PSYCHOENDOCRINOLOGY

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Psychiatrists and Endocrinology

THE last thirty years have witnessed the rise and fall of many theories and therapies on a supposed relationship between psychiatry and endocrinology, and perhaps the time is now ripe to weigh the evidence and attempt to draw at least tentative conclusions. A clear picture of an existing situation not only often leads to improved understanding but also to greater clarity of purpose.

Kraepelin, one of the founders of clinical psychiatry, expected endocrinology to provide the final solution in the pathogenesis and treatment of some psychiatric entities. Freud on many occasions expressed the hope that endocrinological investigations would supply the solution of many psychiatric problems. Bleuler (1954) has recently published a comprehensive book reviewing the endocrine investigations in psychiatry which have been published, but this admirable collection covers so many controversial and incomplete results that the author cannot even attempt to construct out of the chaos any concept about the actual role of endocrine function in the development of mental disease.

Mayer-Gross, Slater and Roth (1954) have recently published a book on clinical psychiatry which will certainly remain for many years to come a standard work on the symptomatology and diagnosis of mental disease. However, in spite of mentioning in the introductory notes that it is necessary to take account of biochemical investigations in modern psychiatry, endocrinology is only dealt with in a very cursory manner when considering the psychopathological phenomena occurring in the course of endocrine disease.

For various reasons the psychiatrists, of whom a majority had an entirely open mind about endocrinological psychiatry thirty years ago, have now sheered away from all discussion based on material which at first sight has no safe foundation.

First of all the great specialization of psychiatric research has led into various channels so divergent that the different investigators scarcely understand each other, and therefore cannot be expected to devote too much attention to each others work.

Then again many clinical psychiatrists have been dissuaded from further research by the frequent and often very rapid, though sometimes temporary, beneficial results obtained with E.C.T.

Some have embarked upon endocrinological experiment expecting a quick return from their efforts and, disappointed by their failure, have concluded that the endocrinological approach was altogether unsound.

So much of the experimental work has begun before satisfactory measuring methods had become available in endocrinology, and in any case the investigations were either carried out by psychiatrists who had no understanding of endocrinology and its methods, or by endocrinologists who had little or no experience with mental disease.

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Endocrine Function and Precipitation of Mental Disease

There can really be no doubt that hormones do have an influence on the mind. The obvious high incidence of mental disorder in adolescence, at post-partum and at the climacteric, three phases of endocrine instability, and the unmistakable action of thyroid hormone and cortisone on the mind, are enough in themselves to make it a safe deduction that the level of endogenous production of hormones exerts a powerful influence on the mental processes both under physiological and pathological conditions.

Progress in the analysis of psycho-endocrine interrelationships has unfortunately been retarded and for the most part only the extreme and clinically obvious cases of glandular disturbance have been studied from the psychopathological point of view. As endocrine diagnostic techniques become more accurate it will be possible to recognize earlier stages in the disturbances. For example, myxoedema, which is always associated with psychopathological disturbance, is rarely thought of as having developed by a continuously deteriorating thyroid function for a period of five to seven years before the final clinical diagnosis is made, and very few attempts have been made to correlate endocrine and psychiatric developments during this long phase. Indeed it may often be, and in the personal opinion of the author there is no doubt about it, that during this developmental phase such striking psychiatric diagnostic entities occur as to leave no occasion for considering the possibility of an underlying somatic disturbance.

The question is "where can the endocrine factor fit into the dominant theories in psychiatry?" Most psychiatrists agree about the importance of the pre-morbid personality pattern (mostly genetically determined). This is the factor deciding the quality of psychopathological manifestations that may be precipitated by various external or internal emergency situations.

The question, which, however, is only rarely asked, is why do some people who are able to withstand the same emergency situations for years ultimately break down, while others of quite similar personality make-up never break down mentally in spite of meeting even more severe emergency situations.

It is at this point that the somatic element must be introduced. Response to stress and emergency depends on the ability of the organism to maintain its biochemical equilibrium. When this equilibrium is sufficiently disturbed, whether permanently or only temporarily, the organism breaks down. Obviously this dis-equilibrium always affects the mind and the mood; and the direction of the mood changes, and whether the mental function remains within the range of normality or is sufficiently upset to result in a more or less severe psychopathological condition depends on the severity of the dis-equilibrium and the pre-morbid personality.

The probability of a break-down occurring under given stresses depends on the capacity of the various forces maintaining the biochemical equilibrium, and the width of the equilibrium which represents its adaptability varies considerably from individual to individual. One might compare it with an elastic rubber band, the quality of which determines how far it can be stretched. This is seen, for example, when after running for a short time one individual shows a decreased blood sugar, while another shows no change, or when an individual starts to show clinical symptoms during starvation or other stresses.

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 equi-

librium, which can ultimately be defined as a tendency to maintain a constancy in the chemical pattern of blood and tissue, is dependent on the co-operative effort of various ductless glands.

It is obvious that a decrease or an increase in the function of a ductless gland will have its repercussions on the width and stability of the biochemical equilibrium. Such a disturbance can, as a sequel, influence the work performance of another gland, so that once a disturbance of the biochemical equilibrium has started, a process of continuous deterioration has begun, which, if it is lasting, leads finally to a breakdown of the organism.

One of the mechanisms of adaptation of the organism to stress has been described by Selye in his general adaptation theory. This theory however, is only based on the pituitary anterior lobe-adrenal cortex axis, and certainly describes a very small part of all the forces at the disposal of the organism for maintaining its biochemical equilibrium, but it was a very useful beginning in regarding the adaptational efforts made by the organism. Similar adaptation theories can certainly also be made on the basis of the pituitary–thyroid axis (Badrick, Brimblecombe and Reiss, 1955).

To come back to the question which was asked previously, i.e. where the endocrine factor fits into the dominant theories in psychiatry, one can, on the basis of our present knowledge of endocrinology, say that the endocrine factor is wedged between the emergency situation and the pre-morbid personality pattern. The endocrine function determines, when an existing emergency situation will lead to the precipitation of psychopathologic phenomena in an

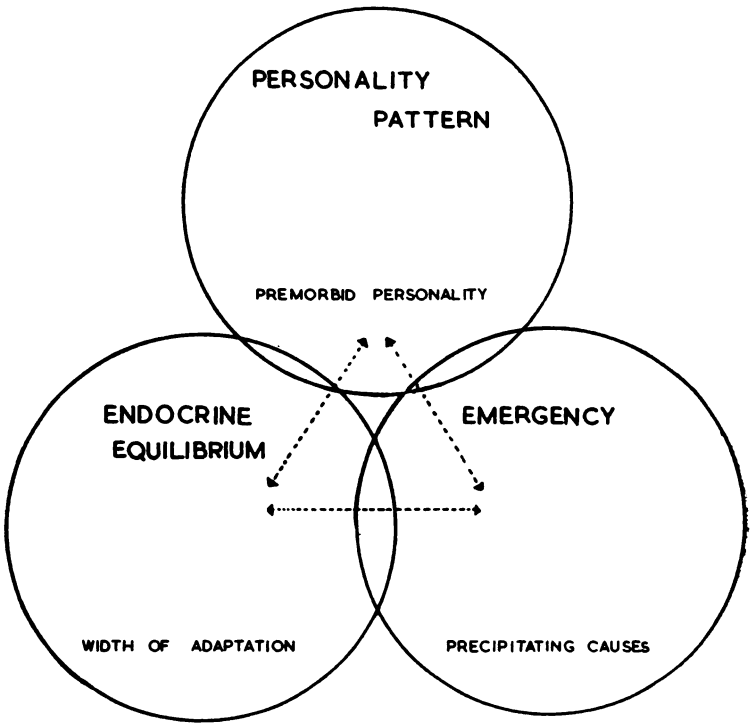

FIG. 1

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individual of a certain personality pattern. A good working endocrine system is an efficient cushion between arising emergencies and the individual.

The diagram in Fig. 1 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 pre-disposed personality patterns, of much greater significance than in others.

The Neuro-endocrine Interrelation

The author has dealt repeatedly with the neuro-endocrine interrelationship in this journal (1939, 1944, 1954) and outlined its significance for changes in both brain and endocrine function. It was pointed out how emotions and psychic-trauma can, for instance, through a pathway over the hypothalamus, influence the pituitary to increase or decrease production of some trophic hormones, whereupon the quantitatively changed hormone output of the "target" gland acts back on the brain function, thus closing a vicious circle. It was pointed out how such a vicious circle can start by primary disturbance in any one of several levels; in the body periphery, peripheral ductless glands, pituitary anterior lobe, hypothalamus or higher brain centres. Such a disturbance taking place on any level must upset the whole neuro-endocrine equilibrium, starts a pathogenic cycle of events and often becomes progressively worse. Disturbances in the neuro-endocrine circle need not necessarily include the pituitary in their pathway in the first instance. They can, particularly under conditions of acute stress, start in the periphery by mobilization of large quantities of vaso-motor substances. It has been shown lately that certain endocrine reactions to stress take place at the same rate in hypophysectomized and normal control animals (Badrick, Brimblecombe and Reiss, 1955). The diagram in Fig. 2 illustrates the various components essential in psycho-neuro-endocrine equilibrium.

A clear realization of the neuro-endocrine circle can help us to a better understanding of the pathogenetic interplay between personality pattern, endocrine function and events precipitating mental disease. One realizes, for instance, that any lasting psychopathologic event must have an influence on the endocrine function. However, this change need not by any means be clinically recognizable since it is often much too new to express itself in a well-developed endocrinologic clinical disease entity which could be easily diagnosed.

The changes are mainly intermediate disturbances which should be detectable by investigation with laboratory methods. It is to be hoped that in future such sensitive and reliable methods will be developed which will enable us to detect any such intermediate disturbances inside the hormone equilibrium. At present only a method permitting the detection of intermediate thyroid disturbances is at the disposal of the author, yet even with this method alone a mental hospital population screened over three consecutive years showed thyroid deviations in about 30 per cent. of the patients (Reiss and Haigh, 1954).

The mental pre-disposition and nervous sensitivity of the individual is in many way decisive for the direction in which a neuro-endocrine vicious circle will develop. It is known, for instance, that Graves' disease develops

mainly in predisposed persons. This state very often starts after a psychic trauma, which presumably produces more thyrotrophic hormone and this increased thyroid function; while in other persons the same trauma has no influence on the thyroid activity at all.

And again, it depends on the personality pattern how the increased production of thyroid hormone acts back on the brain. In some individuals there will be only slight effects on the brain function, or slightly increased nervous tension will be seen, while in others much more severe psycho-pathologic phenomena develop. Further, the same trauma or emergency situation that

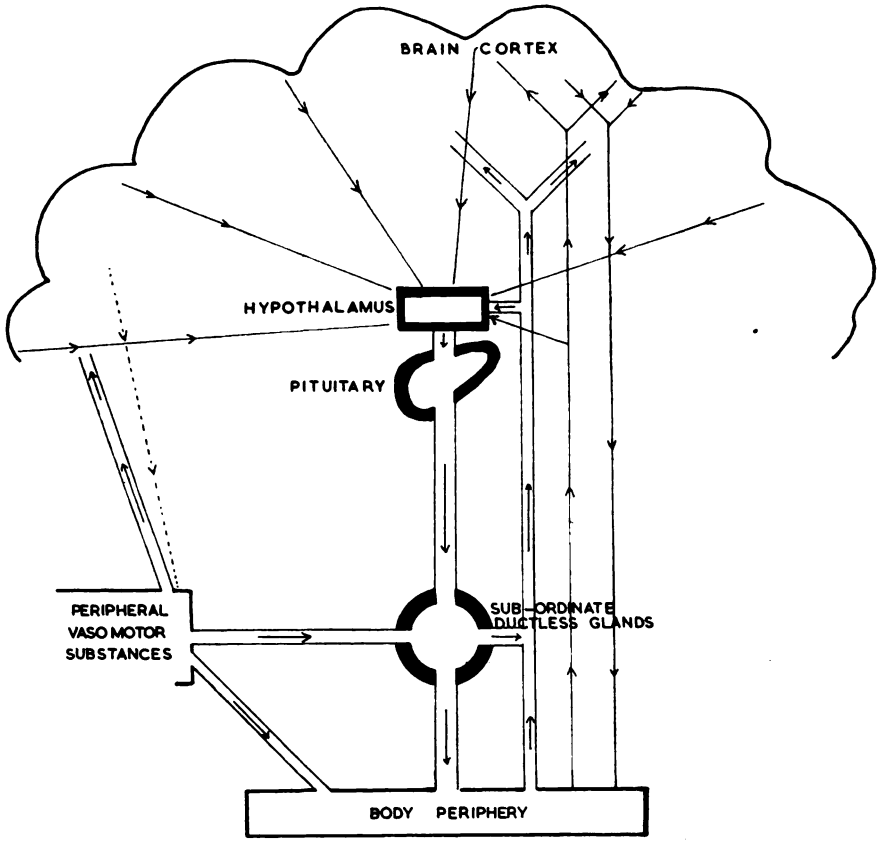

FIG. 2

results in a disturbance of the thyroid activity in one person can produce in another individual menstrual disturbance instead with all its special psychologic consequences. The influence of worry on different personalities is very interesting. Some people will stop eating, others will eat much more than usual; some lose weight, others gain weight. This is another example of how an existing personality pattern can be decisive for the direction and the extent of a disturbance of the neuro-endocrine circle. The main decisive factors in this case being adrenal cortex and thyroid activity.

Many other examples could be mentioned here to illustrate the inter-play

between personality pattern and the neuro-endocrine circle, but only one will be mentioned here, namely that, according to M. Bleuler (1954), even brain lesions produce, in different personalities, different psychopathologic symptoms.

Psychopathological Manifestations in Endocrine Disease

Endocrine disease can, either alone or in combination with other emergencies cause psychological changes, which occasionally can reach pathologic dimensions. Quality and extent of the psychopathological changes depend apparently on the pre-morbid personality of the individual. A severe endocrine disturbance can be accompanied by a great variety of psychotic pictures or none at all. Bleuler has admirably and comprehensively reviewed the psychiatric symptomatology of the various endocrine disease entities. Surveying the whole material one finds, surprisingly, that there is but little difference between the psychopathology of hyper- and hypofunctional endocrine disease. Bleuler found, for example, no characteristic difference between the psychopathology accompanying Addison's or Cushing's disease.

This fact is very interesting in the light of our experiences (Reiss *et al.*, 1951) which show that identical psychiatrical diseases can be accompanied by different endocrine states. Under-function or over-function of the thyroid, for example, can be found in depressive states or in schizophrenia.

One must not forget that there are also many patients who, in spite of showing severe endocrine disease, do not show any psychopathological deviations. Emergency situations, however, which are easily overcome by most normal people, can lead to mental breakdown in endocrine patients. As already pointed out the psychopathological features in such patients can often be so predominant that the endocrinologic condition is easily overlooked, and one is surprised if relief of psychological or other stress does not immediately lead to improvement.

Bleuler comes to the conclusion that there are no specific psychological sequels of endocrine disturbance. He is of the opinion that all psychoses occurring during a severe acute disease fall into the frame of the acute exogenous reaction type as defined by Bonhoeffer. This assumption is also entirely in agreement with our own views, if one is permitted to circumscribe it as has been done above, namely, that quality and extent of the psychosis are determined by the personality pattern of the patient.

Psychopathologic disturbances seen in long lasting chronic, severe endocrine disease are likened by Bleuler to the mental disturbance seen in chronic diffuse brain lesions, the different symptoms being summarized under the collective title of the "amnestic psychosyndrome".

It is very regrettable that so few studies have been published of psychological investigations during the development of endocrinological disease. One may instance the frequently slow development of a state of adrenal cortex over-function when, at an early age, a child recovers from scarlet fever without any apparent complications, the adrenal cortex, however, remaining hypersensitive, particularly to the adequate trophic influences of the corticotrophic hormone, so that at the time of the adrenarche the adrenal cortex starts to grow and function abnormally, causing a multitude of somatic deviations, many of which are accompanied by various psychopathologic features.

Another example is the absence of investigations into the psychology of the occasionally slowly decreasing adrenal cortex function, a process terminating with Addison's disease. There are, however, some data already available about

psychologic changes during the progress of thyroid under-function, culminating after a number of years in myxoedema.

These show that it is by no means always correct to assume retardation of the mental processes and sleepiness in thyroid under-function as it is so regularly described in the text-books of clinical endocrinology. Among the first complaints encountered in many patients in the initial states of hypothyroidism is the diminution of the 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 pathogenetic factors mentioned above are then present, also the emergency situation and the disturbed hormone equilibrium which, according to the pre-morbid personality of the patient, can lead to a multitude of psychopathologic phenomena.

It is only a question of time until sufficiently exact investigation methods have been developed enabling us the better to detect intermediate endocrine disturbances which can be correlated with the accompanying psychologic and psychopathologic changes.

Endocrinological Deviations in Psychiatric Disease and Their Changes During and After Empirical Treatment

A considerable drawback to progress in endocrinological psychiatry is the present classification system of psychiatric diseases. If a number of patients have even only one or two symptoms in common (such as ideas of persecution or hallucinations, etc.) it already suffices to shelve them diagnostically into one of the psychiatric disease entities. This happens even if the great part of the remaining psychological spectra of the various individuals in the rather enforced common group differ considerably.

The majority of clinical psychiatrists adhere strictly to this principle of classification and it is within the framework of these classifications of disease entities that the majority of all biochemical and endocrinological investigations have been carried out. The results were and still are much more controversial than the results of investigations carried out on patients belonging to a single nosological group of any other branch of medicine.

The "homogenous" psychiatric patient groups values of numerous biochemical blood and urine components were found to be either above or below or within the normal range, and in endocrinological investigation, normal, increased or decreased functions of the glands were found. The results were, of course, mostly evaluated statistically and one reached the obvious conclusion: "no statistically significant change."

The present dominant conclusion drawn in clinical psychiatry is to be found in the recent text-book by Mayer-Gross, Slater and Roth (p. 233) in their discussion about schizophrenia. "Thyroid, sex glands, adrenal cortex and pituitary have all been suspected as the primary site of the disturbance but with no conclusive evidence." No other conclusion can be expected if one considers the great lack of homogeneity in the physiological functions and pathophysiological disturbance in the investigated "homogenous" groups of schizophrenics.

Considering everything we know about the neuro-endocrine interrelationship and the decisive influence emotions and psychic trauma must play on the normal functioning of the ductless glands, it is probable that some disturbance in their function will exist in every serious neurotic or psychotic disturbance. If no concrete changes have been found so far in many of them, this conclusion is not invalidated considering how crude most of the endocrinologic investigation methods are at present. One can expect that with the progress in the development of these methods, many more endocrinological disturbances will be found in psychiatric patients.

We have indeed found (Reiss *et al.*, 1953, Reiss, 1953) many deviations in thyroid and adrenal cortex function in mental patients; in some of whom such changes were least expected since clinically they showed no sign of endocrine disease. The extent of the endocrine deviation varies from case to case, some being very far above or below the normal range, some having intermediate disturbances, indicating only a stage in the development of endocrine disease.

In the course of the investigations we also found an endocrine dysfunction which seems rather important in mental cases, namely, an insensitivity of the body periphery for certain hormones such as the thyroid hormone or adrenal cortex hormones (Reiss *et al.*, 1952). In such cases the B.M.R. is low in spite of undisturbed thyroid function, and even large doses of thyroid do not increase the B.M.R. Or, there is very little development of secondary sex characteristics in spite of the fact that normal or even increased amounts of 17-ketosteroids are being excreted.

However, no special endocrine disturbance was ever found in any of the disease entities, and vice versa. No significant correlation between the function of one single gland and any of the known psychiatric disease entities can therefore be claimed. However, if one looks at the changes in the total hormone equilibrium as such, and particularly at the equilibrium of the thyroid and adrenal cortex function, irrespective of the direction in which the function of the glands is changed, one finds a much closer correlation to disturbed mentation.

It seems that endocrinologic research in mental cases can only proceed with some hope of success if it is carried out on individual patients and the results carefully co-ordinated with psychopathologic symptoms, and later on statistically correlated in such a way that one of the factors is the result of the biochemical analysis and the other (if possibly measurable), a psychologic factor. It is feasible that in this way, in time to come, a system of classification will be found which takes into account not only a few psychologic criteria, but also body constitution and biochemical changes which may very well prove to be the cause of the psychopathologic deviations or the reason for their persistence.

Single biochemical investigations giving a static picture at a certain stage of the disease contribute comparatively little to the understanding of the pathognomonic significance of the biochemical change. Longitudinal investigations of the biochemical changes, repeated investigations throughout the duration of the disease and after recovery, and very careful chronological coordination of the changes in the mentation, permit more decisive conclusions about pathogenesis.

It has been found during the past few years that disturbed hormone equilibria often returns to normal when the mental state improves (Reiss, 1953). An extensive study was made (Reiss, 1954) in which the thyroid activity of over 400 psychiatric patients before and after treatment was investigated

with a radioactive tracer method that permitted the detection of intermediate states of thyroid disturbance. A highly significant correlation was found between normal thyroid activity after treatment and mental improvement, and between thyroid activity outside the normal range and failure to improve. This correlation held good in all the disease entities investigated and was independent of the treatment applied (E.C.T., Coma Insulin Therapy, Modified Insulin Therapy and treatment with various hormones). Patients who showed spontaneous improvement after general hospital care and attention also showed a correlation between mental improvement and improvement of the thyroid activity. The changes in the thyroid activity which were found were regarded mainly as indicating more extensive alteration in the total hormone equilibrium of the patient.

It was particularly surprising to see that the same treatment, as for instance E.C.T., could be associated with increase of the thyroid activity in patients showing an initially decreased thyroid function and also with reduction of a previously increased activity towards the normal range. The explanation was given that E.C.T. does not influence the thyroid directly but interferes with the function of the pituitary anterior lobe and its production or release of the various atrophic hormones. All these hormones are known to be antagonistic amongst each other, thus, in some cases of thyroid under-function the endocrinologically relevant sequel of E.C.T. consists in an increased production of thyrotrophic hormone which might act either by stimulation of the thyroid or by suppression of thyroid antagonistic hormones; while in cases of increased thyroid activity secretion of more antagonists such as corticotrophic or gonadotrophic hormone result in the observed reduction of the thyroid activity. E.C.T. apparently influences the total hormone equilibrium. Changes in the thyroid activity indicate on this occasion only that a multitude of changes in the endocrine system take place.

It was pointed out that the action of other routine treatments on the hormone equilibrium as indicated by changes in the thyroid activity takes place in a way similar to the action of E.C.T., with the difference that other levels of the neuro-endocrine circle are acted upon.

Expectation for a Rational Hormone Therapy in Psychiatry

It has been made clear above that hormone therapy cannot be used in mental disease simply according to the disease entity as classified at present.

At present one can 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 for the introduction of a rational hormone therapy is the tendency to ask how many 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, how many per cent. of acute female schizophrenic patients were cured with this particular treatment, but at the best only how many 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.

It should finally be clear that our ideas of causation of the disease must be changed. If one succeeds in curing a patient, whose thyroid activity was found to be disturbed, by treating him from the thyroid angle, and mental normalization follows the regularization of the thyroid activity, that still does not mean that the disturbed thyroid activity was the cause for a disturbed mentation. We can think about the endocrine disturbance only as a part of a disturbed hormone equilibrium, and further, these endocrine changes are only inside the neuro-endocrine vicious circle (as explained above). Therefore, such improvements as are being seen after hormone therapy can only mean that the vicious circle was interrupted and do not give any indication of the place of the primary cause of the mental disturbance.

The therapeutic approach which can be made after the endocrine status is defined is in many instances still very much a research subject. It is comparatively easy in cases where the endocrine disturbance is so far developed that it can easily be clinically diagnosed, and where the clinical psychiatrist speaks of the occurrence of psychopathologic complications. That is the case in states now described as "myxoedema madness" or during Addison crises. The only precaution in the treatment of such cases is that it should not be started in a too precipitate fashion and only with small doses of the hormone required.

The therapeutic approach to intermediate disturbances which are mainly diagnosed on the basis of laboratory methods where only a few clinical symptoms, if any, are to be seen, is more difficult. One of the most important outcomes of the laboratory investigation of the hormone equilibrium (investigation of excretion of 17-ketosteroids and thyroid activity only) is the occasional ability to predict spontaneous mental improvement. A newly admitted patient occasionally shows, for instance, decreased 17-ketosteroid excretion and increased thyroid function. However, after a few days in a changed environment, the ketosteroid excretion starts to rise spontaneously, ultimately reaching a normal level, while the thyroid activity decreases simultaneously. In several of such cases we have correctly predicted spontaneous improvement.

Mental improvement can also occasionally be predicted in cases showing psychopathological features on admission or after completion of some routine treatment, but no outstanding disturbance in the thyroid–adrenal cortex equilibrium.

Study of the endocrinological changes seen after routine treatment with electroshock or during spontaneous improvement gave, in cases where spontaneous improvement could be excluded, the opportunity to try to imitate the action of E.C.T. by a less dramatic hormone treatment. For instance, in cases where the 17-ketosteroid excretion was low, the adrenal cortex responsitivity to A.C.T.H. disturbed, the thyroid activity high and no sign of a tendency to spontaneous change noticed, the hormone equilibrium could be restored by treatment with testosterone combined with small doses of oestrogen, this regularization being accompanied by mental recovery. In a case where both thyroid and adrenal cortex activity were very low, and where, therefore, an under-function of the anterior pituitary lobe had to be assumed, stimulation of the hypothalamico-pituitary system by implantation of testosterone led to

the same result. By taking into consideration only 2 parameters of the hormone equilibrium, thyroid activity and adrenal cortex activity, a great variety of disturbances in the various patients can be found which should be dealt with individually if rational hormone therapy is to be introduced. In many cases the question of how to influence a disturbed hormone equilibrium is still very much a question of pure endocrinological research.

In cases of adrenal cortex under-function, for instance, under-production of a great number of various steroid hormones may be concerned which can, to some extent, be determined by chromatographic analysis, though this is still being developed. One of the outcomes of these investigations is a definition of a group of patients excreting decreased amounts of epi-dehydroandrosterone. They are mainly young, inadequate psychopathic types who occasionally overlap with a schizophrenic group.

Strauss *et al.* (1952) and Sands and Chamberlain (1952 and 1953), Zubiani and Caricchia (1953) have reported very encouraging results after treatment of such patients with epi-dehydroandrosterone (Diandrone).

Many satisfactory results of treatment of psychiatric patients with oestrone or testosterone have been reported. E. L. Margetts (1952) in particular recently reported beneficial results in a number of psychiatric conditions.

There is at present, however, a real danger that if such treatments are repeated without first establishing on the basis of hormone analysis an indication for the treatment of the individual patient, the application of sex hormones will become as discredited as previously the general application of thyroid therapy became. One of the simplest ways of testing the indication for treatment with sex hormones is an analysis of the prolan in the morning urine specimen. If the result is positive, which is quite usual in male and female climacteric conditions, treatment with sex hormones is certainly indicated, and can be continued as long as the prolan I reaction is positive. A low 17-ketosteroid excretion rate with or without accompanying positive prolan reaction can be an indication for the use of testosterone.

Some examples of the treatment of mental patients, after the thyroid activity has been investigated and found abnormal, have been published by Reiss *et al.* (1953) and Reiss (1954). Treatment of patients from the thyroid angle is by no means a simple matter. In mental patients, perhaps even more than in others, a decision must be made first as to whether the disturbance in the thyroid activity is primary or secondary to a pituitary disturbance. The possibility of peripheral over- or under-sensitivity to thyroid hormone has also to be taken into consideration (Reiss and Haigh, 1954).

The Significance of Endocrinologic Psychiatry for Clinical Endocrinology

The endocrinologist is so dazzled by the enormous progress made in endocrinology during the last 25 years that he has tended to forget his original roots, which are the only guarantee for steady progress in endocrine therapy.

The chemical isolation of hormone compounds and the further development of hormone chemistry has, of course, opened a wide vista of possibilities in the further study of hormone chemistry and physiology, and last, but not least, for the use of the new methods as a basis for hormone therapy. However, at the same time this progress in the exact methodology has somehow made the chemist and biochemist forget that his work could not possibly have been started before exact biologic standardization methods made it possible to

isolate, in ever-increasing purity, the hormone compounds he is investigating. The development of specific and exact biologic methods was never easy and could never have been begun if certain reliable physiologic actions of the hormones had not been demonstrated. The impetus to the later development came in the first instance from clinical observation of the endocrine disturbance.

We know that at present by no means all the hormones which play an important role in the organism have been discovered. There is, for instance, little doubt that the testosterone and other known androgens are not the essential hormone, nor are they the only endocrine product, of the male gonad. However, preoccupation with the presently much more easily obtained crystalline substance, and the absence of adequate biological standardization methods, discourages the research worker from further investigation of the endocrine function of the male gonad.

Endocrinologic psychiatry could supply the clinical endocrinologist with a mine of further information. The mental hospital contains a multitude of patients who are only just beginning to develop endocrine disturbances, and patients with intermediate disturbances where perhaps the only manifest clinical symptom consists of the mental deviation. The endocrinologist who at present deals mainly with fully developed endocrine-pathological symptoms has here the opportunity to learn something about causes and development of endocrine disease.

There is ample scope here for improvement in clinically useful and reliable hormone analytical methods, which permit the detection of borderline and intermediate stages of disease. But there is also an opportunity for reviewing and supplementing the methods of endocrine treatment. The basis of endocrine treatment was originally *substitution* therapy. Further progress in our knowledge of endocrine regulations—where the gland in the body starts to produce more hormones, under certain conditions—has opened up other possibilities for hormone therapy which may be called *supplementary* therapy.

One sees, for instance, that after severe burns when the adrenal cortex produces more corticoids, that it is useful to supplement this effort by the application of even further corticoids. Another instance, which fortunately occurs rarely at present, is the great effort made by the parathyroid during rickets, which in the end usually leads to tetany. This can be prevented by supplementation of this effort by parathyroid gland extracts.

However, particularly in emotional disturbance, one very often has to deal with hyperfunctional states, and their development. The endocrinologist bases his experiences in hyperfunctional states mainly on *surgical* methods. Methods dealing only with the conservative inhibition of an increased functional state are few. Work concerning the *inhibition* therapy is proceeding only in connection with thyroid hyperfunction. There are, however, many states of hyperfunction in other glands, in particular the adrenal cortex, where the hyperfunctional states have intermediate stages between the normal state and adrenal cortex adenoma. Such disturbances are certainly not clinically irrelevant, but next to nothing has been done to circumscribe them clinically.

Finally, clinical endocrinologic psychiatry gives the endocrinologist the opportunity to study spontaneous changes in glandular function. He can see how, for example, hyperfunctional states of the thyroid can occasionally improve in a comparatively short time after the patient's entry into hospital, in other words, by change of environment. There is still open to the endocrinologist a wide field for therapy by *environmental* and other unspecific factors.

We have tried in this paper to show that there is still a wide field for investi-

gation of minor and unclassified endocrine variations, and that the application of the detection of these deviations to the treatment of mental disease, irrespective of the clinical psychiatric diagnostic labels, can often result in improvement in mental health.

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