human relationships, within the individual lifetime, are able to promote the development of infantile constitution.

The question therefore arises as to whether the supposed influence of infantilism on schizophrenia is really connected with the particular infantile body constitution as such, or whether the simultaneous occurrence of infantilism and schizophrenia cannot be referred back to another factor in the individual's life history (e.g. an emotional disturbance in the pattern of interhuman relationship). In other words, does the releasing influence derived from a particular family milieu produce a schizophrenic illness and promote the formation of an infantile constitution?

Should this supposition be confirmed, if only for single families, we are still faced with fundamentally different inner connections in the acromegaloid and infantile body constitutions and schizophrenia, despite the apparent external similarities between them. In the first case genetically established somatic disturbances deter-

mine the body formation, as well as the predisposition to schizophrenia; in the second case, the influence on the formation of infantile body constitution and psychosis derives from a particularly created emotional milieu.

Needless to say, the above considerations are mostly theoretical and, their underlying basis in fact is still not complete.

Family research, it seems, has shown without any doubt two things: primarily that endocrine influences are able, in various ways, to modify the schizophrenic illness (the influence probably depends less on the nature of endocrine changes than on the individual and family peculiarities of the psychosis), and secondly, that there is little reason for looking for endocrine influences in all schizophrenics and that we might expect more from careful research on small groups.

We shall discuss this question again later. Here we should like to report further examples in family research of endocrine disturbed schizophrenics. We have selected as a basis, not constitutional peculiarities of which the endocrine origin is still awaiting proof, but proven endocrine hyper- and hypofunction states, namely hyperthyroidism and myxedema in combination with schizophrenia. The endocrine disturbances in such patients were not much different than similar disturbances would produce in the mentally sound, and were accessible to the usual medical or surgical treatment. It was, however, remarkable, that the endocrine pathology in all the 17 examined cases with only one exception preceded the psychosis.⁷ Often the two illnesses, at least for a time, run a parallel course. The last observation is principally true for these the psychosis. Often the two illnesses, at least for a time, run a ical symptomatology of schizophrenia. We mean mainly the either acute, excited-catatonic or anxious-stuporose which do not follow the typical schizophrenic picture. In this group were also found the sub-acute depressive-catatonic mixed psychosis and atypical paranoid psychosis. All the above psychotic forms have this in common. In their appearance that they are close to schizophrenia, and, in part they may be indistinguishable from schizophrenia but at the same time may show many atypical forms. The research of blood

relatives of these patients with regard to mental manifestation and endocrine disturbances revealed surprising results. Sometimes among the relatives were found psychotics who presented more typical schizophrenic pictures than the accumulation of atypical psychotic forms found in the patient. The total inheritance of schizophrenia was not substantially different from the distribution of schizophrenia in general. In so far as it is possible to draw a conclusion from the small numbers which we have had at our disposal, it seems that the factor of inheritance of the disease is not unlike that in the acromegaloid schizophrenic. In addition there was found among the relatives of the patients a recognizable positive correlation between ordinary goiter and mental manifestations of an unspecific nature. The members of the family with goiter were considerably more often afflicted with some psychological disturbance than the goiter free members. The simple psychiatric experience in goiter endemic areas, like Switzerland, teaches us that the above finding is not an every day occurrence. We were also able to gain some information from other research workers who tested the correlation of psychiatric manifestation and goiter. They based their investigations on mentally normal inhabitants, drawn from a goiter endemic area, and they found that the correlation is not higher than could be expected by chance. We must assume that in the families investigated by us there existed a tendency to personality disturbances, so that the added development of even a slight disease of the thyroid, like the common goiter promoted the manifestation of most varied forms of personality disturbances in the patient.

On the other hand, it is conceivable that the same exogenous noxic influences which generally lead only to the development of a goiter (in families with a special disposition to mental imbalance) may also unfold an unspecific action on the mental happening. Should however, a thyroid disease coincide with a schizophrenic psychosis in such a family, then a strong illness shaping influence directs the acute episodes of the psychosis towards a more benign form. What is the significance of the observations, which we made with a great expenditure of work and time, on our

knowledge of the pathogenesis of schizophrenia? Until now a total of 128 strains of endocrinological stigmatized schizophrenics together with 16,000 of their relatives, have been investigated in the above described manner in our clinic. This number is large enough to allow more than just a chance observation. In the first place the view is becoming apparent that the endocrine imbalance does not equally affect all schizophrenic patients, but acts rather selectively on a single patient or on a whole family. It is possible that in such circumscribed families a strong illness shaping action arises, which is certainly not applicable to the entire schizophrenia. Therefore, it is highly probable that there are sub-groups of schizophrenia in which endocrine disturbance create a pathogenic as well as pathoplastic factor. Moreover, the disturbance in the endocrine balance may have a different cause, for instance inheritance in the acromegaloid, or psychosomatic explanations in certain forms of infantile constitution, of it may depend mainly on exogenous noxic influences as in the thyroid disturbances in the form of goiter. Our observation therefore gives reasons for the assumption that all the different factors and influences do effect basically the schizophrenic illness (though not all schizophrenics in the same manner). This however, is not applicable in all cases of schizophrenia but depends to a great extent on the peculiarities of each family, and, possibly also of the individual. An influence, which in one family assumes a strong illness producing or illness shaping character, is of no importance in other families. The logical consequence of this point of view is that it is rather pointless to investigate any endocrinological function on large heterogeneous institutional schizophrenic populations, and then to attempt to draw conclusion with regard to schizophrenia in general. On the other hand, it might be fruitful in the future to observe extensively single patients or whole families from many angles and over a long period. Our conclusions are close to the conditions laid down for research by Max Reiss and his colleagues, who turned successfully to research in endocrinological problems (disturbances of the single hormonal balance in individual schizophrenic patients). It seems that from the combination of our methods of investigation of

family research and modern laboratory methods of Max Reiss we may expect important advances in endocrinological psychiatric pathogenetic research in schizophrenia.

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XI

Physiological Changes in Schizophrenia*

G. E. HOBBS, J. A. F. STEVENSON, CAROL BUCK
and E. V. METCALFE†

WHEN KRAEPELIN first delineated the schizophrenias from other psychoses they were looked upon as the psychic component of some type of underlying organic disease. This belief rested on no firmer foundation than the current psychiatric philosophy of the time, lacking, as it did, any supporting factual evidence. The work of Freud, Bleuler and Meyer led to a complete change of emphasis, with all interest now being centered on the mental mechanisms involved. Although it was not specifically stated, the impression developed that this disorder could be understood, and perhaps prevented, by studying cases purely from the psychological point of view.

However, the concept of organic etiology was never completely abandoned. In the early stages effort was directed to identifying anatomical changes in the brains of schizophrenias. Although many positive reports were current in the literature, these have never been substantiated. The general feeling now is that if there is an underlying organic cause it is to be found in some more subtle fashion than changes within the nerve cells.

Studies on the physiology of schizophrenia have overlapped in time with both the psychological and anatomical concepts. To a large extent they have tended to follow closely the progress in medicine and its basic sciences. With each new development in medicine this new knowledge was rapidly applied to the study of schizophrenias. The early studies, which consisted essentially of

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†Department of Psychiatry, Westminster Hospital, Department of Veterans' Affairs (Canada) and the Departments of Physiology, Psychiatry and Preventive Medicine, The University of Western Ontario.

point values of many substances, provided little of a concrete nature other than to demonstrate that most values had a greater range of distribution about the mean in the schizophrenias than in comparable groups of normals.¹ Gradually there evolved the concept, however, that no single component in the physiology of the schizophrenic would explain this condition. The abnormalities were to be observed more adequately in a study of the variation of homeostasis over a period of time.

For approximately 10 years now, we have been studying physiological changes in schizophrenia at Westminster Hospital, Department of Veterans' Affairs. This was initiated in a very limited way. More recently funds and facilities have expanded to allow an investigation of the more subtle factors. In this paper, I would like to review briefly our findings.

STUDIES IN BODY TEMPERATURE REGULATION AND LOBOTOMY

Temperature in Schizophrenia²

Our studies began in the initial postwar period when the veterans' hospital embarked on a rather extensive and well controlled lobotomy project. As part of this project it was suggested we might make more fundamental studies in an attempt to determine more about the nature of the changes produced by this procedure. Our initial premise, by no means an unique one, was that the beneficial effects of lobotomy were probably to be found within changes in the autonomic nervous system and thus would be more readily demonstrated by tests of function directed in this area, than by anatomical study of brains of lobotomies who had deceased. Thus we looked about for an easy measurement of autonomic function which could be applied to a large group of patients without getting us involved in the difficult technicalities of measurement. As a result of a conference held between the psychiatrists at the veterans' hospital and the professors of physiology and biophysics, it was suggested that studies in the temperature control field would most likely meet these requirements, since it represented an aspect of homeostatic function which depends upon a fine degree of

autonomic integration at the hypothalamic level. In addition, there were a considerable number of references in the literature which suggested a disturbance of thermo regulation in schizophrenia, the group in which most lobotomies have been performed.

In this study, we limited our investigation of the temperature pattern in schizophrenia to a study of the diurnal cycle over a period of 4 days and the reaction of schizophrenics to a cold bath. The subjects included 40 schizophrenic patients and a comparable series of orderlies who served as controls.

In the schizophrenias, the individual temperature measurements at any hourly period showed the usual increase in scatter of results characteristic of many measurements in this group. In addition, there was a significant disturbance in the normal cycle pattern of the temperature throughout the 24-hour period. From a statistical point of view, this showed up readily by a reduced mean daily range between the maximum and minimum values recorded, e.g.: patients $1.5\text{ F} \pm 0.09$, controls $2.0\text{ F} \pm 0.09$; $P. < 0.01$. Moreover, the time of occurrence of both the daily maximum and daily minimum temperatures showed a marked discrepancy from that found in normal subjects, with, again, a marked scatter in the values. Further information of a descriptive nature was obtained by the study of the individual records of patients. The cycle tended to be erratic or absent and marked by irregular spikes and fluctuations.

Observations of patients and controls during and after a period of 2 hours in a cold bath simply tended to confirm the observations on the rigidity of the patients' temperature control noted in the daily cycle, e.g.: total change in temperature after bath—patients $-0.2\text{ F} \pm 0.16$, controls $-1.0\text{ F} \pm 0.12$; $P. < 0.01$.

Thus the abnormalities in temperature were chiefly in the form of irregularity and rigidity of pattern. The irregularity was demonstrated by reduced day-to-day variation in the size of the diurnal temperature range as well as in the timing of the maximum and minimum temperatures. The rigidity or lack of adaptability of the thermo regulation was apparent in the flat diurnal cycle or in the cycle whose essential flatness was broken periodically by abrupt

changes in temperature. The clearest demonstration of rigidity, however, was in the reaction to the cold bath, where frequently the schizophrenic subject's temperature remained in a steady state, both during and after the bath, in direct contrast to the normal tendency to fall on contact with the warmer air of the room.

When these results were analysed by duration of psychosis, some interesting findings were clear. The abnormalities tended to be most pronounced and most obvious in those cases of psychosis of under 4 years' duration. Once 4 years of psychosis was experienced by the subject, then his temperature pattern tended to revert toward the normal, e.g.: mean daily range for those with psychosis under 4 years' duration $1.3\text{ F} \pm 0.09$, for those above 4 years' duration $1.9\text{ F} \pm 0.15$. Since many studies of this nature are reported as "schizophrenic" without consideration of even such an elementary factor, it is apparent why contradictory findings are to be found in the literature.

Relation of Lobotomy to Body Temperature

After lobotomy the temperature pattern in the schizophrenics changed markedly. It was comparable to that found in the more chronic schizophrenics without lobotomy, and as a group tended toward the normal. There was no apparent relationship between clinical improvement and changes in this basic physiological measurement.³

There are references in the literature which are concerned with the relationship, between the oral and rectal temperature in schizophrenia. One observation tends to show a greater correlation in the schizophrenic than in the normal group. If correct, this is in direct contradiction to the usual finding of greater variability in physiological measurements in schizophrenia than in normal. As part of our study we compared these findings in 14 schizophrenic patients before and after lobotomy and in 10 normal subjects used as a control. In the normal group we found a mean difference of 0.7 F between these two readings in contrast to 1.0 F for the schizophrenics preoperatively and 0.8 F following operation. Moreover, the correlation of the individual measurements was much

lower in the schizophrenics both before and after operation than in the normal controls. In the normals the correlation coefficient of the two values was 0.73 compared with a correlation in the schizophrenics of 0.35. It is interesting to note here too that the values in the schizophrenic group after operation narrowed in the direction of normal.⁴

Weight Changes with Lobotomy⁵

As part of the lobotomy project we investigated changes of weight following the operation. The marked increase in body weight following this procedure has been mentioned frequently in the literature,⁶ and numerous hypotheses have been offered to explain it. By a comparison of patients who show marked improvement following operation, and by comparison of their ultimate weight with the standards provided for the same age, sex and height as that of the patient, we were able to show that these changes were limited almost exclusively to patients who had improved following the procedure and that their weight simply tended to revert closer to the hypothetical normal.

ADRENOCORTICAL FUNCTION IN THE SCHIZOPHRENIC

For a number of reasons, we changed the emphasis of our studies on schizophrenia from temperature control to exploration of adrenocortical function several years ago. Initially our facilities were limited to one technician and we explored only the Thorn test of adrenocortical function, but more recently the facilities of a well-equipped and extensive metabolic unit have been available to us. This has allowed us to expand the study and to explore other indices.

The Diurnal Cycle⁶

Because of our previous interest in temperature cycle, it was natural that we should begin a study of adrenocortical function by a survey of this particular cycle. Using the eosinophil count as an index of adrenocortical function, since this had previously been observed not only in the eosinophils but in other indices of adrenocortical function. Our study here added little to our basic under-

standing of schizophrenia but did confirm the work of others that a marked cycle in eosinophil levels was present throughout the 24-hour period. The magnitude of this cycle was in the vicinity of 50 per cent of the 24-hour mean level, varying from —31 per cent at noon to +18.8 per cent at midnight. One interesting finding was the consistency of the eosinophil count in psychotics at intervals of several months. When individual counts were compared for the same patients over a period of 3 to 6 months, it was found that there was an extremely high correlation of 0.84. The general nature of the cycle was inverse of that of the temperature cycle, namely, the eosinophils having the highest values when the temperature was lower and the reverse. Since the eosinophil cycle is the inverse of the adrenocortical function, it, therefore, follows that the adrenocortical function has a cycle that is in phase with that of the temperature.

Differences in Reactivity of Adrenocortical Function in Schizophrenics and Normals

Using the Thorn eosinophil test, the reactivity of the adrenocortical function in a group of 30 schizophrenics in response to test doses of A.C.T.H. on one day and epinephrine on another was investigated. In this test, a fall of 50 per cent in the eosinophil level is considered indicative of normal adrenocortical function. In our schizophrenic group, however, only 18 of the 30 schizophrenics showed such a response on the corticotropin morning. Thus, by this test, there is a group difference in the reactivity of the adrenocortical function in schizophrenics as compared with normals. Some schizophrenics show a fall that is within the normal range, but others fall outside this range.⁷

The next procedure was to study multiple indices of adrenocortical function on 39 schizophrenics approximately equally divided between catatonic and paranoid and 20 orderly controls.⁸ Again the tests were carried out on 3 successive mornings, a normal control on the first morning and A.C.T.H. and adrenalin on successive mornings. No specific new finding emerged from this more elaborate investigation, but confirmation of previous observa-

tions on schizophrenics has resulted from the study. Schizophrenic groups showed the previously reported tendency to polyuria, and increased sodium and 17-ketosteroid excretion. Another extremely interesting finding which we decided to follow up with more detailed studies was the reduction in the excretion of phosphate, which appeared to be more in one diagnostic group than the others. The findings on the eosinophils were again confirmed.

*Differences between Catatonic and Paranoid Sub-groups
of Schizophrenia*

In our early studies of adrenocortical reactivity of schizophrenics, using eosinophils as an indicator, we noted some interesting differences between the paranoid and catatonic groups.⁷ As far as the resting levels of eosinophils was concerned, the values for the 11 catatonics (172 ± 24) approached closely the normal resting level in the orderly group (173 ± 28), and a high percentage of the catatonics showed a fall of 50 per cent or greater after 4 hours following epinephrine or corticotropin. The 12 paranoid, on the other hand, differed from both the catatonics and the normal group in the same indices. The resting level of eosinophils was twice as high (327 ± 62) and the mean relative response to epinephrine and to corticotropin was under 40 per cent with a low proportion showing a fall of greater than 50 per cent 4 hours after the epinephrine or corticotropin. Thus the general impression gained from these observations is that the paranoid shows evidence of subnormal activity and response of the adrenocortical system, whereas the catatonics appear to have a moderate hyperactivity or at least a hyperactivity of this system.⁷

When the adrenocortical study in the paranoid and catatonics was extended by the use of multiple indices, other interesting findings were obtained.⁸ During the control periods (7:00 to 9:00 a.m.) our schizophrenics showed no difference from normals in the rate of urinary excretion of water creatinine, uric acid or potassium, but did show a higher level of sodium and 17-ketosteroid excretion, and a lower level of phosphate excretion. When the whole control period (7:00 to 12:15 p.m.) is included these

differences are still apparent and the tendency of schizophrenias to polyuria also becomes apparent. When the schizophrenias are separated into catatonic and paranoid the increased excretion of water sodium and 17-ketosteroids is common to the two groups, whereas the decreased excretion of phosphates is peculiar to the catatonics.⁸

Our current investigation is centered about the more complete investigation of the metabolic changes involving phosphorous in schizophrenics.

SUMMARY AND CONCLUSIONS

With the increase in knowledge of basic metabolism, various tests have been applied to schizophrenia that have increased our knowledge of this condition. Up to the present time we have no clear-cut indication to determine the vital question of whether we are simply measuring secondary phenomena induced by the state of the psyche, or whether the data investigated have more fundamental significance. Although a great deal of the work has been contradictory, and at times opposite results are obtained by differing workers, yet out of this whole gamut of information come some fairly clear-cut consistent findings.

To us it would appear that the real need in this area is not only the application of more refined and more delicate tests, but a real reorganization of the clinical material upon which we base our conclusions. There has been no clear-cut relationship established between the laboratory findings and the description of the clinicians, although our findings on catatonics and paranoid look suggestive. What we think is needed is a more careful attention to what we mean by schizophrenia. It would seem reasonable, and a worthwhile result of a conference such as this, to set up a working party which might define various categories of schizophrenics in a more clear-cut, objective manner, so that workers in one part of the world would refer more readily to workers in other parts. Our own findings on the differences in body temperature control with duration of psychosis or diagnostic sub-categories would suggest that much of the confusion might originate in the makeup of the schizophrenic

group investigated. Also, many of the findings may have a more mundane explanation, e.g.: our findings on weight gain.

Other needs, of course, would be a long-term study on a limited number of patients in which the clinical observations and the laboratory findings are coordinated over a period of time.

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XII

The Endocrinology of Deep Insulin Coma Therapy

W. W. KAY*

DEEP INSULIN coma is a form of severe stress. The effects of stress on a reactive organism are twofold: first to stimulate, then to fatigue. In an organ already fatigued, stimulation may not occur and fatigue may be intensified to the point of exhaustion. Although its primary point of impact may be on the adrenal cortex, stress acts on the endocrine system as an integrated whole. There is an interplay of the endocrine glands, increase of outflow from one, suppression of another, feed-back and reciprocal relationships. It is evident, therefore, that the effect of a stress as complicated as that started by insulin, a hormone which has various antagonists among the other hormones, cannot be described by such simple terms as "stimulation" or "fatigue" of any one gland. We must look at the problem as involving the whole endocrine system, and investigate the function of not one gland only, but of as many as possible. We can investigate adrenocortical function and thyroid function, and by combining the results get some idea of the state of the function of the anterior lobe of the pituitary. We can also take into account gonadal function and somatic maturity. If this is done, the problem almost automatically extends to the elucidation of the relationship of insulin coma therapy to its results for the patient.

Three years ago we (Batt, Kay, Reiss, Sands 1957) started to study, longitudinally, the endocrine concomitants of successful and unsuccessful insulin coma therapy. So far we have studied 83 patients on a multifactorial basis. At first, our main attention was directed only to clinical endocrinological investigations and the

*Mental Hospitals' Group Laboratory at West Park Hospital, Epsom, Surrey, England.

total 17-ketosteroid excretion rate. Then the clinical investigations became broadened when we started to see the enormous role played by sexual immaturity and prematurity on the result of the treatment. Ketosteroid investigations alone give an incomplete picture of the activity of the adrenal cortex; corticoids must, therefore, be estimated also. The great fluctuations seen in the daily steroid excretion rate, particularly in the very florid schizophrenics, make it necessary to have steroid determinations for at least two weeks before starting insulin treatment. In addition, full investigation of thyroid activity is necessary. When all these investigations are done, we are able to attempt to coordinate the results of treatment with the changes, not in one gland only, but also simultaneously in other members of the endocrine circle. Even then, it has to be recognized that the lasting success of any course of insulin coma treatment depends very much on a stabilizing factor related to somatic maturity; hormone equilibrium reached after insulin coma therapy can only be maintained in patients whose constitution has reached a certain degree of maturity. Many factors, then, have to be taken into consideration in a longitudinal investigation. Their number prevents us at the moment from carrying out valid statistical analyses since our homogeneous groups so far are small. If we made bigger groups of our cases, the basic samples would not be homogeneous or comparable.

At present, therefore, we can only discuss some factors which have started to crystallize out as the essential determinants for success or failure of insulin coma therapy. A prognosis can only be made by very carefully combining all the data available as the basis for a conclusion. For insulin treatment to be successful, all the factors mentioned as being necessary for success must be present. The absence of one single positive factor appears to doom the whole treatment to failure even when the other factors are all in agreement.

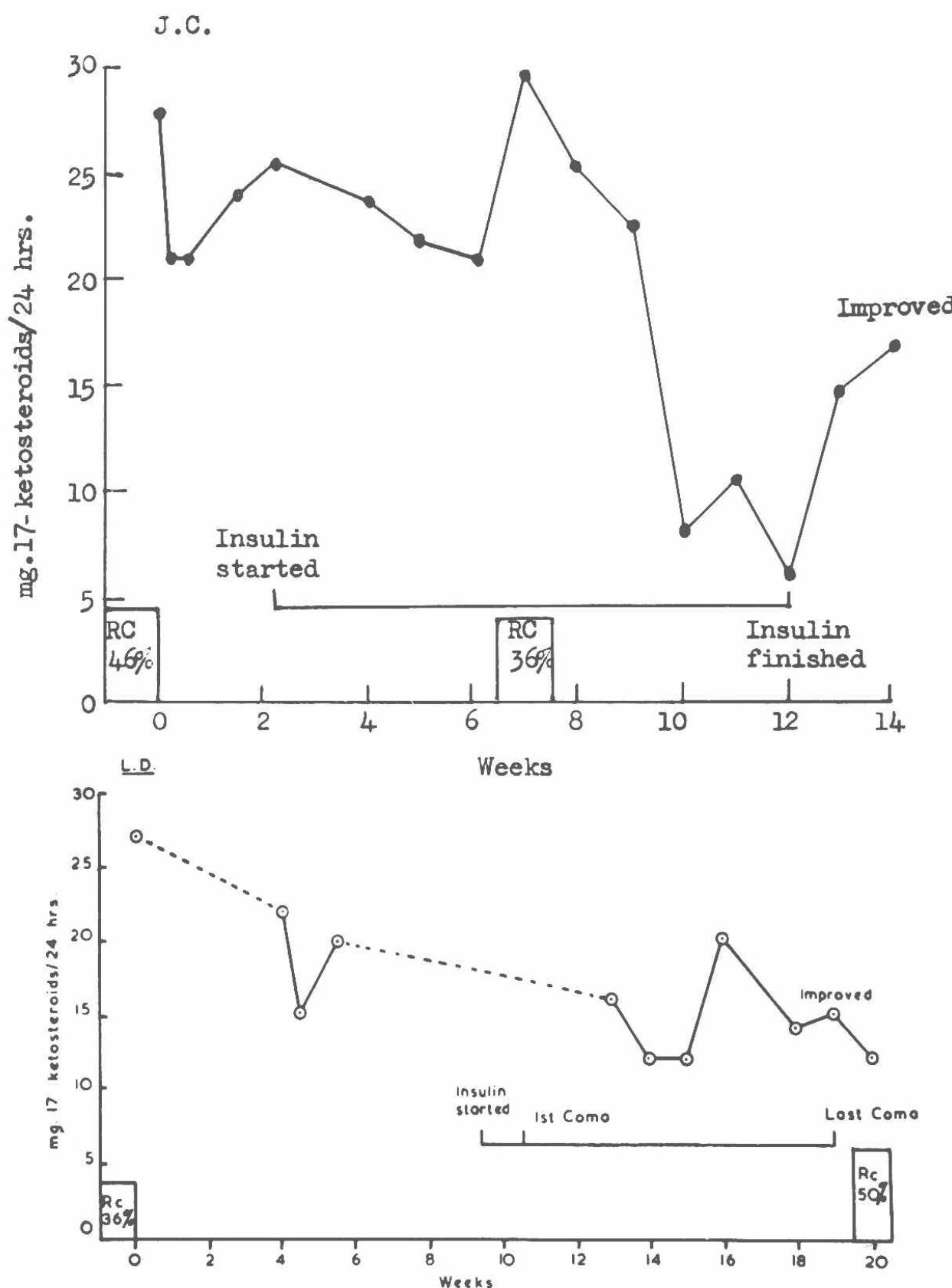
The somatic factors involved in successful and unsuccessful deep insulin coma treatment will now be enumerated and discussed. They are as follows:

Table 1
ENDOCRINE FACTORS INVOLVED IN THE PROGNOSIS OF
INSULIN COMA TREATMENT

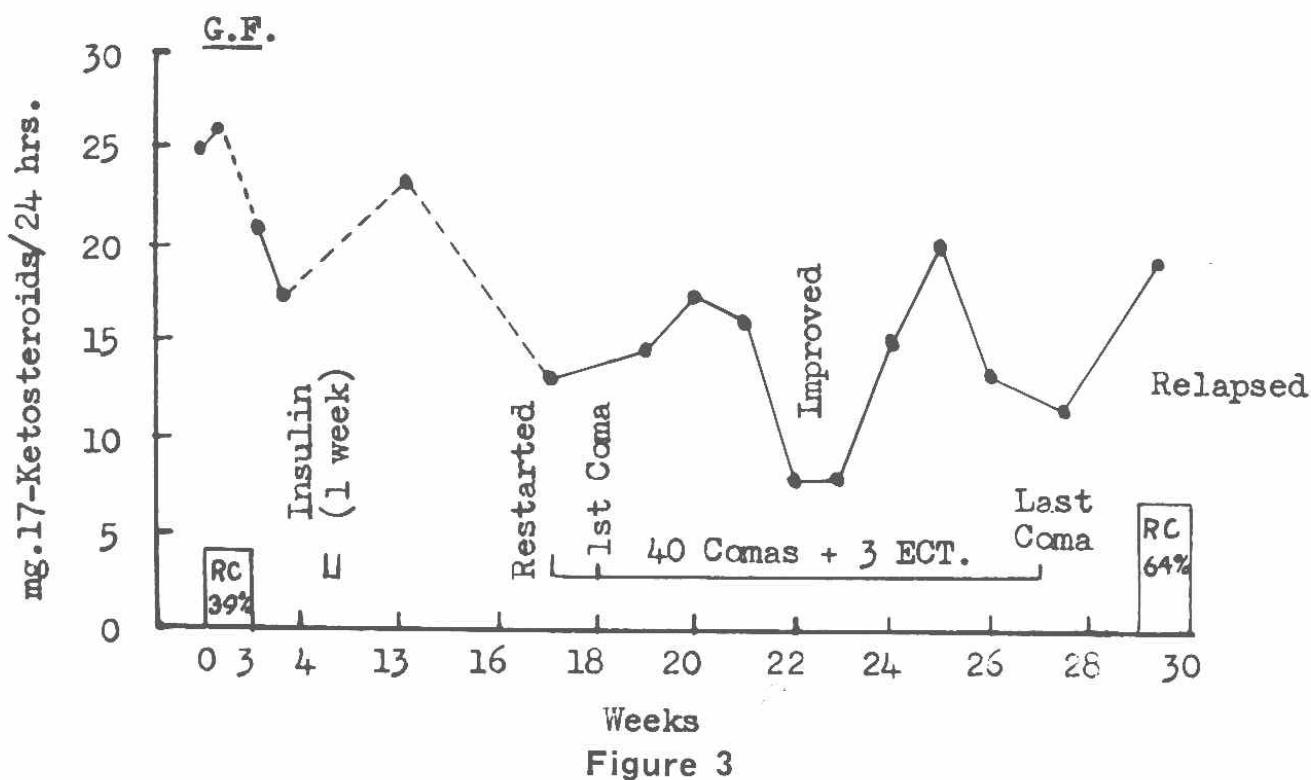
FACTORS	GOOD PROGNOSTIC SIGNS	BAD PROGNOSTIC SIGNS
1. Hormone balance.	Achievement of normal hormone equilibrium.	Failure to achieve normal hormone equilibrium.
2. Degree of physical maturity.	Full maturity or pre-maturity. Mature body form. Acne. Fully developed secondary sex characteristics. Normal menstruation pattern before mental breakdown. Prematurity secondary to adrenocortical hyperactivity.	Immaturity. Immature body form. Imperfectly developed secondary sex characteristics. Open inguinal canals. Small testicles.
3. Pattern of Ketosteroid excretion during coma treatment.	Initially high or high normal Ketosteroid excretion falling, maybe to low levels, then stabilizing in the normal range. Initially low, then rising into normal range and becoming stable there.	Initially high excretion falling and then rising above normal range and remaining unstable. Initially low excretion remaining low. Initially low excretion rising and then falling to low levels again.
4. Thyroid activity.	Low activity secondary to pituitary anterior lobe underfunction can normalize. Low thyroid activity reciprocal to adrenocortical activity can normalize. High thyroid activity secondary to high pituitary anterior lobe activity can normalize.	Primary low thyroid activity. Primary high thyroid activity (may be aggravated).

Normal hormone equilibrium

THE ACHIEVEMENT of a normal hormone equilibrium (Figs. 1 and 2) especially in the thyroid-adrenocortical axis is essential for a successful result. If this does not occur, (Fig. 3) it is almost invariably right to predict a relapse, however promising the immediate result of the coma course may appear.



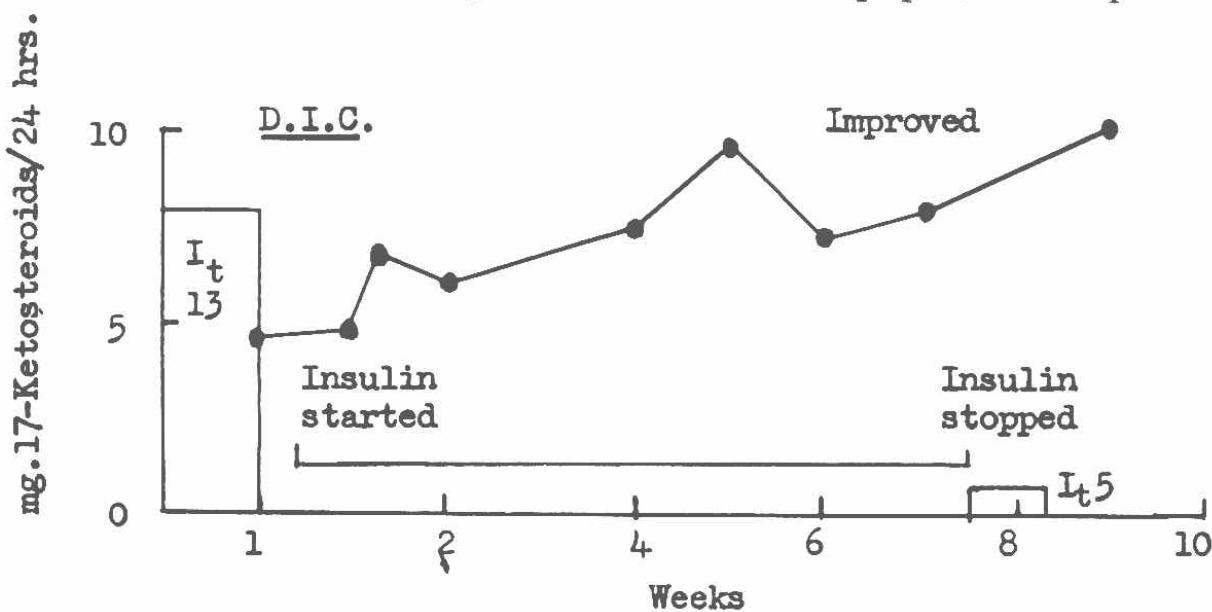
Figures 1 and 2

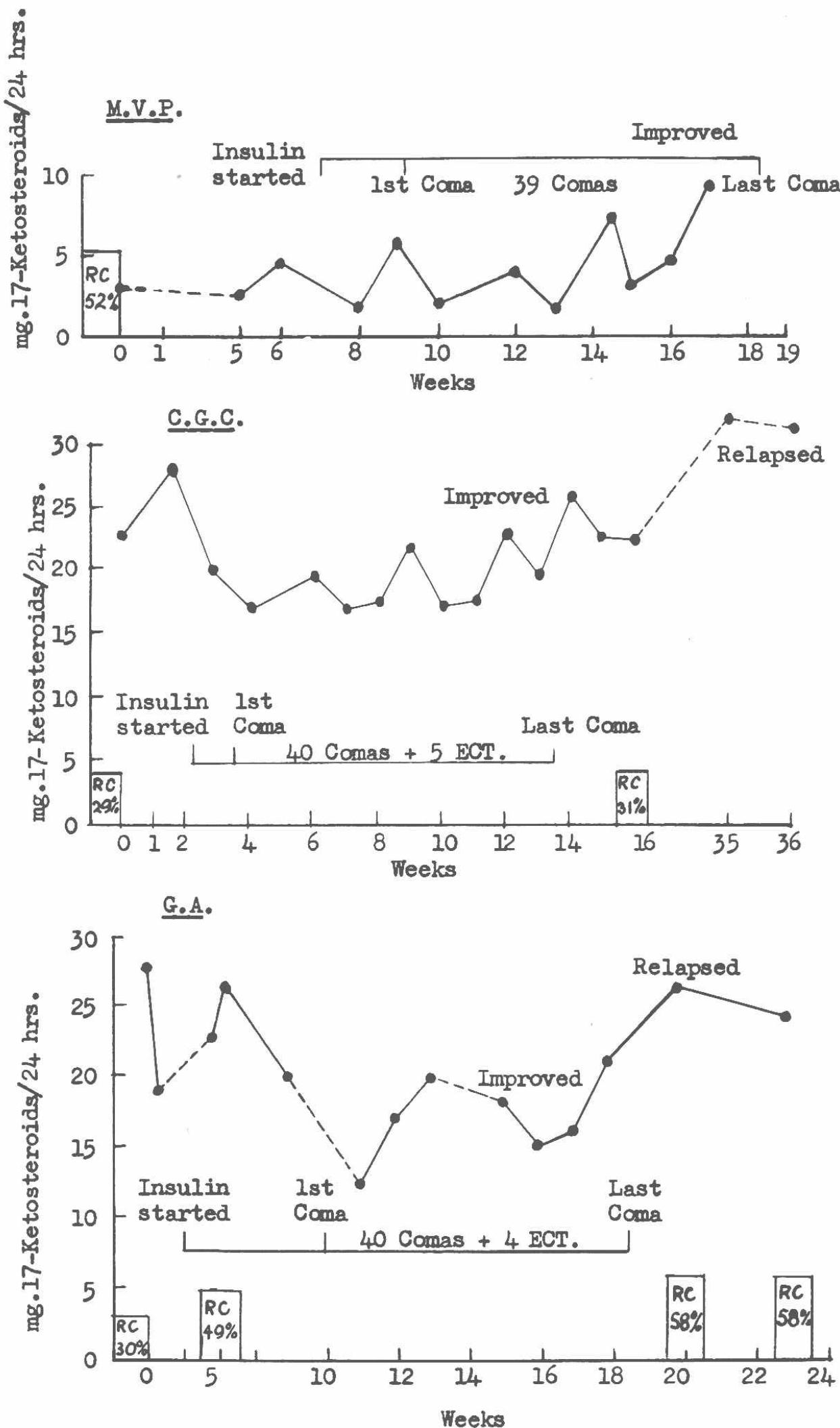


Physical maturity

(1) IN WOMEN. Before the mental breakdown there should have been normal menstruation in normal cycles. Body formation should indicate maturity. Immaturity in this sense predicts failure of deep insulin therapy, prematurity success. The presence of acne is a good prognostic sign.

(2) IN MEN. Immaturity in juveniles (Fig. 4 and Fig. 5, mature and immature contrasted) as discussed in the paper by Bullmore, Reiss and Smith (1957), and as seen in later ages also (Figs. 6 and 7), characterized mainly by open inguinal canals, small testicles, and not fully developed secondary sex characters, regularly leads to failure. As pointed out in that paper, these patients





Figures 5, 6 and 7

generally have a low ketosteroid excretion rate, but some may have excretion rates in the upper normal range owing to the effect of precipitating stress (Figs. 6 and 7).

Prematurity as a sequel of adrenocortical hyperactivity is usually a very good prognostic sign. As in women, the presence of acne is a good sign.

The pattern of the ketosteroid excretion rate curve

IF THE ketosteroid excretion rate starts at a high level, in the upper range of normal or above, or even in the normal range, and starts falling below the normal range, usually the patient starts to improve. Improvement is maintained if the ketosteroid excretion rate steadies itself in the normal range (Fig. 2). If, however, the ketosteroid excretion starts to rise again above the normal range or is not stabilized, (Fig. 3) then a relapse can be definitely predicted even if the patient leaves the hospital classified as "recovered." This type of instability is very often seen in people with open inguinal canals.

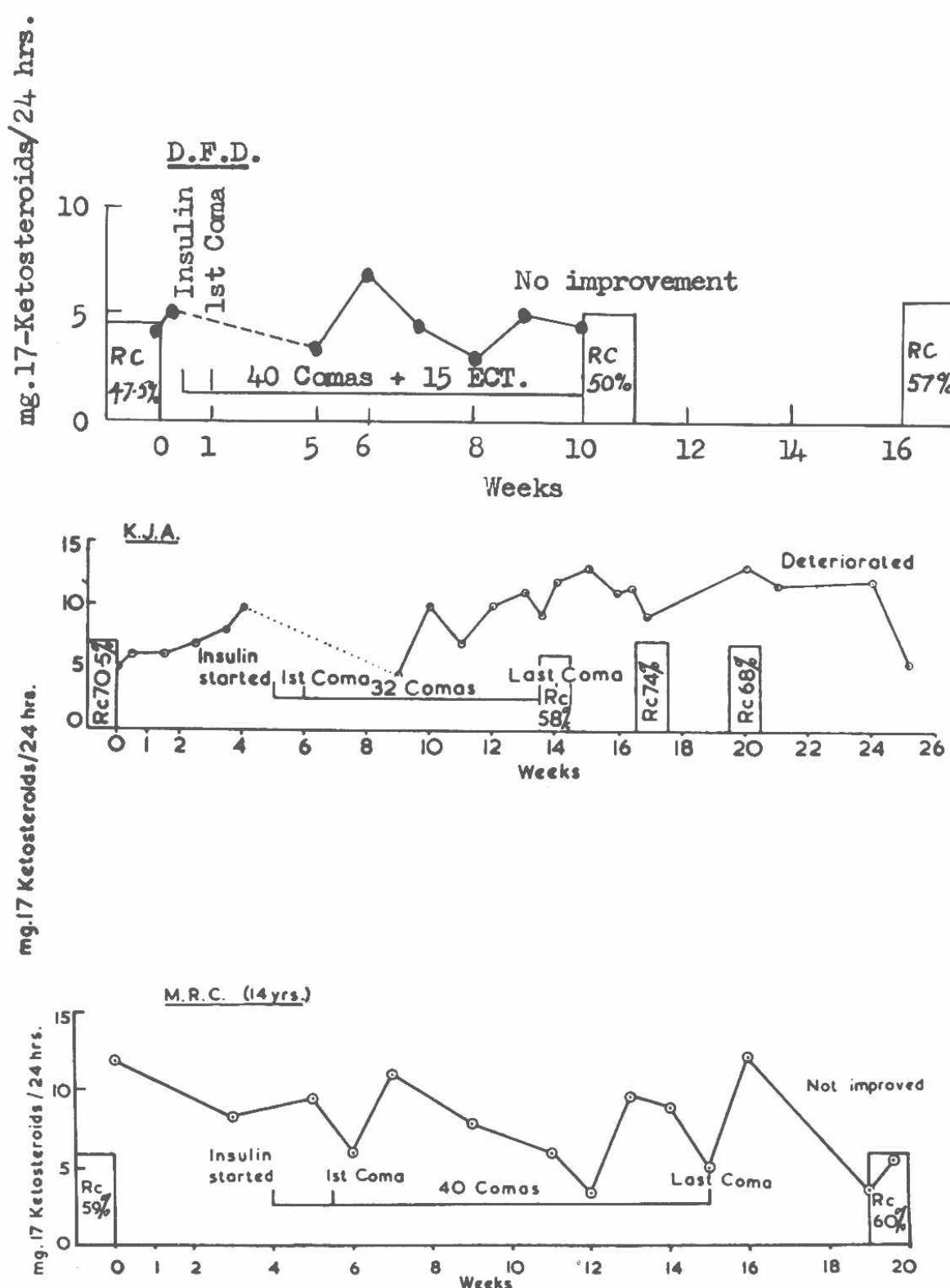
When the ketosteroid excretion rate is low initially and remains low (Fig. 8) without reaching the normal range, then the reserve power of the adrenals is so reduced that even the intense stress of the insulin comas is unable to mobilize more cortical hormones. The reserve power may become even more reduced and this seems to be connected with clinical deterioration. There are other patients with a low initial ketosteroid excretion rate, in whom, owing to some residual cortical activity, (Fig. 9) a rise in the ketosteroid excretion rate occurs after the stress of insulin comas, but when the last reserve has been exhausted (Fig. 10) there follows a sudden fall in the ketosteroid excretion rate which also is connected with clinical deterioration. There are others (Fig. 11) in whom the ketosteroid excretion rate is stabilized in the normal range. These are mainly people who would probably have improved spontaneously due to well preserved reserve power of the adrenal cortex.

Thyroid

LOW THYROID activity, if primary, is usually a bad prognostic sign. If, however, it is secondary to pituitary underfunction, it can normalize under insulin coma stress as after E.C.T. Low thyroid

activity which is reciprocal to high adrenocortical activity may become normal with improvement of the patient. If it remains normal, the improvement is maintained: if, as sometimes happens, it becomes high, the patient relapses.

Normal thyroid activity is not often influenced by insulin stress. In only a few instances it is caused to move outside the normal range owing to activity of the anterior pituitary lobe. When this happens, the prognosis is usually poor.



Figures 8, 9 and 10

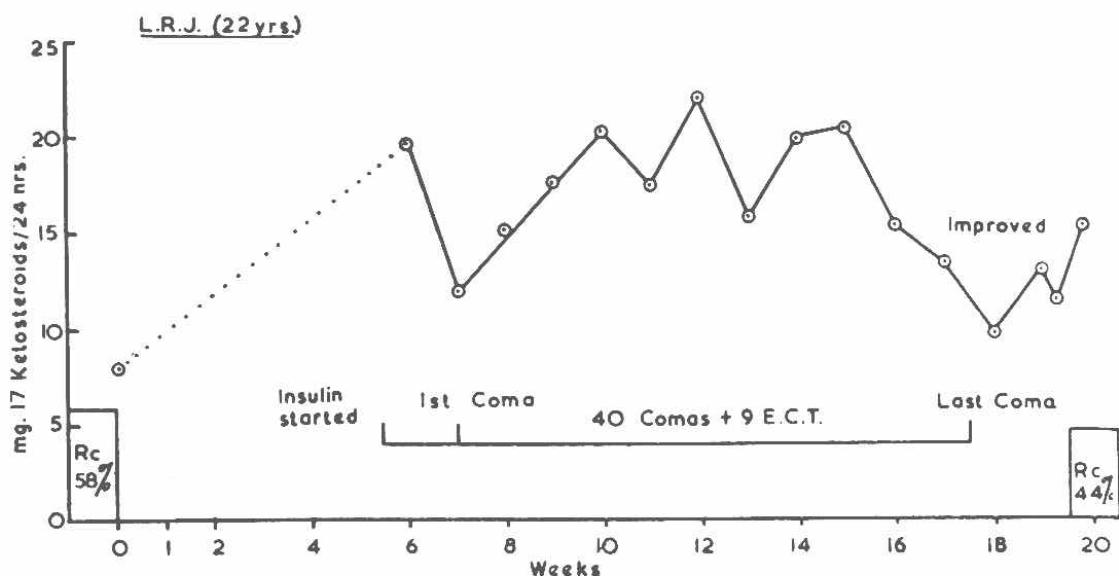


Figure 11

High thyroid activity (Fig. 12), if primary, is very often a bad prognostic sign and is often aggravated during insulin coma therapy owing to additional stimulation of the anterior pituitary lobe and increased mobilization of thyroid stimulating hormone. In cases of secondary hyperthyroidism where the pituitary anterior lobe is already at maximum activity, the production of TSH may become exhausted under the additional stress of insulin coma, thus causing an improvement in the secondary hyperthyroidism.

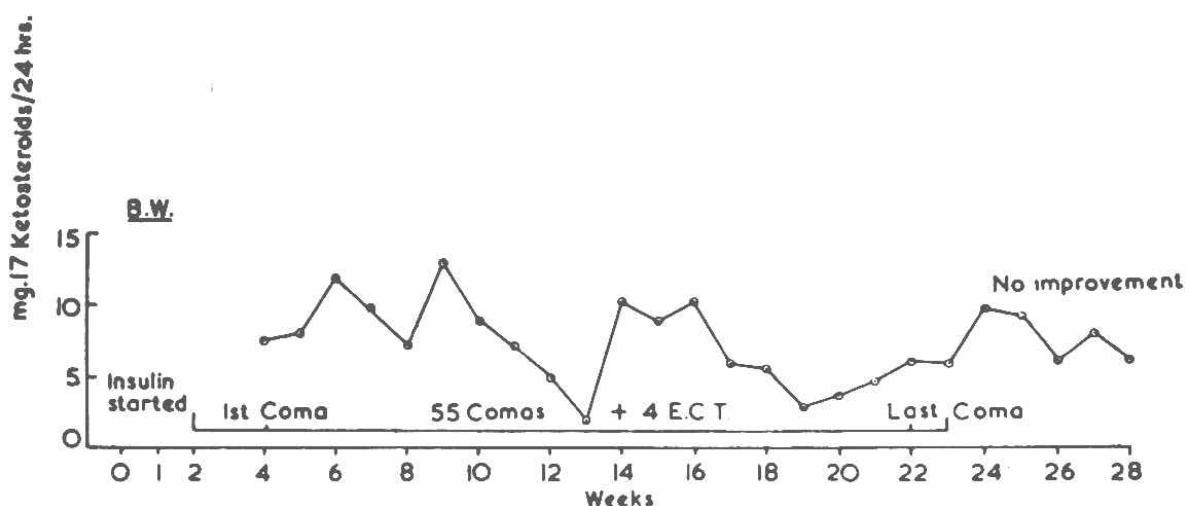


Figure 12

Whatever may be the psychiatric state of a patient and the assessment on clinical grounds of his suitability for treatment with deep insulin coma, *all the somatic factors* discussed must be considered before starting deep insulin coma therapy, if a reliable prognosis is to be made.

The results on which the foregoing tentative conclusions are based have bearing on the pathogenesis of schizophrenia. In the paper on thyroid function (Bullmore, Kay, Smith and Stott 1957) presented by my colleague during this Symposium, we discussed the relationship of thyroid dysfunction to mental illness and suggested ways of breaking into the endocrine vicious circle as a rational basis of treatment. Similarly, schizophrenic illnesses are often based on endocrine dyscrasias, which, as the result of external or mental stress, become themselves a form of internal stress. An endocrine vicious circle is thus established which in appropriate cases can be successfully broken by deep insulin coma treatment, the reestablishment of endocrine normality forming the basis on which stable mental improvement can be maintained. Having regard to the significance of adrenal function in relation to the mechanism and result of deep insulin coma treatment, it is possible with some certainty to single out one special group of schizophrenics, the adrenal hyperfunctional group. These have a good prognosis for treatment with deep insulin coma.

The relationship of adrenocortical response to deep insulin coma treatment needs further discussion. The results presented indicate that there are phases of stimulation and depression during the treatment course. In the early stages there is stimulation, in the middle stages fatigue or depression, and at the end there may be stimulation or depression. The course of events depends on the initial state of the adrenal cortex and its reserve of reactivity. We are at present engaged on a more detailed study of these aspects.

From studies of the blood chemistry during insulin coma some years ago (Kay and Thorley, 1951), our opinion inclined towards depression of adrenocortical function by large (coma) doses of insulin and stimulation by small doses, a view supported to some extent by later results. Other workers have estimated the blood corticoid concentrations at different stages of a single coma. This approach is not as simple or direct as it seems, for it cannot take into account the failure of utilization of circulating corticoids by a body that is inactivated by the almost complete interruption of its metabolism during the period of profound hypoglycemia.

Bliss (1954) and his co-workers have made a competent study of the blood corticoids during E.C.T. and insulin coma therapy. They are very cautious in their inferences and are content to leave the results obtained as facts stated. It is not to be expected that the eight schizophrenics they studied during insulin coma comprised all the endocrine types that occur, but an analysis of their figures (Fig. 13) does show three patterns of responses which they have obscured by averaging all their results. Six of their cases can be grouped in three pairs whose corticoid concentrations have different patterns, which may be described as hyperresponsive, normoresponsive and hyporesponsive. These are shown in the figure. Evidently many more investigations are needed before a conclusive answer is achieved by this method.

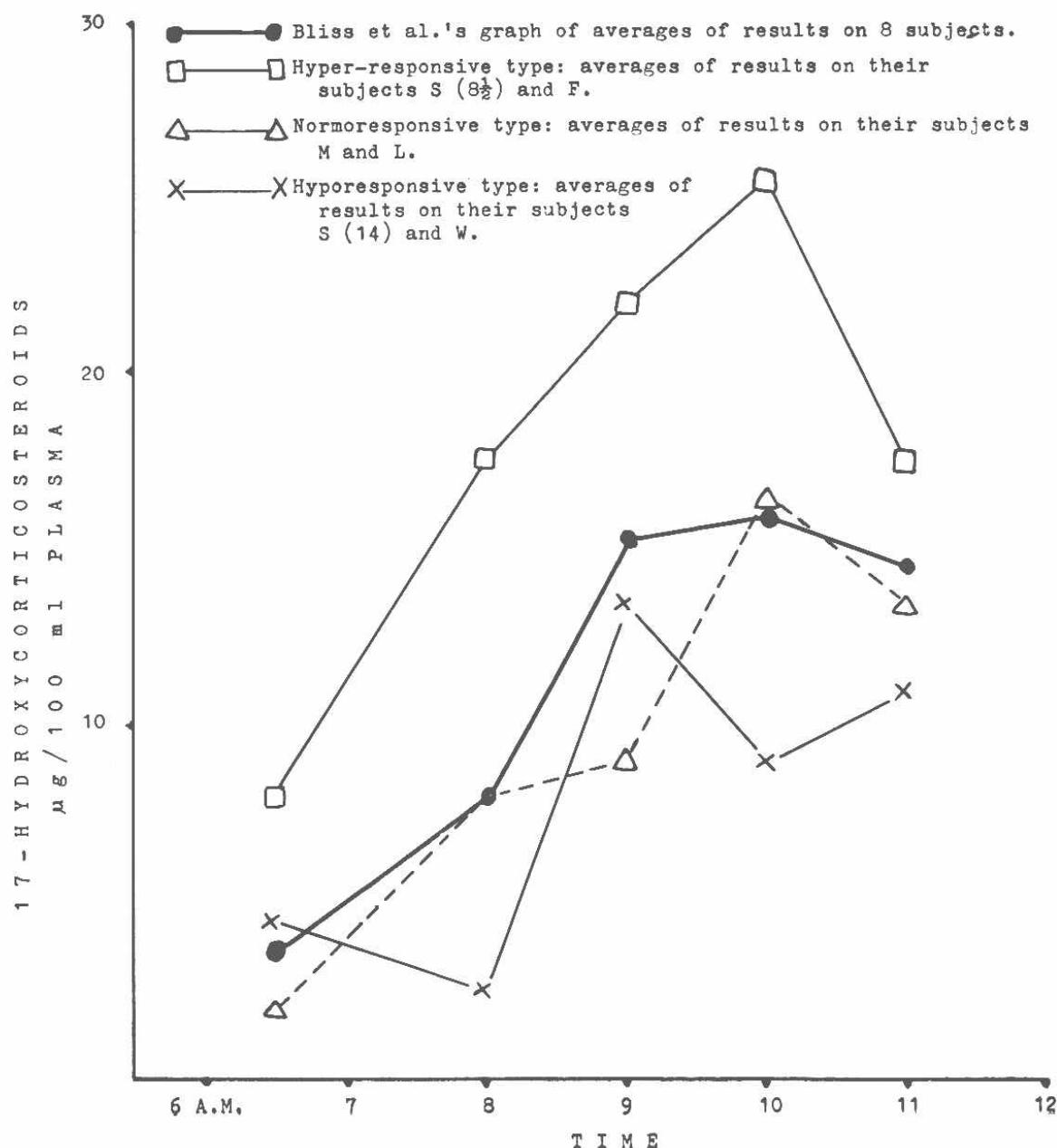


Figure 13

Some time ago, I investigated the effects of injections of A.C.T.H., cortisone and saline in patients in normal deep insulin coma just before their interruption. Reference will here be made only to the effect of these injections on the circulating eosinophils. In some cases, A.C.T.H. produced a significant fall in the eosinophil count and failed in others. We thought that this might indicate that at the end of the deep coma, some adrenals were capable of being stimulated by A.C.T.H. and others not, but to our surprise cortisone itself failed more often than not to evoke a fall in eosinophil count, thus suggesting that the hormones may be ineffective during hypoglycemia. Saline was mostly without effect, but in one case produced a fall of more than 50 per cent in the circulating eosinophils and roused the patient out of coma! Nearly all the patients had significant falls in circulating eosinophils after their coma had been interrupted by glucose administration. This suggests that rousing from coma may itself be a stress comparable to waking after sleep. Evidently their adrenal cortices were capable of responding to stimulation when they were again receiving glucose. Evidently, also, the function of glucose given to interrupt insulin coma is not only to raise the blood sugar but also to stimulate the pituitary. It is clear that the patient recovered from coma is physiologically different from when he was in coma: there is no continuity between the coma state and the restored state after interruption. Recovery from coma is a complicated process requiring restoration not only of the blood glucose, but also of pituitary and adrenocortical function. This is borne out by my studies of prolonged coma.

In many patients in prolonged or irreversible coma who fail to recover when given glucose, the administration of A.C.T.H. or cortisone induces prompt recovery, provided that the blood sugar is at least normal. This suggests that at the end of their coma they had poor adrenal function which was a factor in their failure to come out of coma. Where it was possible to estimate ketosteroid excretion in these patients, their excretion was invariably low. Many patients in prolonged coma and some at the end of a normal coma have transient achlorhydria, a sign very suggestive of poor adrenocortical function. We infer, therefore, from these observa-

tions that many patients at the end of deep insulin coma have poor adrenocortical function. These would correspond to those referred to in the first part of this paper who have low ketosteroid excretions, either *ab initio* or developing during the coma course. As the highest incidence of prolonged comas is at the start of the treatment course (Fig. 14), 40 per cent occur in the first five comas, Kay 1957), it is evident that many of the patients start their treatment course with low adrenocortical function: in others the reduced function is probably the cumulative effect of the series of coma stresses, which although they may at first stimulate, eventually fatigue the pituitary-adrenocortical axis.

RELATIONSHIP OF PROLONGED COMA

TO TREATMENT COURSE

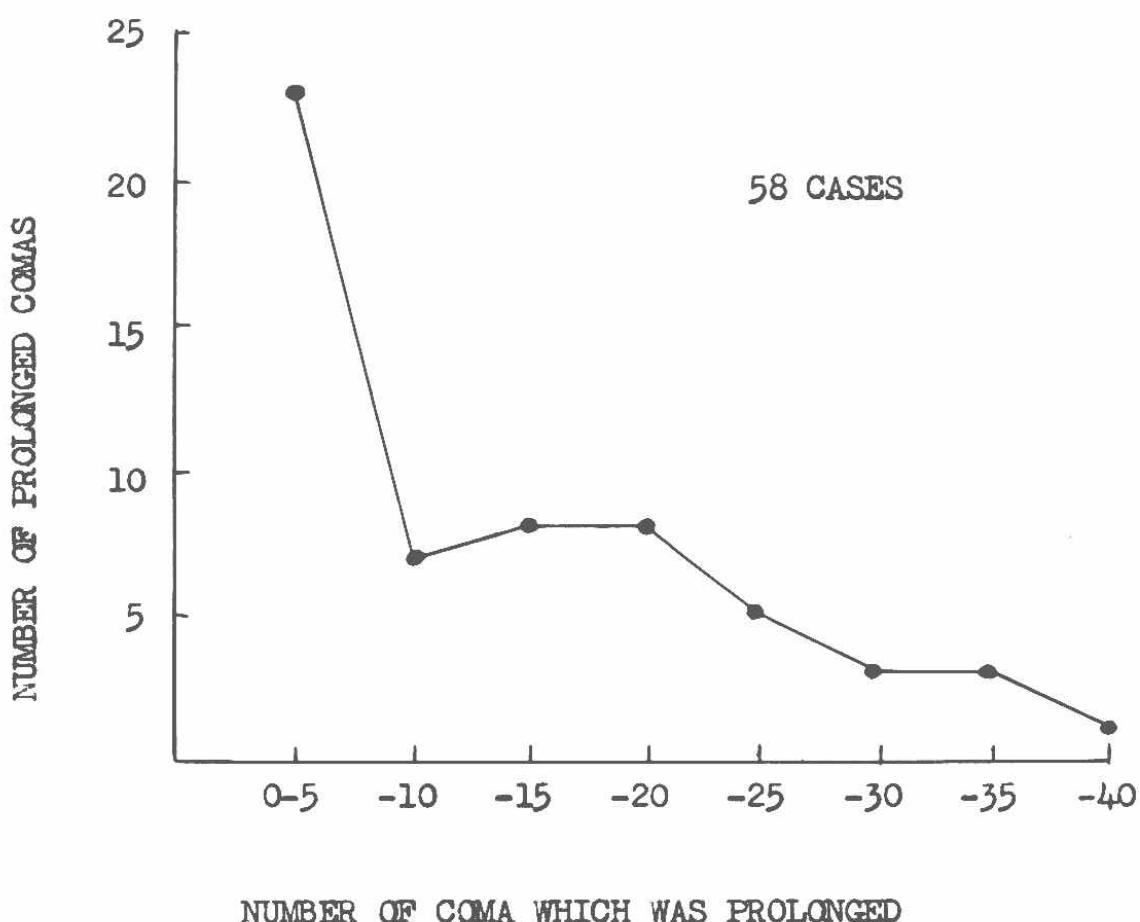


Figure 14

Before concluding this paper, it is well to remind ourselves again that the whole of the endocrine system and not the adrenal cortex alone is involved in the mechanisms of deep insulin coma. In rats given insulin, sometimes in coma doses, Reiss (1957) and his

co-workers (unpublished data) found changes in weight and function of thyroid, thymus, testes, seminal vesicles, as well as in adrenals and pituitary. Moderate doses of insulin tended to produce slight increases in weight of pituitary and adrenals and decreases in thyroid weight. The pituitary showed an increase of TSH content and first an increase and then a decrease of A.C.T.H. content. Larger doses of insulin produced decreases in both TSH and A.C.T.H. content of the pituitary with losses in weight of thyroid, pituitary and testes. The adrenals first showed a loss and later a gain in weight.

It is evident that the complicated interplay of factors involved in the endocrine reaction to insulin, especially in coma-producing doses, will not permit of a simple explanation of the mechanism and effects of insulin coma. The stress of the comas may stimulate or fatigue, but the ultimate result depends on the reserve power and resilience of the endocrine system as a whole and involves other factors, such as maturity and so on. This paper offers, therefore, not final conclusions, but a basis for prognosis of the result of insulin coma treatment of any given patient, that is itself the starting point of further investigations.

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XIII

Endocrine Studies and Hormonal Effects in Periodic Catatonia†

A. G. GORNALL, B. EGLITIS and A. B. STOKES*

THE OBSERVATIONS reported here form part of a multidisciplinary study which, although carried out on the limited number of five patients, has extended over periods ranging from two to seven years. During most of the time these patients were maintained on a constant diet under metabolic ward conditions. They represent that small group in the vast territory of schizophrenia with a rhythmical, periodic psychosis. Each exhibited features seen in periodic catatonia. The opportunity is presented in these cases not only to compare normal intervals with disturbed periods but also to follow the clinical, metabolic and endocrinological changes that occur during the transition from one phase to the other. A detailed report of the full investigation of each patient will appear in subsequent publications.

Clinical information on these patients was obtained not only from the physician in charge but also from records made at frequent intervals throughout each 24-hour period by a specially trained nursing staff. Basal metabolic rates were determined under standardized conditions after careful acclimatization to the procedure. Only where satisfactory tracings were obtained from a cooperative patient are the results reported. Steroid hormone excretion was followed almost daily throughout the investigation of these patients but for the sake of brevity the results are presented in summary form. A slight modification of the standard procedure of the Medical Research Council of Britain¹ was used to measure

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*Department of Pathological Chemistry and the Department of Psychiatry, University of Toronto, Toronto, Canada.

17-ketosteroids. The excretion of "free" corticoids was followed by the method of Gornall and Macdonald.²

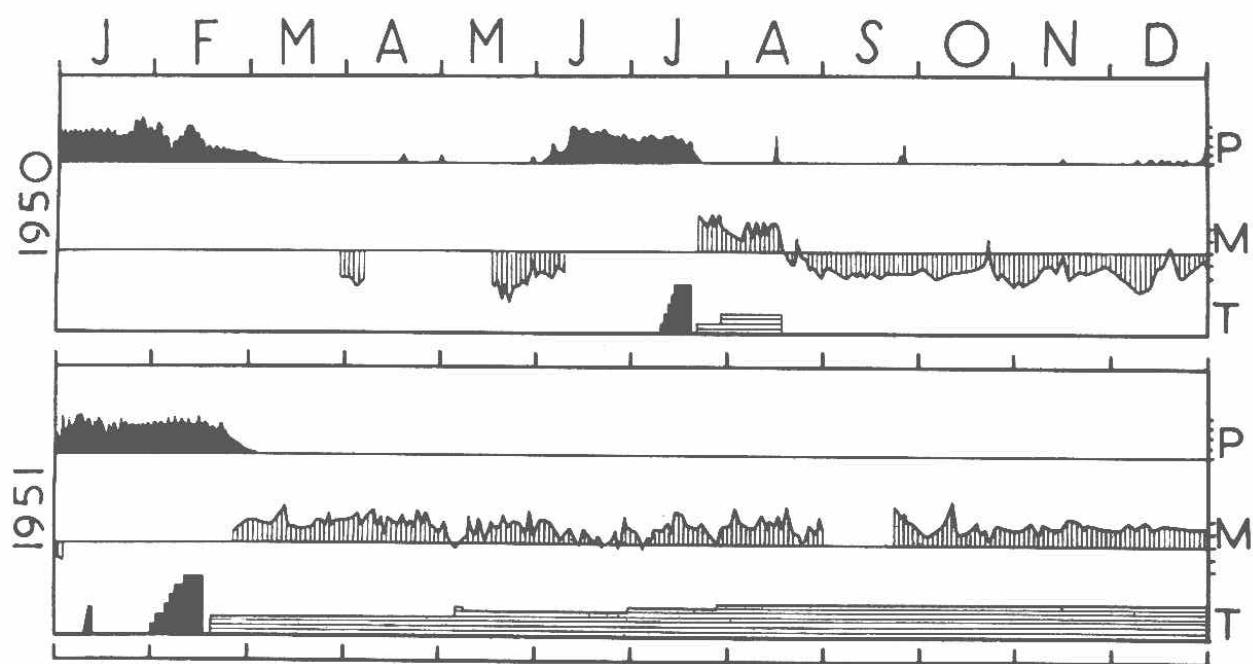


Figure 1.—Mrs. McC. Two year study. P = psychomotor rating, scale 0 to +4. M = basal metabolic rate, scale -20 to +20%. T = therapeutic measures: solid black, thyroxin; shaded areas, desiccated thyroid (each horizontal line represents 1 grain).

Mrs. McC (Figure 1)

This was the first patient treated on the Research Ward at the Toronto Psychiatric Hospital and has been reported fully in an earlier paper.³ After a few mild episodes this woman was first hospitalized for her illness in 1946. In 1949 at age 37 she was referred for possible lobotomy, and because of the periodic nature of her illness was transferred to the research ward. She was found to exhibit a recurrent picture of extreme psychomotor activity and characteristic autonomic changes, with personality disintegration and marked homicidal tendencies. The disturbances were regular, lasted two months as a rule, and were followed by almost four months of relatively normal behavior. In Figure 1 are shown the observations made during 1950 and 1951. The letters across the top indicate months from January to December. The upper line (P) is an individualized psychomotor rating, degrees of excitement being plotted above the line on a scale from 0 to 4. The middle line (M) is the metabolic state as revealed by the basal rate of oxygen utilization, the scale ranging -20 to +20 per cent from the normal average. The bottom line (T) records therapeutic intervention.

A therapeutic attempt made in July 1950, using first thyroxine and then desiccated thyroid, was abandoned when the patient had a brief,

violent disturbance in September. This apparent failure may have been due to inadequate dosage, or poor timing.

Treatment was begun again in January 1951, midway through the next disturbed period. In accordance with Gjessing's experience it was timed so far as possible to coincide with the endogenous shift from nitrogen retention to nitrogen excretion. Thyroxine was given first, by injection, and was followed by oral desiccated thyroid. With the elevation of the metabolic level from -20 and gradual adjustment of the dose to maintain the BMR at +10 per cent, the periodic psychic disturbance was abolished. This patient has remained well since 1951 on a dose of seven grains of desiccated thyroid a day, except for a brief relapse in 1953 due to temporary omission of the hormone. No special thyroid or adrenal studies were possible at the time this patient was in the ward.

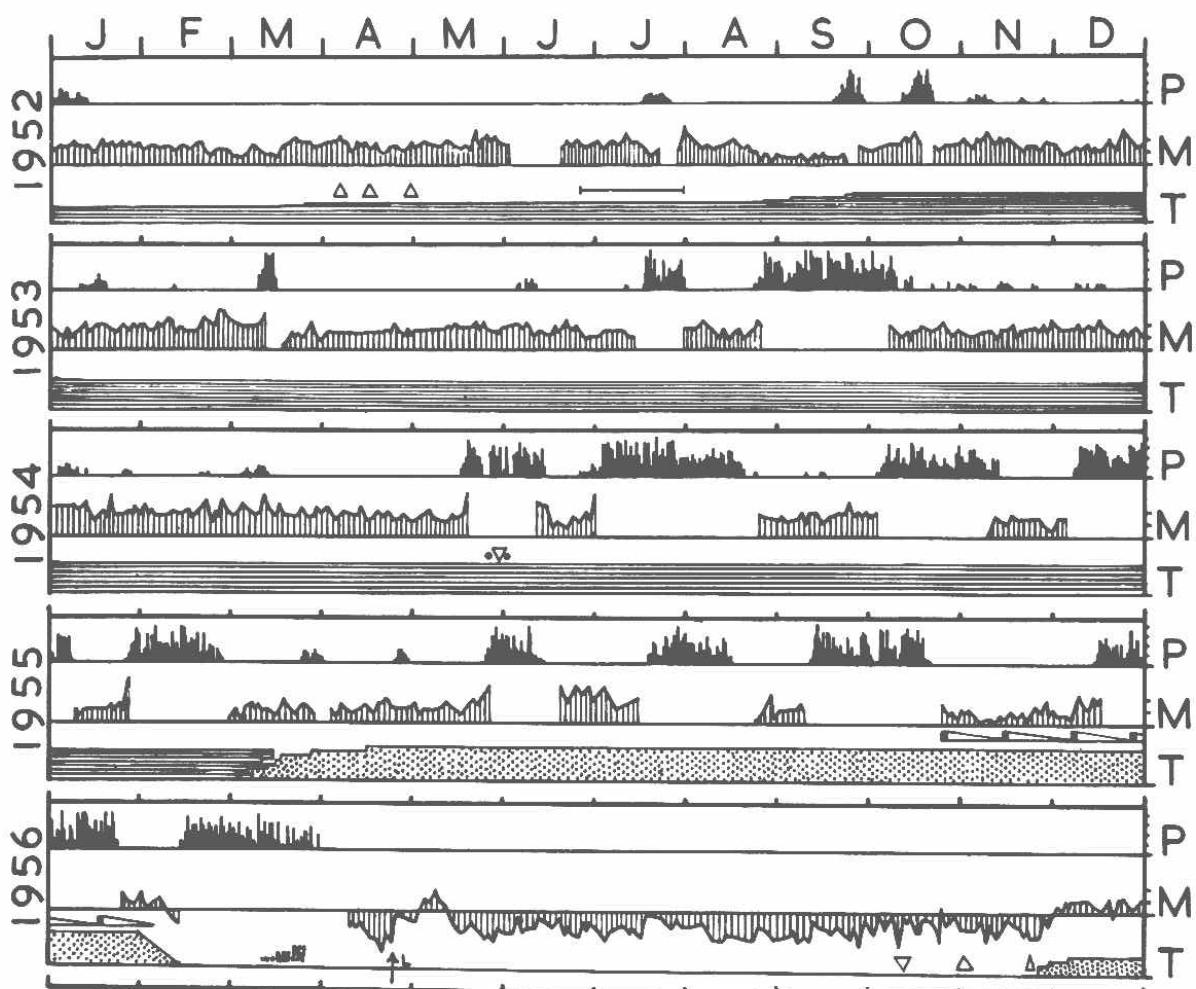


Figure 2.—Mr. W.L. Five years of a seven year study. Psychomotor rating, scale 0 to +4. Basal metabolic rate, scale 0 to +20% Therapeutic measures: Jan. '52 to Mar. '55, desiccated thyroid; Mar. '55 to Feb. '56 and Nov. '56 to present, Triiodothyronine; June-July '52, testosterone, Oct. '55 to Feb. '56, testosterone (for doses see text); Special Tests: \triangle , A.C.T.H.; ∇ , TSH; \circ , radio iodine uptake. L = lobotomy.

Mr. W. L. (Figure 2)

The second patient came under study in 1949; the early part of his investigation has been reported previously.³ This man had been ill since age 20 in 1936. His illness was characterized by periodic episodes of extreme excitement, impulsive behavior, disordered thinking, hallucinations and delusions. These recurred every 40 days and lasted about 20 days, the patient then became relaxed, cooperative, and able to think clearly and relevantly. It was difficult to discern any clear cut cycle of nitrogen excretion, but therapy was initiated in July 1951 in an interval phase. With the BMR elevated from —20 to about +15 per cent five more periods of excitement occurred, each milder than before. The last of them in January 1952 is shown at the very beginning of this chart; at the time the patient was receiving seven grains of desiccated thyroid per day.

Figure 2 tells his story for the next five years, 1952-1957. Three parameters are recorded: psychomotor rating, BMR and therapeutic measures, as in Figure 1. The metabolic rate was maintained at an average of about +15 per cent; each time it showed signs of falling the dose of desiccated thyroid was increased until at the end of 1952 and during all of 1953 and 1954 the patient was receiving 12 grains a day.

The patient was well from January 1952 until July, when some hyperactivity was noted. In this period three A.C.T.H. tests were carried out. Two short periods of excitement were observed in September and October, following which the patient was fairly well until a relapse occurred in July and August of 1953 and then not again until May of 1954. At this time the patient had been receiving thyroid hormone for almost three years and was on 12 grains a day. With the cooperation of Dr. R. A. Mustard surgical biopsies of the thyroid gland were obtained before and after a five day stimulus with thyrotrophic hormone (TSH). Histologically the gland appeared remarkably normal, though signs of lack of pituitary stimulation were present. The response to TSH was normal for such a gland, showing good activation. The protein-bound iodine (PBI) rose from control values of 7.5-7.8 to 10.0 μg . per cent. The I^{131} uptake rose from 3 to 22 per cent.

From this time on a complete relapse seems to have occurred. In March 1955 the patient was changed from 12 grains of desiccated thyroid to 160 μg . of Triiodothyronine, which dose had to be increased to 200, 240 and finally to 280 μg . per day in order to keep the BMR at +10 per cent. The patient appeared to miss one disturbed phase but quickly relapsed again, 280 μg . of Triiodothyronine being no better than 12 grains of desiccated thyroid.

One possibility had not been excluded, namely that androgen support might help this patient; his 17-ketosteroid output had been consistently

at or below the lower limit of normal. An earlier trial in 1952, with what were probably inadequate doses, had been ineffective. Beginning in October 1955, 200 mg. of a long-acting preparation (Upjohn, Depo-Testosterone) were injected every 3 weeks for 15 weeks. No benefit was obtained.

In February 1956 all therapy was withdrawn. During the disturbance that followed Frenquel was administered without much effect. Because of the difficult nursing problem this patient presented, he underwent a lobotomy on April 25, 1956. The psychomotor rating scale was no longer applicable, and although a Malamud-Sands rating was used the results are not recorded because they would not be comparable. No further psychomotor disturbances occurred but the patient could be considered 'normal' only by postlobotomy standards. After the effects of the operation had subsided his BMR was around -20 per cent, and his PBI had risen from 2 to about 4 μ g. per cent. In October his response to TSH was normal but the PBI fell back subsequently to the low normal limit. In the hope of improving his energy level and perhaps his initiative, which were not adequate, the patient was treated again with 160 μ g. of Triiodothyronine to maintain his BMR at a +10 per cent level. This seemed to have some beneficial effect and under these conditions at the present time a partial rehabilitation is being attempted.

Steroid data are recorded in Table 1 for the various clinical periods of this patient's investigation. The BMR values are representative averages for the period. The range of 17-ketosteroid and corticoid excretion values is given. Mr. L. had 17-ketosteroids in the "low normal" range, no different in the well intervals and the excitement periods. This tendency to low "androgen" output persisted throughout the treatment periods, except when testosterone was being administered. The "free" corticoids were normal, but showed a tendency to higher values in the disturbed periods, except when receiving testosterone. In the postlobotomy period this rise is particularly noticeable. This patient's bromsulfalein retention averaged 14 per cent in normal intervals and 12 per cent during disturbed periods. Postlobotomy the values were around 4 per cent.

The adrenal response to ACTH administration was tested on seven occasions in the different clinical periods. The dose is shown as mg. or units—number of injections per day—number of days. The maximum levels of 17-ketosteroid and corticoid excretion that resulted are recorded. These figures should be compared with the control values for the same period, shown above. The pretreatment tests, in 1950, are not as reliable as those carried out after treatment was begun. The latter show a low normal ketosteroid response and a normal corticoid response. In the postlobotomy period the response of both 17-ketosteroids and corticoids was poor.

After all treatment was withdrawn in February 1956, urine was collected in the middle of the subsequent disturbed period and in the

Table 1. MR. W. L.

CLINICAL PERIOD	BMR	RANGE MG./DAY	
		17-KETO-STEROIDS	'FREE' CORTICOIDS
Pretreatment			
INTERVALS	—20	10-15	(1.5-2.0)
DISTURBANCES	(+15)	10-15	
On Desiccated Thyroid			
CONTROLLED	+15	10-16	2.0-2.5
DISTURBED	(+15)	8-14	2.2-4.5
On Triiodothyronine			
INTERVAL	+10	7-13	2.3-2.9
DISTURBED	(+15)	8-12	2.5-4.5
On Triiodothyronine + Testosterone			
INTERVAL	+10	9-23	2.0-3.0
DISTURBED	(+20)	8-20	1.8-2.5
Off Therapy—			
PRE LOBOTOMY	—20	7-12	2.2-2.8
POST LOBOTOMY	—20	8-9	3.0-5.0
Post Lobotomy			
+ Triiodothyronine	+10	12-16	3.0-4.5
MAXIMA			
A.C.T.H. TESTS	BRAND*	DOSE	17-KETO-STEROIDS 'FREE' CORTICOIDS
Pretreatment			
INTERVAL	A —	100.1.5	17 (3.4)
DISTURBED	A —	100.1.5	14 —
On Thyroid			
CONTROLLED	A,18411	100.1.4	19 5.1
	A,18411	25.4.4	23 5.8
	C,5-2	25.4.4	25 12.1
Post Lobotomy			
	D,56001	20.1.4	14.8 4.3
	D,56005	100.1.2	15.5 5.0

*A.C.T.H. brands & lot numbers: A- Armour, C- Connaught, D- Duracton (Nordic Biochemicals).

following normal interval for aldosterone determinations. The results were 4.9 and 4.5 μg . per day respectively, providing no evidence that this hormone plays a part in the psychomotor change. Electrolyte balance studies likewise showed no significant change.

Mrs. E.Y. (Figure 3)

The initial stages of this patient's investigation also were described in our 1953 report. This woman's illness first appeared in 1945 and after two years settled into a periodic pattern. When seen in 1949 at age 33 her illness recurred every three months and lasted one month. In the morbid phase she was withdrawn and untidy, showed psychomotor retardation, disorganized thought, delusions and hallucinations. After a brief euphoric period, she would pass into a semistuporous state for a few days; in the chart degrees of retardation are plotted

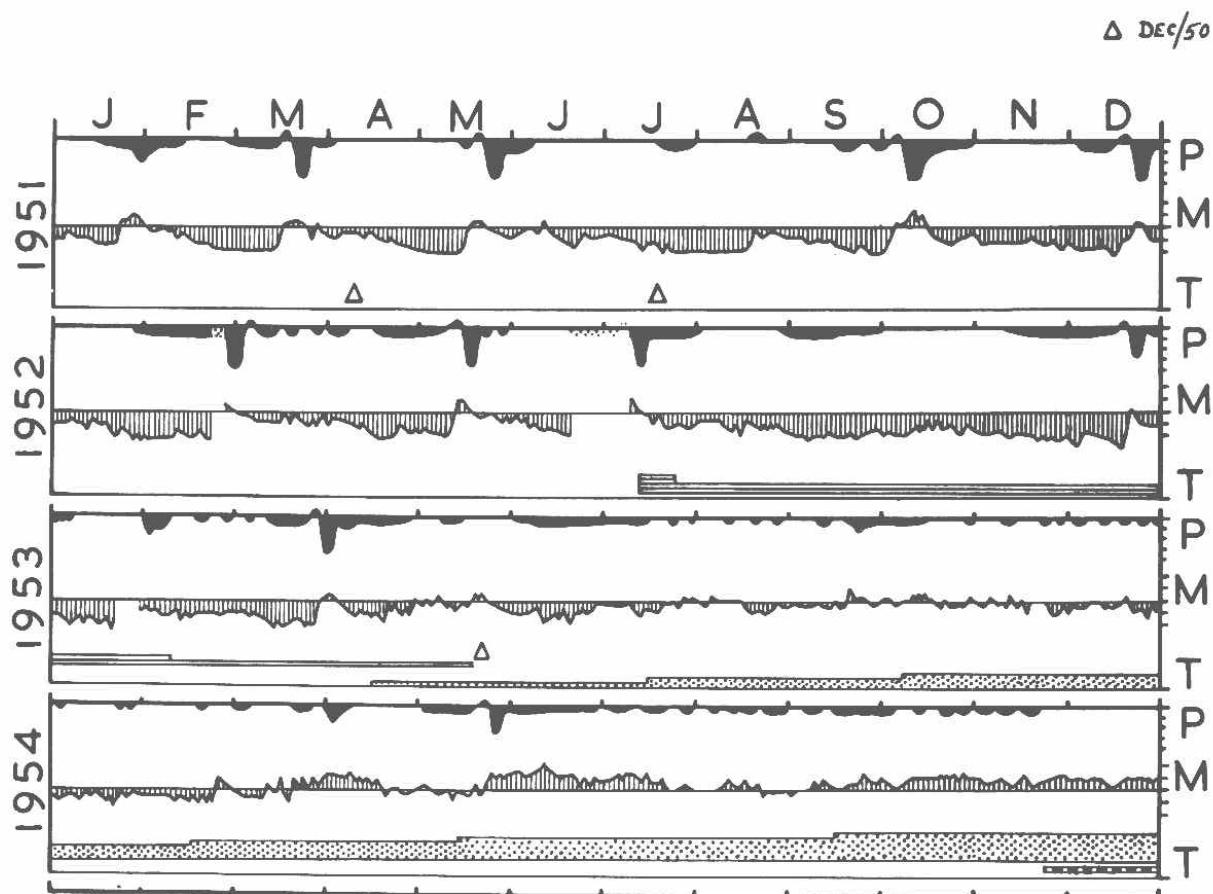


Figure 3.—Mrs. E.Y. Four years of a six year study. Psychomotor rating, scale 0 to -4. Basal metabolic rate, scale -20 to +20%. Therapeutic measures: July '52 to May '53, cortisone; April '53 to present, desiccated thyroid; Nov. '54 to present, Triiodothyronine. Special Tests: Δ , A.C.T.H. (one in Dec. '50 also shown).

below the line. Her BMR, usually about -20, became elevated to 0 to +10 per cent at these times. There were characteristic skin changes in the disturbed periods, pallor, oiliness, and localized pigmentation

and acne. In her well periods she was pleasant and cooperative and her skin cleared. An attempt was made in 1950 to treat the patient with thyroid hormone but she showed such a marked overstimulation that it was discontinued. Following this the former periodicity and BMR changes were resumed as illustrated in the year 1951.

This patient presented one particularly interesting feature. Her excretion of 17-ketosteroids was usually at the high limit of normal and at the onset of each semistuporous phase the values frequently rose to about 30 mg. a day. An A.C.T.H. test in December 1950 appeared to modify the disturbed period due in January 1951. A second test in April gave a poor response and had no clinical effect. A better preparation in July gave a good stimulation, caused a relatively greater rise in corticoids than in 17-ketosteroids and abolished the psychomotor disturbance due at this time. This observation led us in July 1952 to attempt treatment with cortisone, using at first 100 mg. per day, then 50 mg. for several months, and finally tapering off with 25 and 12.5 mg. a day. It can be seen that one disturbance was averted and the next was delayed but finally occurred in December.

In April 1953 treatment with desiccated thyroid began again—not according to Gjessing's usual regimen because of this patient's previous hyperactive response, but by gradual increments $\frac{1}{2}$ grain at a time. Her mental state improved considerably, but on $4\frac{1}{2}$ grains per day some retardation was still present. In November 1954 a supplement of 20 μ g. per day of Triiodothyronine was begun and since that time her health has been very good indeed and she has been rehabilitated successfully.

Steroid data on this patient are shown in Table 2. Note the rather high range of 17-ketosteroids excreted in the normal intervals of her pretreatment period. The first few days of her disturbed phases were accompanied by an even greater output of androgen type hormones, often up to about 30 mg. per day. Corticoid excretion was normal. The period of cortisone therapy suppressed the production and excretion of 17-ketosteroids very markedly, and this was a permanent change, not affected significantly by treatment with thyroid hormone.

A.C.T.H. tests in this patient gave a good response, if we ignore the one in April 1951 which was attributed to an inferior preparation.⁴ It is interesting to note that the maximum 17-ketosteroid values obtained with A.C.T.H. were no higher than the patient sometimes produced endogenously at the onset of her semistuporous phases. Corticoids, which did not change at all endogenously, rose sharply under the influence of A.C.T.H. After cortisone administration the 17-ketosteroid response was smaller, but relative to the control values still showed quite a good rise. The corticoid response was normal. Thyroid hormone administration did not alter the adrenal response to ACTH.

Table 2

MRS. E. Y.

CLINICAL PERIOD	BMR	RANGE MG./DAY		
		17-KETO-STEROIDS	'FREE' CORTICOIDS	
Pretreatment				
INTERVALS	-20	12-20	1.5-2.0	
DISTURBANCES	+10	13-32	1.6-2.4	
After Cortisone Therapy				
On Desiccated Thyroid	0	4-8	1.5-2.8	
On Desiccated Thyroid + Triiodothyronine	+10	5-9	1.5-2.0	
A.C.T.H. TESTS				
MAXIMA				
A.C.T.H. TESTS	BRAND	DOSE	17-KETO-STEROIDS	'FREE' CORTICOIDS
Pretreatment Interval April, '51	A,16305	100 I.V. 20 I.V.2	18.7 22.3	3.0
Beginning of Disturbance July, '51	C,5-2	100 I.V. 20 I.V.2	34 34.3	7.5 10.0
End of Cortisone Period	C,13-2	25.3.3 15.3.1 10.3.1	17.2	10.5
On Desiccated Thyroid	C,13-2	25.3.3 15.3.1 10.3.1	21.1	10.8

Mr. R.H. (Figure 4)

This man first became ill in 1950 and came under observation at Toronto Psychiatric Hospital in December 1952 at age 24. His illness was characterized by sudden lapsing into a stupor from which he emerged slowly after a variable period of 15 days or more. These attacks recurred about every 27 days and the normal intervals gradually became shorter and shorter until on several occasions one stupor period would merge into another.

In the deeper stages of stupor he was totally uncooperative, lying on his side, extremities flexed, covers over his head, eyes closed. He was mute and resisted any movement. Degrees of his psychomotor dis-

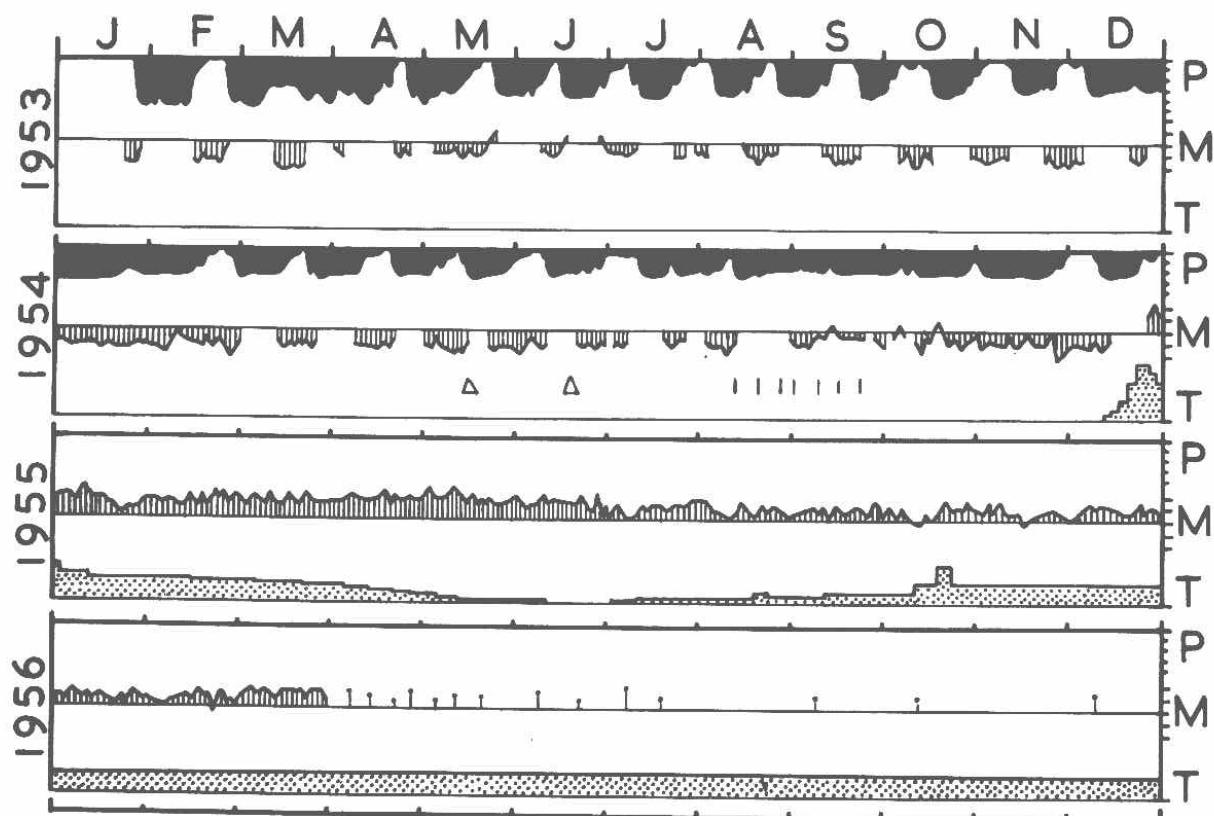


Figure 4.—Mr. R.H. Four year study. Psychomotor rating, scale 0 to — 5. Basal metabolic rate, scale —20 to +20%. Therapeutic measures: Dec. '54 to June '55 and July '55 to present, Triiodothyronine only. Special Tests: △, A.C.T.H.

turbance were graded 1 to 5 and are plotted below the line, grade 3 being a semistupor. As time passed the depth of stupors lightened from grade 5 to grade 3 and some degree of cooperation was obtained at this level. For the most part however, the investigation had to be curtailed during the disturbed phases in the early pretreatment period. This is illustrated by the interrupted BMR record which, during the brief well intervals in 1953, averaged —15 per cent and showed some tendency to rise just at the onset of the deep stupor.

In 1954 two A.C.T.H. tests were performed, without evidence of any significant effect on the psychomotor state. A little later a series of Metrazol injections was without effect.

In December 1954, at the onset of a stupor phase, treatment with Triiodothyronine was initiated. It was timed to coincide with the endogenous shift to a negative nitrogen balance, this patient being a good example of the synchronous variety of periodic catatonia. The dose was increased every few days from 40-80-160-320-480 $\mu\text{g}.$, at which time signs of adequate metabolic stimulation were present and the dose was reduced stepwise every few days to 400-320-280-240-200-180 $\mu\text{g}.$ On this dose level the BMR was still around +20 per cent while the PBI was less than 2 $\mu\text{g}.$ per cent. Over the next four months the dose of Triiodothyronine was lowered to 160-140-120-100-80-60-40 — and finally to 20 $\mu\text{g}.$ All this time the BMR remained elevated and toward the end of this period the PBI had risen to levels of 6-7 $\mu\text{g}.$

per cent which were above his pre-treatment values of 4.5-5.5 µg. per cent. We had reason to suspect that we might have so altered the patient's endogenous hormone production that the Triiodothyronine could be withdrawn, but within three weeks of doing so there were signs that deterioration was occurring and the hormone was started again. It was not until a dose of 160 µg. per day was reached that the BMR settled satisfactorily at a +10 per cent level. On this treatment the patient has remained well ever since. He has been rehabilitated successfully and is back at work with his former employers.

Steroid data on this young man are recorded in Table 3. It can be seen that both 17-ketosteroid and corticoid excretion are entirely normal in the pretreatment and in the treatment periods. Neither was affected by the alteration in level of metabolism produced by Triiodothyronine. The two A.C.T.H. tests likewise gave perfectly normal responses with the long acting and potent Duracton we were using at that time. Although we should like to have repeated this test after rehabilitation on Triiodothyronine we were thankful to have achieved so gratifying a result and have been reluctant to risk endangering the patient's condition in any way.

Table 3

MR. R. H.

CLINICAL PERIOD	BMR	RANGE MG./DAY	
		17-KETO-STEROIDS	'FREE' CORTICOIDS
Pretreatment			
INTERVALS	-15	15-21	1.3-2.9
DISTURBANCES		14-22	1.2-2.0
On Triiodothyronine	+15	14-20	1.5-2.5
Triiodothyronine Withdrawn	+10	15-19	2.2-2.8
Rehabilitation on Triiodothyronine	+10	16-22	1.8-3.0
 MAXIMA			
A.C.T.H. TESTS	BRAND	DOSE	17-KETO-STEROIDS 'FREE' CORTICOIDS
Pretreatment			
Beginning of Disturbance	D,54004	20.1.4	37 5.7
Middle of Disturbance	D,54004	20.1.4	34 5.7

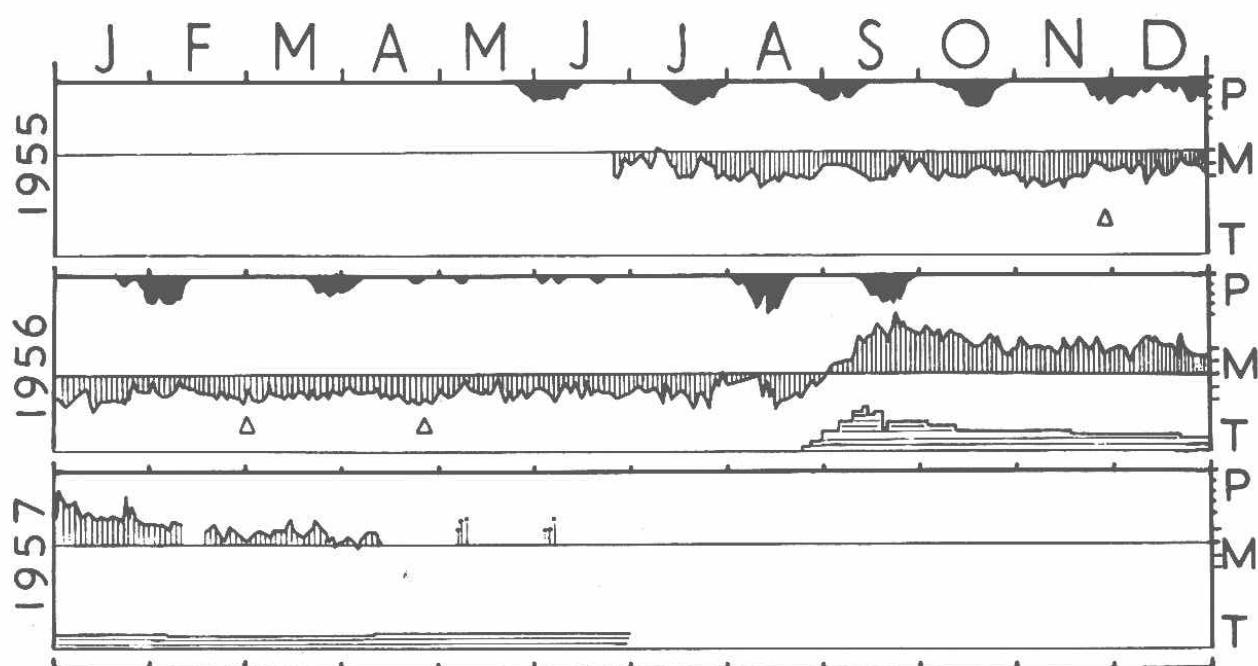


Figure 5.—Mrs. S.A. Two year study, still in progress, shown to July 1957. 'Psychomotor' Malamud-Sands rating 0 to —80. Basal metabolic rate, —20 to +20%. Therapeutic measures: Aug. '56 to Sept. '57, Triiodothyronine. Special Tests: Δ , A.C.T.H.

Mrs. S.A. (Figure 5)

This woman, aged 33, came under observation in 1955 and was transferred to the Research Ward because of the periodic nature of her illness. Her disturbed phases recurred about every 44 days and lasted 17-18 days. The disturbances were characterized by decreased ability to concentrate, psychomotor retardation, purposeless activity, untidiness, disturbed perception, stereotyped speech with thought disorder and delusions. The normal intervals were relatively symptom free.

Because in this case there was a minimal 'motor' component the Malamud-Sands rating was used to describe the patient's deviation from the normal base line. This patient did not show any autonomic changes coincident with her disturbed phases, such as changes in pulse rate, temperature, blood pressure and BMR, that form part of the picture in "true" periodic catatonia. There was some evidence of a nitrogen cycle, but at best the changes were irregular as seen in the asynchronous variety. We have proceeded on the assumption that this patient may represent a borderline form of periodic catatonia. In addition to a recurrent illness she showed a low BMR (-15 to -20 per cent) and, as can be seen, a satisfactory clinical response to thyroid hormone.

An A.C.T.H. test was performed in November 1955, soon after the onset of a disturbance; it can be noted that it prolonged this disturbance. Another test at the first of March 1956 had little effect, but

was associated with poor adrenal stimulation. When this test was repeated with what was probably a better preparation of ACTH, a good adrenal response was observed and the rhythm of the patient's disturbances was affected. No attack occurred until August. Thus ACTH had opposite effects in the different phases, suggesting that the stage of some metabolic cycle may determine what the response to adrenal hormones will be.

In August 1956 treatment with Triiodothyronine was initiated with doses increasing stepwise from 40-80-160-240-320 to 360 µg. per day and adjusted then to 280-320-160 and then 240 µg. Following the disturbance in September the dose was lowered to 200-160-140 and 120 µg. The BMR was maintained at a rather high level for most of this period and pituitary suppression from the Triiodothyronine probably accounted for a reduced duration and flow of the menses in December and January. Urinary follicle stimulating hormone (FSH) was found to be 6 units at this time. On a lower dose of 100 µg. per day the menstrual irregularity disappeared and the FSH value returned to a normal range (15-54 U). The maintenance dose was later set at 120 µg. per day and the menses remained normal.

No psychic disturbances were observed during the next twelve months. A mild relapse occurred during the summer of 1957 when the patient attempted to "get along without her pills." This was followed by a typical disturbance in September and the patient had to be readmitted

Table 4

MRS. S. A.

CLINICAL PERIOD	BMR	RANGE MG./DAY	
		17-KETO-Steroids	'FREE' CORTICOIDS
Pretreatment			
INTERVALS	-20	6-10	1.5-2.5
DISTURBANCES	-15	6-11	1.4-2.0
On Triiodothyronine	+17	11-15	1.8-2.8

A.C.T.H. TESTS	BRAND	DOSE	MAXIMA	
			17-KETO-Steroids	'FREE' CORTICOIDS
Pretreatment				
INTERVAL	D,55015	20.1.4	15	2.3
INTERVAL	D,56001	20.1.4	22.1	6.0
DISTURBANCE	D,55012	20.1.4	24.7	4.4

to hospital. We have reason to think that a good stabilization on thyroid hormone may yet be achieved.

Steroid data on this patient are recorded in Table IV. Both 17-ketosteroid and corticoid excretion appear entirely normal for a woman her age. Treatment with Triiodothyronine seems to have increased her output of androgens somewhat. The A.C.T.H. tests show a moderate but probably adequate adrenal response both in 17-ketosteroids and corticoids.

SUMMARY

Five patients with recurrent psychosis exhibiting features seen in periodic catatonia, have been studied under metabolic ward conditions for periods of two to seven years. During normal intervals all showed a low rate of oxygen utilization (BMR —15 to —30 per cent). Protein bound iodine values were normal, showed little change between normal and disturbed periods, and were altered significantly only during treatment with thyroid hormone. Recurrent psychomotor disturbances were associated generally with a rise in BMR. Following treatment with thyroid hormone the disturbed phases ceased. Temporary relapses occurred when therapy was interrupted. The most chronic case relapsed after about two years and subsequently required a lobotomy. Two of the patients were treated with Triiodothyronine alone and two others received this hormone for periods of time. There was nothing to indicate that Triiodothyronine was either superior or inferior to desiccated thyroid at equivalent dose levels.

Urinary excretion of 17-ketosteroid hormones and of "free" adrenal corticoids was followed closely in four of the patients. In only one was there a significant change coincident with the onset of the psychomotor disturbance and this took the form of a rise in 17-ketosteroids. Treatment with cortisone abolished this phenomenon permanently but caused only a transient improvement in the psychic state. Steroid output was in the normal range except for somewhat low 17-ketosteroid values in one male patient; testosterone treatment was not beneficial in this case. Thyroid hormone administration had no definite effect on adrenal hormone output. Adrenal response to four-day A.C.T.H. tests revealed an average rise in 17-ketosteroids in two cases and a low normal

increase in two. The corticoid increment was normal in each instance. These responses were not significantly different when tested in a normal interval or in a disturbed period. Effects of A.C.T.H. (or of cortisone) on the psychomotor state were varied. In some instances a transient improvement was noted, in others a definite deterioration. Our observations tend to support the hypothesis that the underlying defect in these patients is probably metabolic and that the endogenous effort to effect a compensation can be assisted by raising the metabolic level with thyroid hormone. The adrenal hormones appear to exert only a secondary, superimposed effect on the disorder.

ACKNOWLEDGMENTS

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XIV

Abnormal but Regular Cycles in Behavior and Metabolism in Rats and Catatonic-Schizophrenics*

CURT P. RICHTER†

It has long been known that mental and emotional disturbances in man often occur in isolated attacks—attacks that may recur at regular or irregular intervals.

Psychiatrists in general have been little impressed with the regularity of the occurrences of these attacks and so have not seen in them any etiological significance. Instead they have used them only for diagnostic and prognostic purposes. Only a few psychiatrists have made continuous observations on patients showing cycles.

Part of the unwillingness of psychiatrists to accept the idea of periodic illness may be accounted for by a lack of knowledge of periodic phenomena in general in man and animals.

Some of the most convincing evidence for the existence of periodic diseases comes from the classic studies of Gjessing on catatonic schizophrenics.¹ Over long periods Gjessing kept his patients under ideally controlled conditions—on a constant diet and in bed—and made daily records on many mental and physical functions. He found that under these conditions the attacks of some patients recurred with extraordinary regularity and without any relation to external conditions. Some of the most regular cycles were 20 to 40 days in length.

Further evidence comes from observations on patients with so-called alternating day cycles of normal or abnormal behavior: the

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†On leave at the Institute for Advanced Study, Princeton, New Jersey.

patients are perfectly normal on one day and abnormal on the next. During the abnormal phases, one patient may be manic; another depressed; another paranoid; another stuporous; etc. The transition from one phase to another usually is very sharp, in some instances lasting only a few minutes. These patients show marked changes not only in behavior but in hours of sleep, pulse rate and body temperature. The attacks persist for weeks, or months, or years, or even a lifetime. Bleuler² and Kraepelin³ both saw such patients and commented on the regularity of the attacks. More recently Arndt⁴ and Menninger-Lerchenthal⁵ have collected records of many such patients. We have seen four at the Phipps Psychiatric Clinic at the Johns Hopkins Hospital.⁶

The most convincing evidence for the existence of periodic phenomena in man comes from observations made by medical men on patients with periodic disease in which physical changes predominate: fever, agranulocytosis, arthritis, vomiting, peritonitis, edema, etc.^{7,8,9,10} The cycles may be only 12 hours in length or several months. In any one individual, however, they are apt to be fairly constant. The most common frequency is 20 or 21 days.

Records are at hand at the present time of over 400 such patients showing regular attacks of periodic disease.

Thus, there can be little doubt about the existence of regular periodic attacks of physical and mental disease in man without any relation to external events, but little is known about the origin of the attacks or of the underlying mechanisms or why the attacks should manifest themselves in such different frequencies and in such a wide range of symptoms.

Chance observations made many years ago during studies on the spontaneous running activity of rats indicated that abnormal but very regular cycles closely resembling some of those seen in psychiatric patients and patients with periodic disease can be produced by experimental interference with the thyroid and pituitary glands.^{11,12} Over the course of years these studies have been extended until now we are able to produce abnormal cycles of various types by a number of different methods.

The rat lends itself very well to such studies for a number of

reasons that can not be gone into at the present time. It will suffice to say that daily records can be obtained showing spontaneous running activity, food and water intake, vaginal smears, body weight and many other functions. The cages used for this purpose have been described in previous publications, as have also the methods used in making the observations.¹³

Daily measurements were made of running activity, food and water intake, and of vaginal smears. Figure 1 shows a typical record of the activity, food intake and body weight of a normal female rat. The ordinates show daily running activity in number of revolutions of the drum and food intake and body weight in grams; the abscissas age in days. It will be seen that this normal female rat showed the 4 or 5 day estrous cycles in running activity throughout the period of observation. Ovulation occurred every fourth or fifth day just before the peak night of running activity. The activity of this rat was maintained at essentially the same average level for many months after the end of the record shown in this chart.

Records from many thousands of other normal animals serve

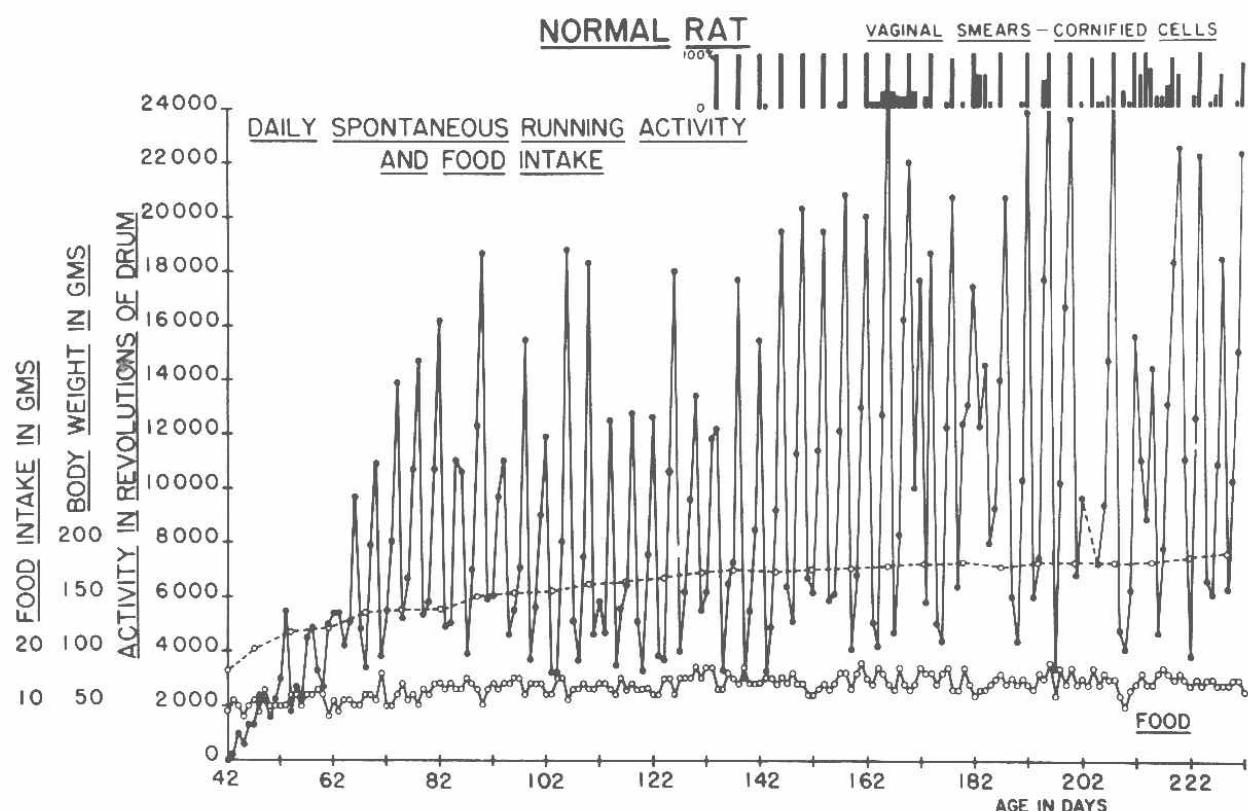


Figure 1. Graph showing daily record of spontaneous running activity, food intake, vaginal smears, and weekly records of body weight of a normal female rat.

as a basis for the evaluation of the significance of cyclic changes that appear after various forms of experimental interference.

It has been found so far that abnormal but regular cycles can be produced (1) by interference with the endocrine glands—the thyroid, pituitary, ovaries and parathyroids; (2) by prolonged treatment with drugs or hormones; (3) by brain lesions or tumors; and (4) by severe stress.¹³

One or two illustrations will be given of the different types of abnormal activity cycles that have been produced by the various methods of experimental interference.

Prolonged periods of thyroxine deficiency whether produced by thyroidectomy, treatment with I^{131} , feeding of sulfa drugs or of Thiourea or its derivatives—Thiouracil or Propylthiouracil, resulted in much the same type of cycle, which is characterized by the presence of a sharply defined inactive phase lasting 13 to 16 days.

Figure 2 shows the daily spontaneous running activity record

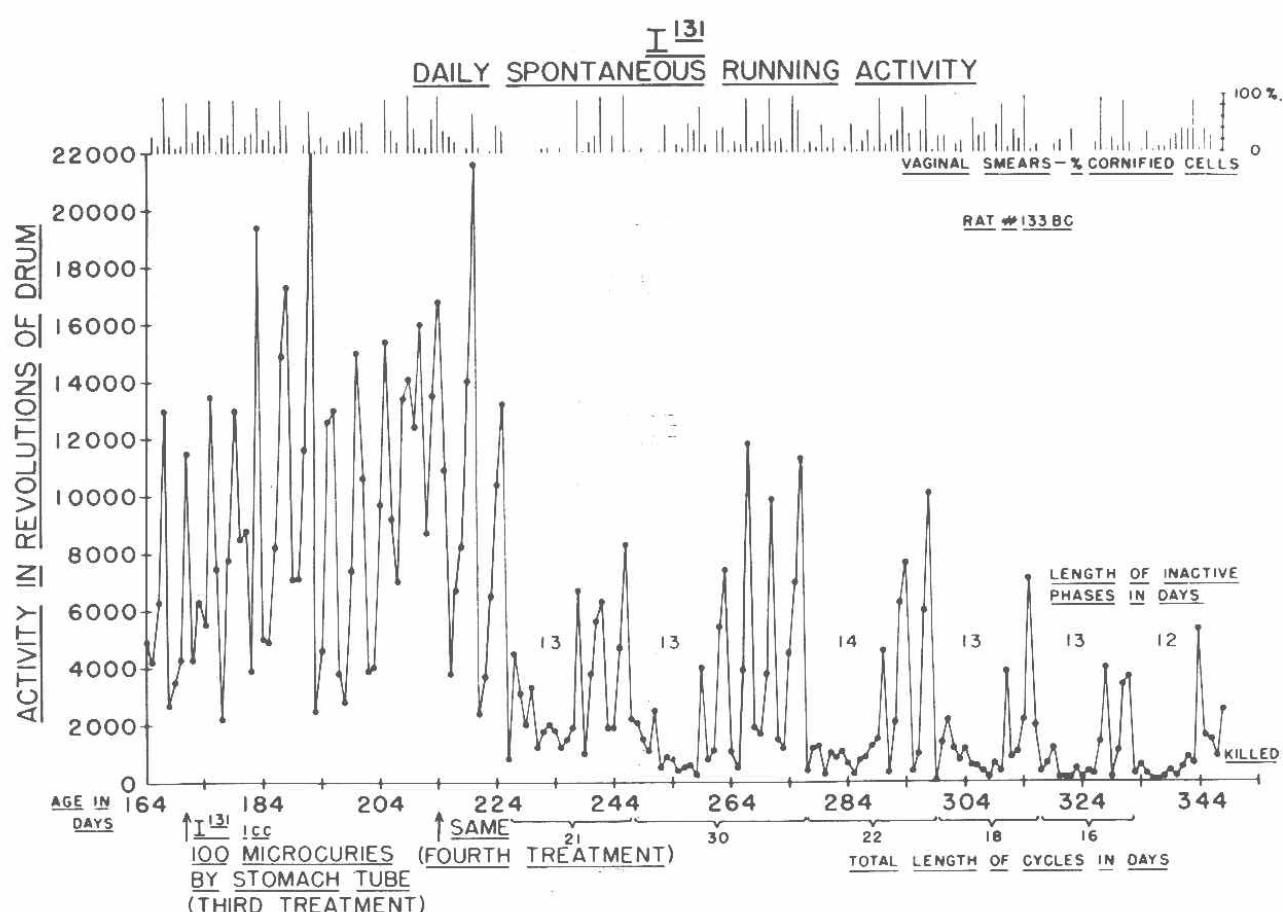


Figure 2. Graph showing record of daily spontaneous running activity and vaginal smears of a rat after treatment with I^{131} .

of a rat that had four treatments with I^{131} (100 microcuries by a stomach tube). The ordinates give running activity in number of revolutions of the drum; the abscissas age in days. The first three treatments decreased the level of activity but had no effect on the 4 or 5 day estrous cycles and did not bring out any abnormal cycles. Eleven days after the fourth treatment, however, activity began to be broken up into regular cycles, each one consisting of an active and an inactive phase. The inactive phases remained quite constant in length, 12 to 14 days; the active phases made up of 3 to 5 estrous peaks at the start became progressively shorter with time. The record at the top shows the proportion of cornified cells in the vaginal smears in per cent. On the days of peak activity during the active phases, the smears showed 100 per cent cornification; during the inactive phases there were only a few if any cornified cells. This record is fairly typical for thyroxine deficient rats. In all instances the cycles progressively shortened with time, finally levelling off at an average length of 14 to 18 days. Thyroid treatment abolished the cycles.

Even more regular cycles were produced by interference with the pituitary gland or its connections with the hypothalamus—stalk section, removal of parts of the anterior or posterior lobes, lesions of the portal vessels in the stalk. Owing to the minute size of these structures and their intricate interrelationship, it is not

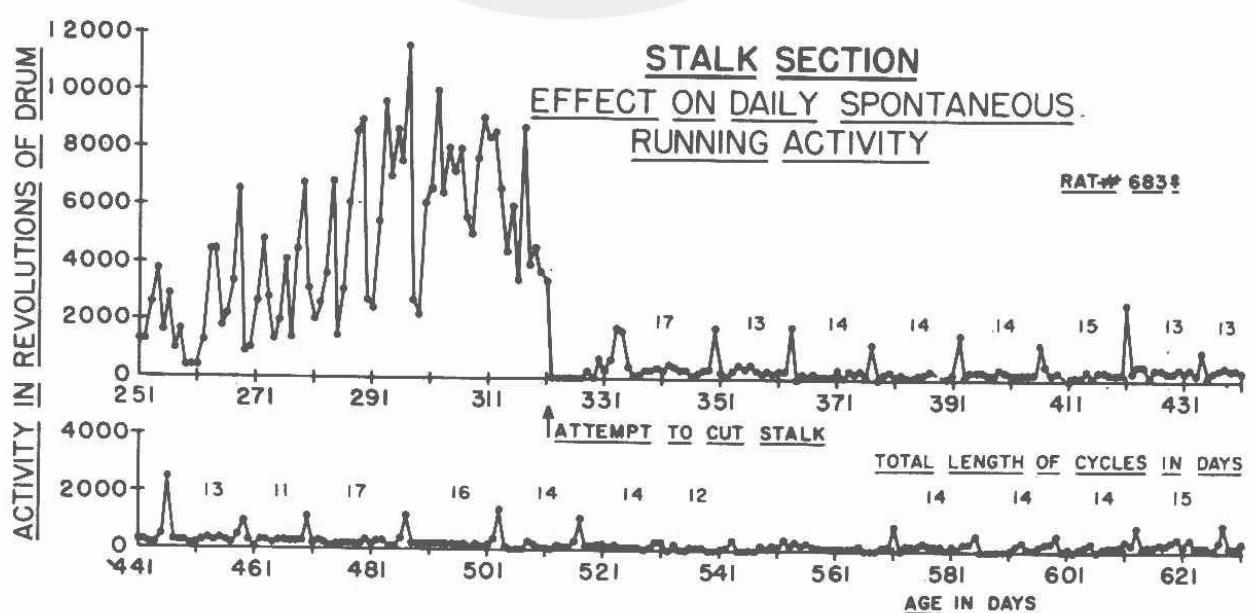


Figure 3. Graph showing record of daily spontaneous running activity of a female rat before and after attempted section of the pituitary stalk.

possible at present to state with any degree of confidence just which structures were disturbed by any of our operations, and to what extent. The fact remains, however, that disturbances in this region do produce extraordinary activity cycles that are never found in normal animals.

Figure 3 shows the daily activity record of a rat before and after attempted stalk section. Before operation the rat was fairly active; its activity averaged about 7000 revolutions per day. Immediately after operation it became almost totally inactive except for one-day bursts of activity that recurred with great regularity at intervals of 11 to 17 days, until it was sacrificed more than 300 days later.

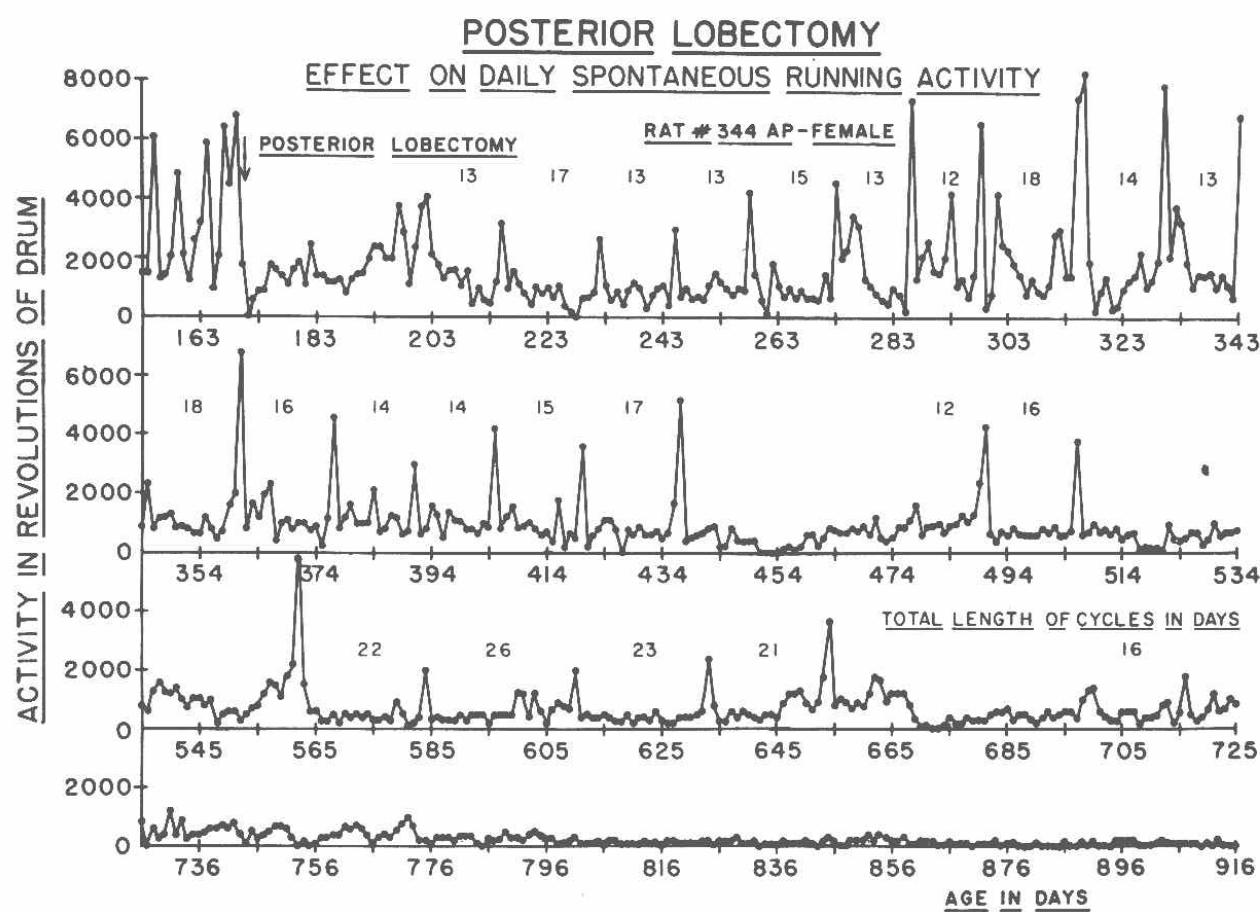


Figure 4. Graph showing the record of daily spontaneous running activity of a rat before and after "posterior lobectomy". Rat 344 AP.

Figure 4 shows 763 days (age 153-916) of the record of a rat with a posterior lobectomy. It must be kept in mind here that in removing the posterior lobe damage is unavoidably done to the portal vessels that connect the hypothalamus and anterior lobe and

to the anterior lobe itself; and that all, or nearly all, of the intermediate lobe comes out with the posterior lobe. This means that the effects of a posterior lobectomy do not necessarily result from removal of the posterior lobe alone. This rat showed single-day bursts of activity that at first came at intervals of 12 to 18 days; later at intervals of 21 to 26 days. They were present for well over a year after which the rat became almost totally inactive—possibly owing, at least in part, to old age.

In contrast to the thyroxine deficiency cycles which became progressively shorter with time, the cycles produced by pituitary lesions tended to remain the same in length or actually to become longer with time. In a few instances, however, although the cycles recurred with great regularity, the length of the cycles changed through a wide range from one period to the other and in some instances the cycles temporarily disappeared altogether. Such a record is shown in Figure 5 which gives 816 days of the record of a rat before and after "posterior lobectomy." Soon after the posterior lobectomy this rat became inactive for several weeks, then very active for several months; after that regular cycles of

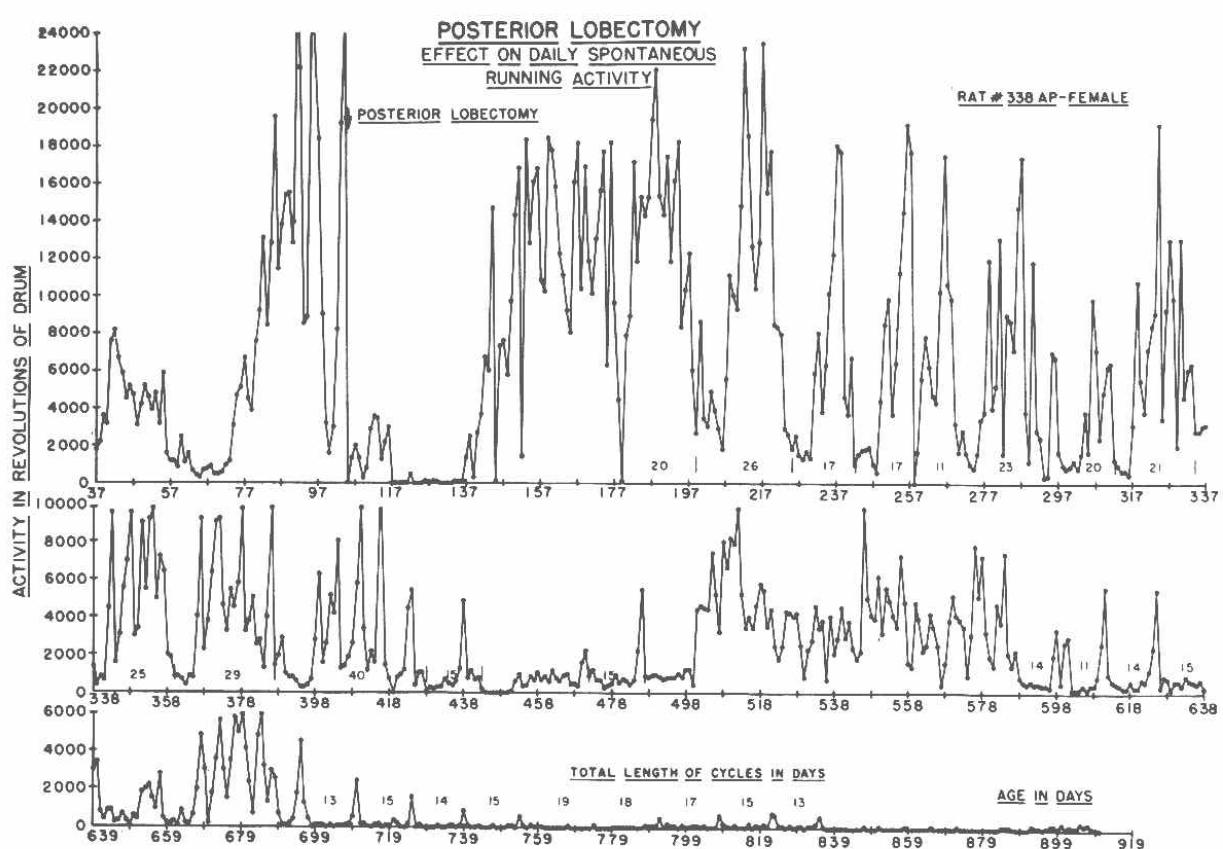


Figure 5. Daily spontaneous running activity for Rat 338AP.

17 to 26 days appeared which then suddenly changed to very regular cycles of 25 to 40 days in length. There then followed active and inactive periods of uneven lengths and finally regular single day bursts of activity at intervals of 13 to 18 days. Here again old age may explain the great inactivity of this rat and the final disappearance of all cycles. Spontaneous tumors in the region of the 3rd ventricle produced cycles of the type shown in Figure 3.¹³

Removal of one ovary and all except a small remnant of the other produced cycles 90 to 110 days in length.¹⁴

Parathyroidectomy produced cycles of 20 days in length.¹⁵

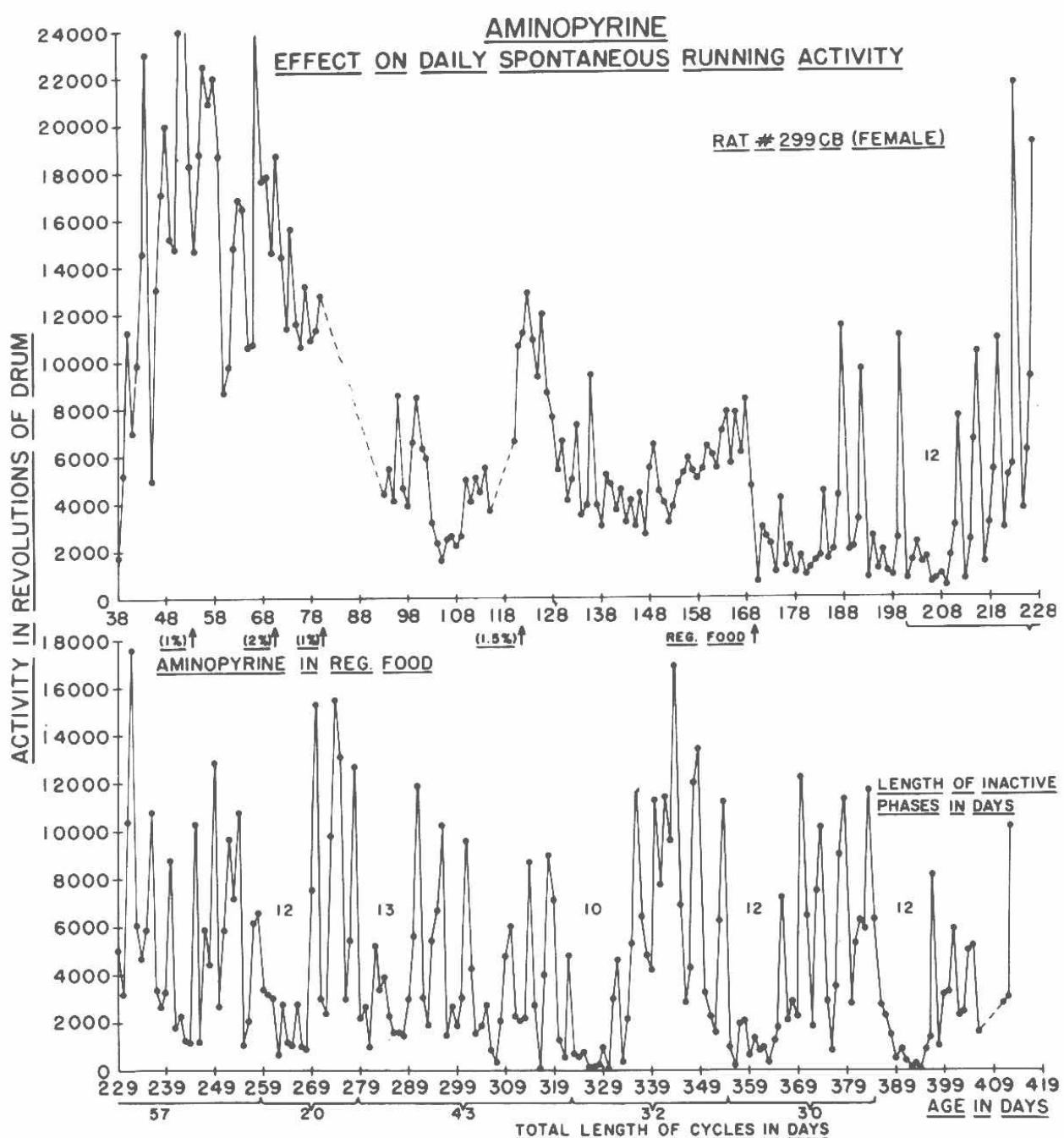


Figure 6. Graph showing record of daily spontaneous running activity of a rat before, during and after feeding with aminopyrine.

Figure 6 shows the record of a rat that had been fed aminopyrine (Pyramidon) in its diet for 78 days. After treatment it showed regular cycles consisting of an active and an inactive phase, the inactive phases tended to remain the same in length, but they were less regular than those of the thyroid deficient rats. Prolonged feeding of the female sex hormone, estradiol, produced regular cycles of 18-20 days in length, with single day bursts of activity.

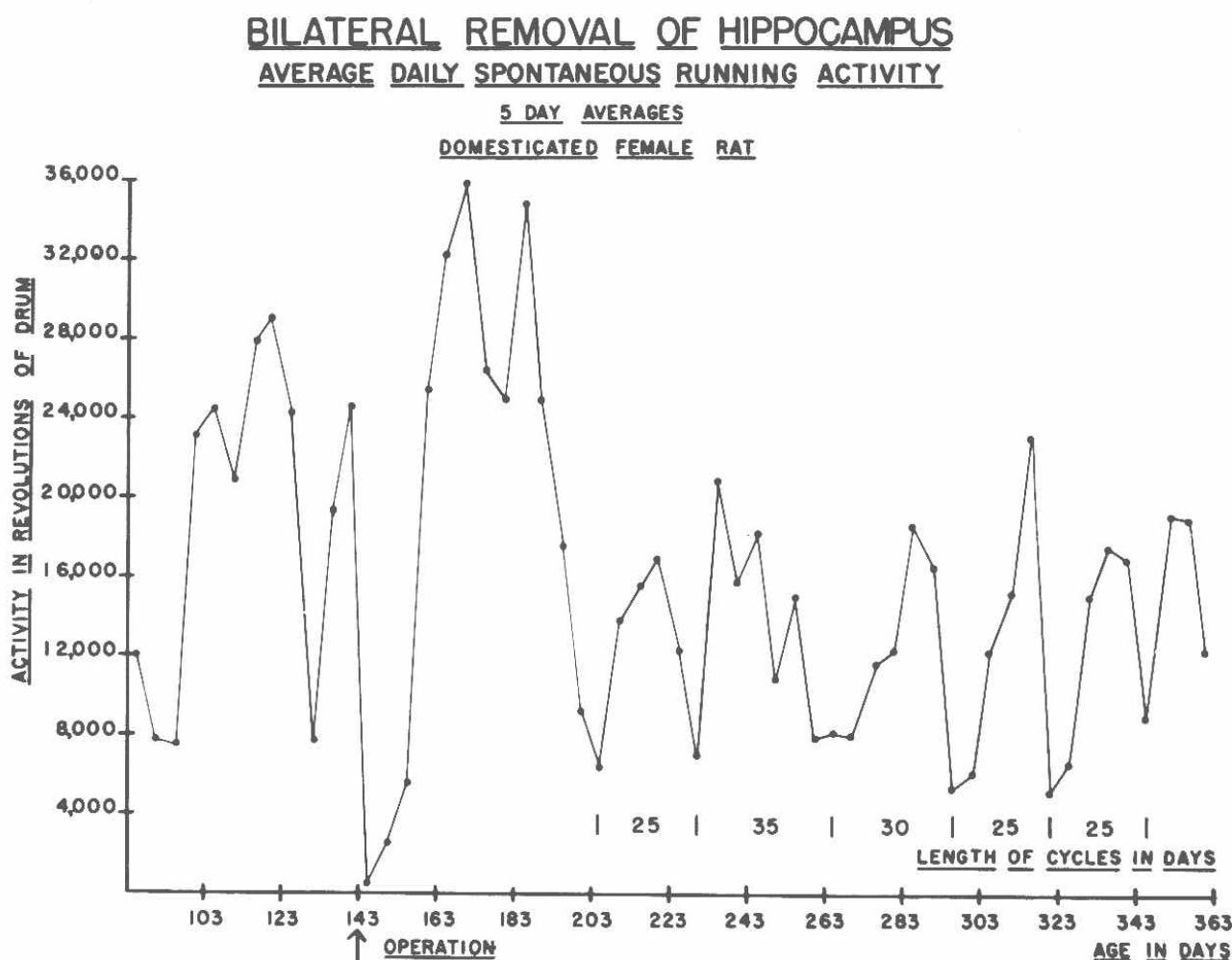


Figure 7. Graph showing record of daily spontaneous running activity (5 day averages) of a rat before and after bilateral removal of the hippocampus.

Figure 7 shows the daily running activity record of a rat before and after bilateral removal of the hippocampus. It gives 5-day averages rather than daily records. The cycles were 25 to 35 days in length.

Some of the most regular cycles were found in rats that had been subjected to severe acute stress: prolonged swimming or intensive fighting. By means of swimming tanks and special methods of pre-

venting floating, it was possible to force-swim rats for long periods—up to 86 hours.¹³ When removed even at the end of 40 to 60 hours of swimming, the rats showed a number of symptoms that indicated damage must have been done to the brain, probably to the hypothalamus:—polydipsia, catalepsy, hallucinatory behavior and sudden wild impulsive jumping into the air and climbing of every available object. Later they showed marked polyphagia and a tendency to obesity.

On return to the activity cages after a prolonged forced-swim, the rats showed marked and permanent cycles in activity. See Figure 8. The cycles looked more like those produced by prolonged thyroxine deficiency but differed from them in that they did not respond to treatment with thyroid hormones.

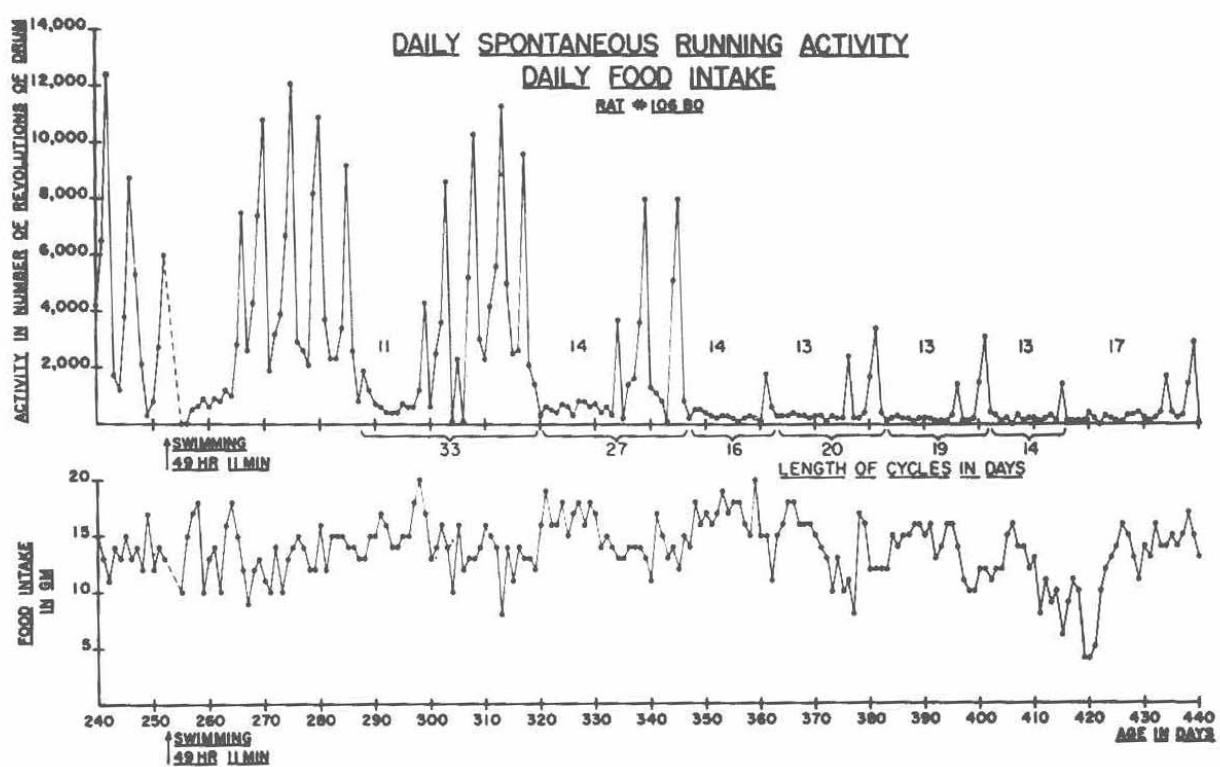


Figure 8. Graph showing record of daily spontaneous activity and food intake of a rat before and after forced swimming.

Similar permanent cycles were produced in wild rats that had been subjected to short periods of severe fighting—20 to 30 minutes. The stress of fighting like the stress of swimming apparently does damage from which the rats never recover.

It will not be possible at this time to discuss the mechanisms underlying the production of any of these cycles with the excep-

tion of those produced by thyroxine deficiency. These cycles we believe are produced by an imbalance in the homeostatic or feedback relationship between the hypothalamus, the pituitary, the functional remnants of thyroid tissue and the gonads; we also believe that the prolonged periods of thyroxine deficiency may do damage to some of the cells of the hypothalamus or closely related structures such as the so-called limbic system. We are not able at present even to offer a theory for the origin of the cycles produced by any other forms of interference.

What light if any do the results of these experimental studies throw on the origin of the cycles of behavior, mood and metabolism in psychiatric patients and patients with periodic disease? In the first place they should remove some of the mystery that has surrounded the subject of cyclic disturbances in man, since they have shown that cycles can be produced by interference with the function of internal organs and without any reference to external events.

Further they have shown that cycles have been produced by a variety of methods: that cycles have quite different characteristics and frequencies depending on their origin. This finding should thus help to discourage the clinical practice of placing all cycles together into one group and in looking for a common origin.

Cyclic manifestations may thus have an etiological as well as diagnostic and prognostic value. The results may help in the search for clues about the origin of the abnormal cycles in man since cycles were produced in animals by:

- (1) Endocrine disturbance in the thyroid or gonads.
- (2) Prolonged feeding of sulfa drugs, Thiourea or Thiouracil derivatives.
- (3) Prolonged feeding of Pyramidon and other drugs and female hormones.
- (4) Brain lesions.
- (5) Severe acute stress.
- (6) Pituitary disturbances, section of the stalk, disturbance in the portal circulation or in the posterior, anterior, or intermediate lobes.
- (7) Tumors in the region of the third ventricle.

Actually some of the abnormal cycles produced by the different forms of experimental interference in rats closely resemble the cycles seen in some of the psychiatric patients and patients with periodic disease. This agreement shows up best in comparisons made between cycles of catatonic schizophrenics and rats with thyroid deficiency. Both respond to thyroid treatment and they have a number of other features in common, as may be seen in Figure 9. This chart shows two cycles from the record of one of Gjessing's catatonic schizophrenics and two cycles from one of the rats in which a thyroxine deficiency had been produced by feeding Sulfamerazine for a 110 day period. To make possible a direct comparison of temporal relationship between the cycles of the patient and the rat, the time scale was made the same for both. The space between dotted lines represents one day. The top curve for the patient gives an estimate of the daily "psychic state"; the second curve shows spontaneous activity in bed as measured by

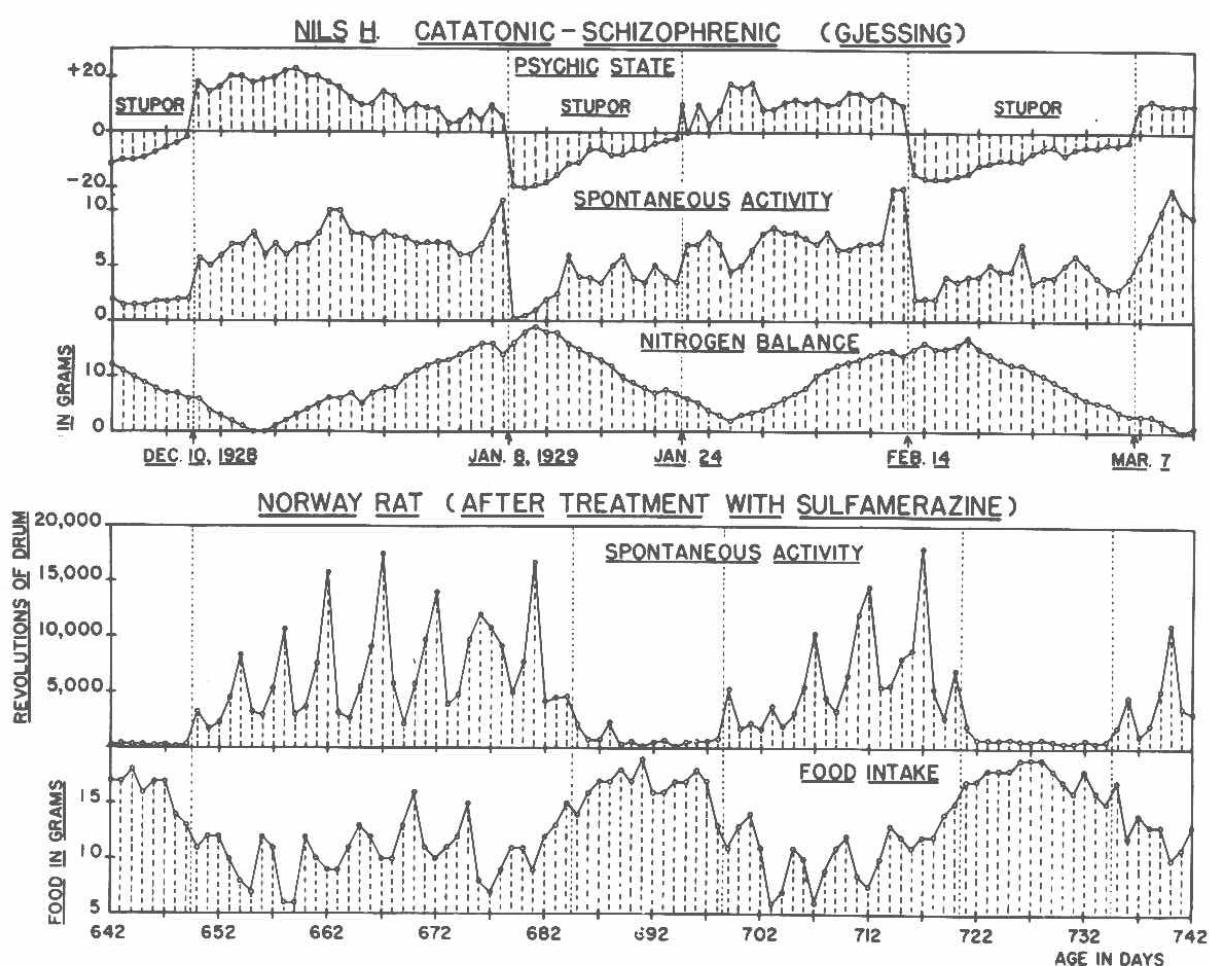


Figure 9. Daily record showing cycles of psychic state, spontaneous activity in bed, and nitrogen metabolism of catatonic schizophrenic; and cycles of spontaneous activity and food intake of rat that had been treated for 110 days with Sulfamerazine.

an actograph; the third curve shows nitrogen balance. The top curve for the rat shows daily spontaneous activity as measured in the revolving drum; the second curve food intake in grams. A close relationship exists first of all between the cycles of "psychic state" and spontaneous activity of the patient and cycles of spontaneous activity of the rat. Both are composed of two phases, that are separated by sharply defined transition zones; the relative lengths of the two phases is much the same. A close relationship exists also between the cycles of nitrogen balance and the cycles of food intake. They both are simple sinusoidal curves and are not broken up into two distinct phases as are the curves for activity.

The results of the studies on rats indicated that the appearance of the cycles depends on a close relationship between the endocrine glands and the hypothalamus—that variations in the place of action of the endocrines in the hypothalamus—variations in the affected nuclei—may account for the variations in organs and systems that are involved in cycles or attacks—physical as well as mental.

It must be pointed out that although regularity of attacks definitely establishes the internal origin of the cycles, irregularity does not mean that attacks do not likewise have an internal origin. Evidence for this statement comes from observations on a number of the rats that had very irregular fluctuations in activity after glandular interference. The record of Rat No. 338AP in Figure 5 was purposely shown to illustrate this point. After posterior lobectomy this rat's activity showed marked fluctuations that for months showed cycles of one length; then for months showed no cycles at all; then for months cycles, but of a different length, etc.

Finally, attention must be drawn to the great opportunities offered, on the basis of the knowledge at hand, by studies of patients as well as animals with cycles since each patient or animal provides its own base line during the free intervals for the evaluation of changes that occur during the attacks or abnormal periods. We have seen that patients who are normal in the free intervals may, during attacks, be hallucinated, paranoid, depressed or stuporous; or may have a high fever, neutropenia, peritonitis or a great variety

of other body symptoms. Since from the rat experiments we know many of the abnormal cycles result from disturbances in the endocrine system, these patients should offer an excellent opportunity for working out the role played by these various endocrines in controlling the normal function of the body, as well as the mind.

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XV

Influence of Chlorpromazine on Endocrine Function

MAX REISS*

IN PREVIOUS INVESTIGATIONS (Batt, Kay, Reiss and Sands 1957) we have repeatedly dealt with the question of why groups of schizophrenics, with clinically identical psychopathological manifestations, can react to insulin coma therapy in most contradictory ways. We have pointed out that some factors in the endocrine constitution of these patients, who have so far only been investigated from the point of view of adrenal cortex, thyroid equilibrium and sexual maturity, seem to be decisive for the success or failure of this treatment.

Chlorpromazine treatment is technically much less complicated than insulin coma treatment, and investigators in various parts of the world have, during the last few years, described their experiences with it. Individual investigations were able to deal with large series of patients, and no one can disagree with the conclusion that there is no single clinically homogeneous group of patients in whom chlorpromazine will produce a hundred per cent clinical success. It is for many an insoluble puzzle that, in two patients showing an apparently identical psychopathological pattern, chlorpromazine should bring complete relief to one while treatment is a complete failure in the other.

According to our psychoendocrine concept the quality of the symptomatology depends mainly on the genetically conditioned personality pattern of the patient, while his break-down and mental illness depends on the precipitating causes and his ability to react to them or to make sufficient adjustment. Any therapy can deal only with the latter two components. The adaptation to changing environmental demands depends on the homeostasis; the ability to

*Biochemical and Endocrinological Research Unit Southwest Regional Hospital Board and St. Ebba's Hospital, Epsom, Surrey, England.

maintain physiological equilibrium in spite of various disturbances. This is dependent on the normal production of hormones, which as we know regulate all the physiological and metabolic functions of the body. When considering the rationale of various drugs, particularly the therapeutic results of treatment of longer duration, it is useful to investigate the action of the drugs on the endocrine functions and hormone equilibrium. This we have done extensively with chlorpromazine.

We have already had considerable experience in treating patients with chlorpromazine, but in order to get some idea about the principles of chlorpromazine action on the endocrinum it is useful first to study the results of animal experiments.

METHODS

The experiments were carried out on Wistar rats (Porton) strain. They were fed on Parkes Diet No. 41 in cube form, and maintained in a thermoregulated room.

The glands were dissected carefully and weighed on a torsion balance.

The I^{131} uptake of the thyroid was generally measured 18 hours after intraperitoneal injection of 2 μ c. of the isotope. In some experiments, where stated in the Tables, the I^{131} was measured two hours after application.

The glands were removed and put into test tubes containing 10 m. 2n-NaOH (1 per cent to NaI) which were heated in a boiling water bath for one hour. The radioactivity of the resulting solution was measured in a liquid counter (Veall 1948).

The A.C.T.H. content of the pituitaries of rats which had been pre-treated with chlorpromazine was measured using the adrenal ascorbic acid depletion method of Sayers et al. (1948) with modifications as described by Reiss, Halkerston, Badrick and Halkerston (1952). The pituitaries were removed from freshly killed control and chlorpromazine pretreated animals, weighed and homogenized by hand in chilled normal saline. The resulting suspensions were diluted to contain 1 mg. of pituitary tissue per ml. Each rat received 0.5 ml. of this suspension. During the experiment the solutions were kept on ice.

The TSH content of the pituitaries was measured by its ability to increase the uptake of I^{131} by the thyroids of suckling rats (method of Reiss and Wyatt 1956). The glands were treated as above and the resulting suspensions made up to contain 2 mg. in 0.45 ml. saline. This was fractionated into three equal doses, and injected subcutaneously once daily for three days preceding autopsy. One hour before the suckling rats were killed 5 μ c. of I^{131} was injected, and the content of the thyroids was measured as described above.

In all experiments the chlorpromazine used was May and Baker Largactil and the dose given is mentioned in the Tables.

RESULTS

The changes in the weights of the adrenals, thyroids, thymus, ovaries and uterus are shown in Table 1. The weight of all these glands, with the exception of the adrenals, decreased after chlorpromazine. This weight loss is most obvious in the ovaries, their endocrine activity being apparently also decreased since the uterus showed a considerable weight loss, which with the larger doses was statistically significant. Only the adrenal weight showed a tendency to rise.

Table 1
CHANGES IN THE GLAND WEIGHTS IN PERCENT OF UNTREATED CONTROLS

Rats		Chlorpromazine Treatment		THYROIDS	ADRENALS	THYMUS	OVARIES	UTERUS
No.	Weight (Gm.)	Daily dose	Duration days					
10	120 to 140	1 mg.	1	-15	+17	-18	-11	-4
10			2	-16	+6	-16	-9	-7
10			4	-11	+9	-17	-12	0
10			6	-4	+15	-4	-18	-35
10			12	-19	+6	-23	-13	-17
10	120 to 140	4 mg.	1	-20	+6	-18	-3	
10			2	-7	+2	-11	-23	-23
10			4	-20	+5	-27	-27	-22
10			6	-13	+13	-31	-23	-39
10			12	-18	+2	-33	-26	-30
10	200 to 220	8 mg.	3	-28	+11	-26	-15	-29
10			12	-25	+2	-37	-26	-38

— Denotes significant change at $P = 0.05$.

— Denotes significant change at $P = 0.01$.

Equivalent changes are to be seen in the organ weights of male rats, Table 2. The weight of the testicles did not decrease as markedly as that of the ovaries. There is apparently an inhibition only in the hormone producing parts of the glands, finding its expression in the much more pronounced decrease in weight of the seminal vesicles.

Table 2
CHANGES IN THE GLAND WEIGHTS IN PERCENT OF UNTREATED CONTROLS
(Male rats weighing 180-200 Gm.)

Rats	Chlorpromazine Treatment		THYROIDS	ADRENALS	THYMUS	TESTICLES	SEMINAL VESICLES
No.	Daily dose	Duration (days)					
10	1 mg.	3	-17	+14	-24	-9	-26
10		6	-13	+7	-20	-8	-27
10		12	-16	0	-17	-9	-38
10	4 mg.	3	-16	+5	-37	-5	-12
10		6	-2	+1	-26	-1	-26
10		12	-12	+9	-32	-9	-35
10	2.5 mg.	20	-15	-2	-11	-5	-7
10		40	-1	-8	-7	-2	-14
10		60	-14	-6	-8	-4	-18

— Denotes significant change at $P = 0.05$.

— Denotes significant change at $P = 0.01$.

Some of our investigations concerned the I^{131} and P^{32} uptake of the thyroid, and the P^{32} uptake of other glands. The results are recorded in Tables 3 and 4.

The changes seen in the thyroid activity after chlorpromazine treatment take place apparently in two phases, the extent of which depends on the dose and duration of the chlorpromazine treatment. The I^{131} uptake of the thyroid after 4 to 8 mg. of chlorpromazine

Table 3
RADIO-ACTIVE TRACER UPTAKE IN PERCENT OF UNTREATED CONTROLS
(Male rats weighing 180-200 Gm.)

Rats	Chlorpromazine Treatment		THYROIDS		ADRENALS	THYMUS	TESTICLES	SEMINAL VESICLES
	No.	Daily dose	Duration (days)	I¹³¹ uptake	P³² uptake			
5			3	-46 =	0	-40 =	-49 =	-16 =
5	1 mg.		6	-11	+33	-22	-21	-23 =
5			12	-21	+17	-27	-31	-3 =
5			3	-9	-37	-12	-54 =	-42 =
5	4 mg.		6	+38	+12	+19	-15	-21
5			12	-12	+12	+9	-16	-23
5			20	-4	-24	+21	+5	
5	2.5 mg.		40	+1	+21	-46	-34	-8
5			60	0	+44	-24	-48	-28

— Denotes significant change at $P = 0.05$.

— Denotes significant change at $P = 0.01$.

was at first decreased, but later rose above the control value. In Figure 1 an experiment is summarized in which the I¹³¹ thyroid uptake of several parallel groups of rats was investigated after 6 mg. of chlorpromazine daily. The I¹³¹ uptake fell below the normal level on the first three days, but rose steeply to well above the normal range by the fifth day. After only 1 mg. of chlorpromazine the I¹³¹ uptake apparently rises without a previous fall.

Twenty to sixty days after the start of treatment the I¹³¹ uptake of the thyroid of male rats was once again within the normal range.

After small doses of chlorpromazine the P³² uptake of the adrenals was generally decreased, but after a larger dose a tendency to rise was shown.

^{131}I UPTAKE BY THYROIDS OF FEMALE RATS
AFTER TREATMENT WITH CHLORPROMAZINE

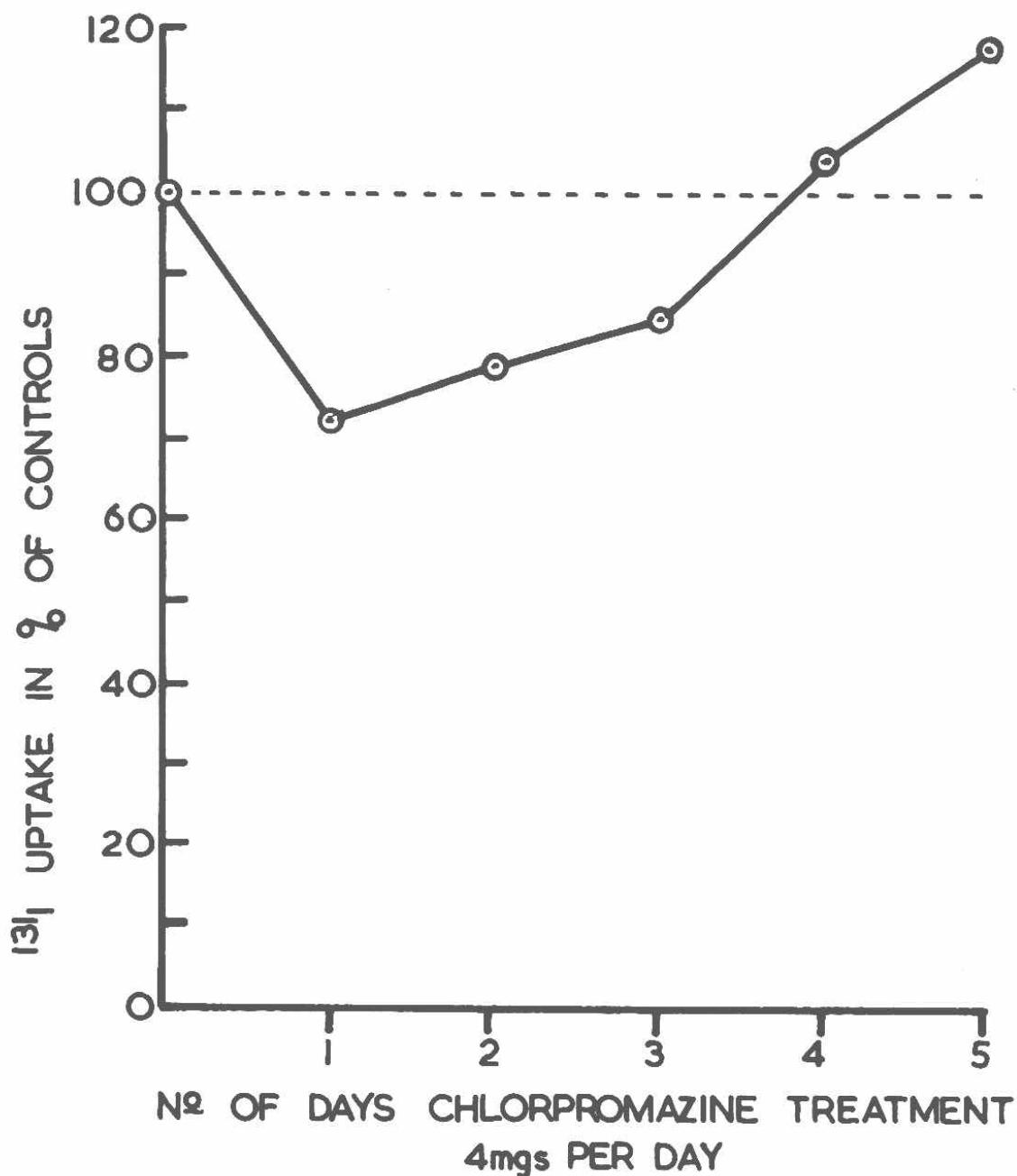


Figure 1

The P^{32} uptake of the thymus, ovaries, uterus, testicles and seminal vesicles was decreased without exception even after the smallest dose of chlorpromazine and the shortest interval of treatment.

The A.C.T.H. and TSH content of the pituitary began to rise two days after the start of treatment with 1 mg. of chlorpromazine daily, and the hormone content remained increased after twelve days (Table 5). No difference was seen between the reaction of male and female animals. After treatment with higher doses of chlorpromazine (4 mg.) the same changes occurred, but the con-

Table 4

RADIO-ACTIVE TRACER UPTAKE IN PERCENT OF UNTREATED CONTROLS

(Female rats)

Rats		Chlorpromazine Treatment		THYROIDS		ADRENALS		THYMUS		OVARIES		UTERUS
No.	Weight (Gm.)	Daily dose	Duration (days)	I ¹³¹ uptake	P ³² uptake							
5	120 to 140	1 mg.	1	+57 <u><u>=====</u></u>	-27	-5	-37	-30	-43			
5			2	+44 <u><u>=====</u></u>	-33	-22	-30	-40	-29			
5			4	+40 <u><u>=====</u></u>	-20	-26	-31	-30	-36			
5			6	+29 <u><u>=====</u></u>	-33	-24	-9	-38	-62 <u><u>=====</u></u>			
5			12	+4 <u><u>=====</u></u>	-20	-57 <u><u>=====</u></u>	-53	-62 <u><u>=====</u></u>	-73 <u><u>=====</u></u>			
5	120 to 140	4 mg.	1	-22 <u><u>=====</u></u>	+14	-20	-19	-18				
4			2	-24 <u><u>=====</u></u>		-24	-27	-41	-47			
5			4	-17 <u><u>=====</u></u>	-14	-11	-27	-39	-27			
5			6	-20 <u><u>=====</u></u>	-14	-27	-42	-49	-60			
5			12	+23 <u><u>=====</u></u>	+86	-29	-18	-31	-31			
5	200 to 220	8 mg.	3	-26 <u><u>=====</u></u>	-31	+21	-22	-29 <u><u>=====</u></u>	-39			
5			12	+24 <u><u>=====</u></u>	-6	+35	-30 <u><u>=====</u></u>	-32 <u><u>=====</u></u>	-39			

===== Denotes significant change at P = 0.05.===== Denotes significant change at P = 0.01.

tent of thyrotrophic hormone fell after about the 12th day. After treatment for 40-60 days no difference could be seen in the content of A.C.T.H. and TSH between the normal and treated animals.

In an attempt to see how chlorpromazine treatment interfered with the endocrine concomitants of various stresses, ECT was given for four days to animals which were pretreated for 10 days with chlorpromazine. Chlorpromazine, like ECT, raised the adrenal cortex weight slightly, and reduced the adrenal ascorbic acid con-

Table 5

A.C.T.H. & T.S.H. CONTENT OF FRESH PITUITARIES AFTER CHLORPROMAZINE TREATMENT

(female rats weighing 120-140 Gm.)

Chlorpromazine treatment before analysis		No. of rats	A.C.T.H.		T.S.H.	
Daily dose	Days		Milli units per pituitary	% change from controls	Milli units per pituitary	% change from controls
Controls		16	9.7		570	
1 mg.	2	8	16.5	+ 70	740	+ 30
	4	8	15.8	+ 63	950	+ 66
	6	8	17.6	+ 73	790	+ 39
	12	8	19.9	+ 101	1210	+ 112
Controls		14	8.7		290	
4 mg.	1	8	16.9	+ 94	790	+ 172
	2	8	21.8	+ 150	690	+ 138
	4	8	22.4	+ 157	520	+ 79
	6	8	35.3	+ 306	820	+ 183
	12	8	24.9	+ 186	250	- 14

tent. Both treatments combined did not show any significant inhibition of the stress effects.

The I^{131} uptake of the thyroid also rose both after ECT and chlorpromazine to a similar degree, the stress effect being increased when the animals were subjected to the combination (Table 6).

Chlorpromazine treatment did not alter the effect of stress induced by Formalin (Table 6).

Table 6
INFLUENCE OF CHLORPROMAZINE PRE-TREATMENT ON E.C.T. & FORMALIN STRESS
(female rats weighing 180-200 Gm.)

Treatment carried out before investigation.	No. of rats	ADRENAL WEIGHT (mg. \pm S.D.)	ADRENAL ASCORBIC ACID (mg./100 Gm. adrenal weight \pm S.D.)	THYROID I^{131} UPTAKE (% of dose after 2 hours \pm S.D.)
Untreated controls	8	68.4 \pm 13.3	311 \pm 53	5.46 \pm 1.10
1 X ECT daily for four days.	8	76.4 \pm 13.7	217 \pm 24	6.54 \pm 1.47
Chlorpromazine 2.5 mg. daily for ten days.	8	72.2 \pm 4.9	252 \pm 44	6.90 \pm 2.36
ECT & Chlorpromazine (as above) combined.	8	63.1 \pm 12.0	235 \pm 28	8.02 \pm 1.78
Untreated controls	8	62.6 \pm 13.2	321 \pm 32	7.4 \pm 0.8
0.5 ml. of 10% Formalin subcutaneously, once daily for 4 days.	8	73.4 \pm 8.9	294 \pm 23	7.3 \pm 2.3
Chlorpromazine 2.5 mg. daily for ten days.	8	74.6 \pm 9.9	20 \pm 43	10.4 \pm 1.8
Chlorpromazine and Formalin (as above) combined.	8	75.7 \pm 6.0	309 \pm 30	9.4 \pm 2.0

INFLUENCE OF SIMULTANEOUS CHLORPROMAZINE & STRESS OF SWIMMING IN COLD WATER OR E.C.T.

INFLUENCE OF CHLORPROMAZINE

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Table 7

Treatment	No. of rats	THYROID WEIGHT Mean \pm S.D. % change from controls (mg.)	ADRENAL WEIGHT Mean \pm S.D. % change from controls (mg.)	OVARIES WEIGHT Mean \pm S.D. % change from controls (mg.)
Controls	7	12.8 \pm 1.2	46.2 \pm 8.6	43.5 \pm 13.3
Swimming in water at 15°C once daily for 3 days.	6	14.9 \pm 2.1 + 16	46.7 \pm 6.8 + 1	44.4 \pm 6.5 + 2
Electroshock twice daily for 3 days.	6	13.9 \pm 1.8 + 9	58.0 \pm 4.9 + 26	51.4 \pm 6.9 + 18
Chlorpromazine 6 mg. twice daily for 3 days.	6	12.4 \pm 1.6 — 3	59.3 \pm 6.1 + 28 =	35.6 \pm 10.1 — 18
Swimming and Chlorpromazine as above.	7	11.7 \pm 2.7 — 9	60.5 \pm 12.1 + 31 =	35.7 \pm 11.0 — 18
E.C.T. and Chlorpromazine as above.	7	10.4 \pm 1.5 — 1	55.7 \pm 7.1 + 21 =	30.4 \pm 8.3 — 30

— Denotes significant change at $P = 0.05$.

— Denotes significant change at $P = 0.01$.

Even the highest dose of chlorpromazine (6 mg. twice daily) did not modify the direction of the adrenal response to the stress of swimming in cold water or of ECT. Thyroid and ovary weight, however, which showed a tendency to rise after these two stresses, were reduced when high doses of chlorpromazine were given in addition (Table 7).

DISCUSSION

When surveying the various actions of chlorpromazine on the endocrine system it becomes obvious that it can by no means be summed up under one common denominator. It appears, for instance, improbable that the action of chlorpromazine can be explained by an impairment of the hypothalamus only, and through it of the anterior lobe of the pituitary, as assumed by Sulman and Winnick (1956). A great number of authors have assumed that chlorpromazine prevents stress reactions. This assumption is not in agreement with the results of our investigations, as far as the endocrine concomitants of stress are concerned.

It seems that the action of the chlorpromazine on the endocrines takes place at various levels of the neuroendocrine circle.

This can best be seen in the action of chlorpromazine on the gonads. After one day's administration the ovary weight is considerably decreased; so also is the P^{32} uptake which is usually taken to indicate the cell activity of the tissue. The endocrine activity of the ovary is also soon decreased as can be concluded from the reduction in weight and phosphorus uptake of the uterus. In extensive investigations of the effect of hypophysectomy on the gonads we have never seen such a rapid reduction in size and activity of the gonads so soon after removal of the pituitary.

The mechanism of this action is much easier to understand if one completely leaves out of consideration the possibility that it might be a primary pituitary mechanism, and views it as similar to the toxic action of chlorpromazine on the liver, which indeed can be assumed from the development of jaundice in some patients.

It seems that this reduction in the gonadal function has, like castration or inflammation of the ovaries, a secondary feed-back action on the pituitary resulting in an increased production on gonado-

trophic hormone. Sulman and Winnick (1956) reported an increase in the excretion of both gonadotrophic hormones of the pituitary in patients 11 to 25 days after the start of chlorpromazine treatment. We, ourselves, have seen considerably increased quantities of gonadotrophic hormone in the serum and urine of some chlorpromazine treated patients, and these results will be published later.

The pituitary cannot keep up this increased gonadotrophic hormone production and so it gradually diminishes; the time needed varies from one patient to another and is usually one to two months. The increased production of prolactin reported by a number of authors seems to be related to the decrease in gonadotrophic hormone, similar to that seen after birth. During the last year we have had the opportunity of seeing this mechanism working in animal experiments. There the gonadotrophic production was completely inhibited in rats by treatment with a long acting Estradiol Depot. A most interesting phenomenon observed one to two months after the start of this treatment was the abundance of milk in the mammary glands. The amount secreted was so great that it overflowed during laparotomy. In a similar manner some house animals, particularly dogs, produce some milk in the period after heat. It appears that the disturbance of the menses in women, and the repeatedly reported occasional galactorrhea seen after chlorpromazine treatment, is due to a primary action of chlorpromazine on the ovary, the changes in the pituitary function being secondary sequels. One can assume that the action of chlorpromazine on the testicles and their hormonal activity is also a primary action.

There is also a more practical conclusion to be drawn from the above described influence of chlorpromazine on the gonads—that chlorpromazine should not be used indiscriminately on the basis of the psychopathological picture only. It is quite definitely contraindicated in patients who show immaturity or a disturbance of the gonadal function. A disturbance of the gonadal function always causes deterioration in any mental illness, independent of whether this disturbance existed before the mental illness developed or was a sequel to it.

It is obvious that if such patients are treated with chlorpromazine

TABLE 8

Treatment	Thyroid weights			I ¹³¹ uptake by the thyroids in % of dose (18 hrs.)			Adrenals weight			Ovaries weight			Uterus weight		
	No. of Rats	Changes in Body wgt (Gm.)	% changes from controls	Mean ± S.D. (mg.)	% changes from controls	Mean ± S.D. (mg.)	% changes from controls	Mean ± S.D. (mg.)	% changes from controls	Mean ± S.D. (mg.)	% changes from controls	Mean ± S.D. (mg.)	% changes from controls	Mean ± S.D. (mg.)	% changes from controls
Controls	8	+ 4	13.2 ± 2.6		21.2 ± 3.3		59.3 ± 8.9		61.4 ± 9.7		327 ± 103				
Pentobarbital (Nembutal) 6 mg. 2 X daily for 5 days.	8	- 3	11.3 ± 2.8	-14	18.3 ± 5.1	-13	57.6 ± 7.7	-3	51.6 ± 6.9	-16	267 ± 84	-18			
Chlorpromazine (Largactil) 6 mg. 2 X daily for 5 days.	7	-18	10.6 ± 2.0	-20	29.6 ± 7.6	+40	75.5 ± 10.7	+27	41.8 ± 12.3	-32	249 ± 66	-24			

— Denotes significant change at $P = 0.05$.

— — Denotes significant change at $P = 0.01$.

one might achieve some momentary relief, but it would be at the expense of considerable deterioration in the pathophysiological concomitants of the original psychopathological status, so that when the chlorpromazine is stopped, the physician may be faced with a patient considerably the worse for the alteration in the endocrine status.

Looking at the changes found after chlorpromazine treatment, the change of adrenal and thymus weights (Tables 1, 2, 6, and 7), the reduction of the I^{131} uptake of the thyroid and adrenal ascorbic acid content (Table 6), it is evident that these are identical with the endocrine consequences of various stresses, as for instance ECT, swimming in cold water, or formalin treatment. The only action which does not conform is the P^{32} uptake of the adrenals (Tables 3 and 4) which is often diminished after small doses. After larger doses the P^{32} uptake was increased as it was after A.C.T.H. treatment or exposure to cold (Reiss and Halkerston 1950). This sole discrepancy cannot be explained but we assume that it is probably due to the interference of a toxic action which affects the adrenal in the same sort of way as described above for the ovaries.

Other experiments which showed that chlorpromazine does not interfere with the endocrine stress reaction, and has even in some cases an additive effect, make it obvious that an important part of the chlorpromazine action in animal experiments is that the substance can act as a stressor. It appears to us therefore misleading, to suggest, as is done nowadays in so many papers, that chlorpromazine is a substance which prevents stress reaction. It certainly does not do so as far as the endocrine evidence is concerned. Apparently the claims that chlorpromazine has a stress countering activity can only be based on its inhibiting action on certain central synapses, interfering with the transmission of emotional and physical stress in a manner similar to that of a number of well known anesthetics, particularly barbiturates.

It might be relevant to compare the action of high doses of chlorpromazine with the action of the same dose of Pentobarbital. One such experiment is recorded in Table 8 and is representative of a number of similar experiments which were carried out using

a variety of doses and time intervals. The table shows that chlorpromazine is considerably more toxic than Pentobarbital. It decreased the body weight much more, it causes a significant rise in the weight of the adrenal cortex, and a significant fall in the weight of the ovary. The changes in the thyroid weight and activity are also very pronounced. It is feasible that in some patients prolonged therapeutic effect may be due to just these endocrine changes; for example in patients with gonadal prematurity, or overactivity. In fact chlorpromazine is at present showing some promise in the treatment of some of our schizophrenic patients who have premature gonadal development, while it often appears useless in immature patients.

No fully satisfactory explanation can be offered for the increased A.C.T.H. and TSH content of the pituitary seen in the first days after chlorpromazine treatment. The increased hormone content could be due to the increased production after stress, the excess in the production mechanism being higher than in the release mechanism of the hormone. It is interesting to see (Table 5) that twelve days after treatment the increased TSH content of the pituitary can no longer be found. These results are in agreement with a number of parallel investigations which were carried out, in which an increased TSH hormone content could not be detected. This change coincides in time with the increased I^{131} uptake of the thyroids of these animals. Twenty to sixty days after the start of chlorpromazine treatment no significant changes could be found in the TSH or A.C.T.H. content of the pituitary.

The decrease in the gland weight and P^{32} uptake seen in the thyroid during chlorpromazine treatment certainly cannot be connected with the changes in the thyrotrophic hormone content of the pituitary. There again it is only possible to assume a peripheral toxic action of chlorpromazine. In this context it is worth mentioning our previous experiments according to which stress or treatment with adrenalin reduces the I^{131} uptake of the thyroid in normal and hypophysectomized rats alike (Badrick, Brimblecombe, and Reiss, 1955). There is no doubt that chlorpromazine treatment initiated a number of changes in the body which acted on the thy-

roid in various ways. The multitude of factors responsible for the change in thyroid activity during chlorpromazine treatment can explain the great variation of changes found in the thyroid activity of patients on this treatment. We have seen deterioration of the confusional state in a thyrotoxic case, and deterioration of the thyroid activity in hyperthyrotic cases. We have also seen improvement of hyperfunctional thyroids, at least as far as the I^{131} uptake and production of protein bound iodine were concerned.

The endocrine changes accompanying chlorpromazine treatment could be summed up under the following headings:

1. The reduction of the sensitivity in certain receptor areas of the brain for emotional and physical stress. In this way the occurrence of the endocrine concomitants of various stresses ought to be quantitatively diminished.
2. A direct stress action which is, in its endocrine concomitants, comparable to other stress actions like ECT, swimming in cold water, or formalin treatment.
3. A toxic action in the periphery which is best demonstrated in the action of chlorpromazine on the gonads.

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XVI

Steroid Response to A.C.T.H. and the Effect of Ataractic Drugs

R. BRUCE SLOANE, M. SAFFRAN
and R. A. CLEGHORN*

Adrenal cortical function in schizophrenia has remained a controversial issue,¹ but, as judged by the mean corticosteroid output following intravenous A.C.T.H.[†], it appeared normal, although with widened range in our studies.² However, what seemed of more immediate interest was the uniform overresponse to A.C.T.H. of psychiatric patients of varying, but nonschizophrenic, diagnosis (Table 1).

Although a similar overreaction had been found by Persky et al.³ in subjects with predominating anxiety it appeared from our material that it was not confined to this group. Furthermore, the procedure of intravenous injection itself probably elicited the release of endogenous A.C.T.H., as indicated by the significant increase of corticoids following placebo injections in these patients (Table 2).^{2,4} A probable explanation for such an over response to A.C.T.H. is increased uptake by the enlarged chronically hyperfunctioning adrenal. Persky, however, has commented that such hyperadrenalinism is probably secondary to primary hyperpituitarism, since the flatness of log dose-response curves for A.C.T.H. suggested that anxious patients had an higher endogenous plasma level of A.C.T.H.⁵ Thus, we were concerned with examining further the possible central mechanisms of such responses.

The problem of neural control of the pituitary has been explored through the use of central nervous system depressant drugs, including the phenothiazine derivative, 10-(δ -dimethylaminopropyl)-2-

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†Adrenocorticotropic hormone ACTON X kindly supplied by the courtesy of Mr. Kell Antoft of Nordic Biochemicals, Montreal.

chlorophenothiazine (chlorpromazine "Largactil").⁶ This drug appeared promising for use in a possible test system, since clinically it is more effective in psychoses or impending psychoses than in anxiety states or psychoneuroses. Thus we would be afforded the two indices of clinical response to the drug and effect on cortico-steroid output.

Table 1

**MEAN URINARY EXCRETION RATES IN GAMMA PER HOUR OF FREE
17-HYDROXYCORTICOSTEROIDS RESTING AND FOLLOWING A.C.T.H.**

Subjects	Number	A.C.T.H.		Percentage† Difference
		Pre	Post	
Controls	9	30.9 ± 6.2	91.1 ± 34.9	+210*
Psychoneurotics	16	19.4 ± 15.9	117.9 ± 73.3	+583*
Anxiety States	9	16 ± 10.4	95 ± 44	+580*
Schizophrenics	10	23.2 ± 13.6	71.4 ± 49	+215

* P = 0.001

†Mean of the individual differences between pre and post rates, each expressed as a percentage of the pre rate. Because of the widened range of values, such percentage differences are not necessarily the same as the differences between mean absolute pre and post rates.

Table 2

**MEAN VALUE OF URINARY 17-HYDROCORTICOID BEFORE AND AFTER PLACEBO
INJECTION IN PSCHONEUROTIC PATIENTS**

Subjects	Number	Placebo		Percentage Difference
		Pre	Post	
Controls	9	25.4 ± 7.1	27.5 ± 12.4	+ 5
Psychoneurotics	16	15.8 ± 9.3	24 ± 12.1	+52†

* P = 0.05

† Difference between mean pre and post rates expressed as a percentage of the mean pre rate.

METHOD

We compared the response to ACTH of a group of psychiatric patients who were randomized in such a way that half received

chlorpromazine* on the first day followed by a control day of saline injections, and the other half vice versa. Testing was done within the first three days of admission to the hospital when anxiety was probably at its height. Consecutive admissions were taken, but patients who were too disturbed to cooperate and those with physical illness were excluded.

Subjects

There were 32 patients, 18 female and 14 male, with a mean age of 32.1 years (range 18-72 years). They were composed of two separate groups tested some months apart.

14 suffered from depressive illness and 18 from mixed psycho-neurosis. 17 received chlorpromazine on the first day and 15 the placebo.

Technique

On waking the overnight urine was voided and discarded. Two glasses of water were given, followed by an intramuscular injection of 25 mg. of chlorpromazine. The urine was collected for the next three hours. A further 25 mg. of intramuscular chlorpromazine was then given, followed immediately by 5 units of intravenous A.C.T.H. All urine was collected for the ensuing four hours. On the control day 4 c.c. of intramuscular saline was substituted for each injection of chlorpromazine.

Estimation of urinary corticoids

The free 17-hydroxycorticosteroids in the urine were measured by an adaptation of the method of Silber and Porter which we have previously described.²

RESULTS (Table 3)

There was good concordance between the two groups. There was no significant difference between the resting levels of corticoid output after chlorpromazine. The increase of urinary corticoids following A.C.T.H. was significantly less, however, on the chlorpro-

*“Largacitil” kindly supplied by Poulenc Ltd., Montreal.

mazine than the control day. (difference = minus 23.5 gamma per hour $P = 0.01$) (Table 3). When the individuals were paired so that each patient became his own control the replicated differences became highly statistically significant ($P = <0.001$).

There appeared to be no overt correlation between clinical response to the drug and the effect upon corticoid output.

Table 3

**MEAN VALUE OF URINARY 17-HYDROXYCORTICOID BEFORE AND AFTER A.C.T.H.
ON CONTROL PLACEBO AND CHLORPROMAZINE DAY**

	No.	Placebo		Chlorpromazine		Dif.	
		A.C.T.H.		A.C.T.H.		Pre	Post
		Pre	Post	Pre	Post		
Group 1	19	28.5	89.7	35.6	71.6	+7.2	-18.2
Group 2	13	31.2	103.4	25.3	72.1	-5.9	-31.3
Group 1 + 2	32	29.6	95.3	31.6	71.8	+1.8	-23.5*

* $P = 0.01$

COMMENT

These findings indicated that a single dose of 25 mg. intramuscular chlorpromazine did not raise the hydroxycorticoid excretion over the ensuing three hours. Such a finding was in contradistinction to the raised plasma level of corticosteroids found in the monkey following intravenous chlorpromazine by Harwood and Mason.⁷ In their study not only were plasma rather than urinary levels used but, as is so often the case in animal experiments, the dosage ranged up to very high levels (5.0 mg./kgm. B.W.), which, by this route, would be regarded as hazardous in the human. However, our collection of resting urine was over a short period and it is planned to repeat this over 6, 12 and 24 hours.

The lowered response to A.C.T.H. following chlorpromazine was extremely interesting. Quantitatively it was of the order of, although somewhat greater than, the increase of corticoid excretion following a placebo injection (75 per cent c.f. 52 per cent of mean resting level) (Tables 2 and 3). A.C.T.H. does not act directly on the cen-

tral nervous system nor is there evidence that chlorpromazine affects the action of A.C.T.H. upon the adrenal cortex itself.⁸ Interference with either the intermediate metabolism or the excretion of the adrenocortical hormone might also cause a lowered output. However, although chlorpromazine is known to cause liver damage, this is probably an allergic rather than toxic phenomenon and unlikely to occur with two doses of chlorpromazine and such regularity in a series of patients. Primary renal disturbance is not known to be caused by the drug. Thus it seems unlikely that our findings can be accounted for by such mechanisms, although they require to be further explored, especially the effect of the drug on the adrenal cortex. The apparent failure of Christy et al.⁶ to show a suppressive action of chlorpromazine on the plasma 17-hydroxycorticoid response to A.C.T.H. might be due to the lack of a control day in their experiment. Moreover, they gave the drug by mouth and their subjects were probably schizophrenics, whom we have previously demonstrated to react differently from the patients we report here.

The lack of correlation between biochemical findings and clinical response might be accounted for by the short duration of drug action necessitated by the experimental design.

Our findings would indicate that chlorpromazine exerts a central blocking action of the anterior pituitary cortical mechanism. Persky has suggested that there is an increased A.C.T.H. production and discharge in the circulation in anxious patients.⁹ At the same time and despite this raised level it appears that psychoneurotic subjects react to stress by further mobilization of A.C.T.H. It is probably this central component of the total overresponse that was blocked in our experiment. Whilst this might result from a direct depressant action of the drug upon the hypothalamus^{10,11} it is more tempting to suppose that it is effected lower in the central nervous system by both its direct depressant action on the reticular activating system and by blockage of the adrenergic component of this system.^{12,13} In this way, although the somatosensory impulses are reduced, the cortical psychosensory ones would remain undiminished. In psychosis with impending or actual breakdown of reality testing a

reduction of excessive conflicting external sensory stimuli may favour psychic integration.¹⁴ In psychoneurosis, however, although the alarm of a test situation may be alleviated, one would not expect a similar phenomenon. Such selective action might explain the empirically poorer response of the latter group to this drug.

SUMMARY

Chlorpromazine significantly reduces the increase of urinary 17-hydroxycorticoids following intravenous A.C.T.H. in psychiatric patients suffering from depressive and mixed psychoneurotic illnesses. The reduction is of the order of the increase occasioned by placebo injections. It is postulated that it is this central component of the response that is blocked by chlorpromazine, probably at the level of the reticular activating system. Such a reduction of conflicting external stimuli might be expected to produce the clinical alleviation noted in psychosis or impending psychosis whilst leaving psychoneurotic conflicts unrelieved.

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