PRESIDENTIAL ADDRESS

PSYCHOENDOCRINOLOGY AND BEHAVIOUR

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Words are inadequate to express my deep sense of gratitude to you for electing me to the prestigious office of the President of the Indian Psychiatric Society. In the same breath I express a haunting sense of awareness of the stupendous responsibility associated with this high office. Indeed, you have put a “giant’s robe” on a dwarf’s shoulders. But “apparel oft proclaims the man”. I assure you, I shall endeavour to rise to the occasion and play to the best of my ability the role you have assigned to me. I swear to protect, preserve and defend the image, interest and dignity of the society. In the discharge of my duties as the President of the Indian Psychiatric Society, I will do everything humbly possible to promote all that the Society stands for. The aims and objectives of our Society, as I see them, are inseparably interwoven with the past, present and future of Psychiatry in India. This holistic view of our profession and association inspires to embark upon a task that will demand the last ounce of my energy.

The Indian Psychiatric Society was born in the year India won freedom. The tremendous upsurge of activity generated in all spheres of life in the wake of freedom created a social, cultural and scientific climate that motivated the founding fathers of our society to establish a professional organisation befitting a free nation. In the late forties and fifties they built it up almost from a scratch. But they worked with great fortitude and vision. There was a time when psychiatry—in all aspects of the profession (practice, teaching and research)—was a weakling surviving in isolation behind the high walls of the mental hospitals. Today it has grown up to be a strong and younger number of the scientific community both professionally and academically. A profession born of the biosocial sciences cannot maintain its spurt of growth without the fresh blood of new knowledge.

During the last quarter of a century our members have contributed significantly to the pool of new knowledge in Psychiatry. It is heartening to note that the members of the younger generation have taken up research work with enthusiasm and have shown power and promise. This orientation to research is a sign of vitality and augurs well for our profession. Thanks to this academic tilt in our attitude, we have been able to keep abreast of the recent advances made at International level in our speciality—at least in ideas, if not in facilities for rendering relief.

The dichotomy between “pure” and “applied” in modern science is hardly tenable today. What was considered “pure” yesterday will find its “applied” significance tomorrow. This is true for many areas of psychobiological research. Psychoendocrinology is one such area. From a pure laboratory science, it has spread its sway over us from the classroom to the clinic. I feel, the time is ripe for a careful consideration of the nature, content and relevance of Psychoendocrinology to Psychiatry.

Psychoendocrinology is a field of psychobiology which studies the interrelationship between the endocrine system and behaviour, that is—the influence of hormones on behaviour and the effect of behaviour and psychological stimuli on the

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functioning of the endocrine system. Among the principal aims of psychoendocrinology are (a) the identification and measurement of manifestation and parameters of the reciprocal endocrine—behaviour influence, (b) the elucidation of the neuro-endocrine mechanisms involved in this influence and (c) understanding of the implications of endocrine—behaviour relationship for adaptive behaviour as well as for physical and mental health.

Though psychoendocrinology has come of its own as a special branch of psychobiology during our lifetime, its foundations were laid many, many years ago. Those who are inclined to see things from historical perspectives, may trace the origin of this science in the humoral theory prevalent in the days of Hippocrates and Galen or the concept of “Tridosha” propounded by the Indian sages of Ayurveda which precedes Charaka and Susruta. Even those who are not prepared to delve so deep into the archives of history must concede that the seeds were sowed in the clinical observations and studies made in the early nineteenth century. In 1825 C. H. Parry referred to the emotional and behavioural changes in exophthalmic goitre. Many physiologists and psychiatrists have corroborated him and noted behavioural changes, at times severe psychopathology, in patients with endocrine disorders or in those with accidental or surgical destruction of ductless glands. In 1849 the German scientist A. A. Berthold did some animal experiments and came to the conclusion that testicular secretions were responsible for their sexual behaviour and some other behavioural characteristics. In later years experimentations were extended to humans. The first known experiment was performed by C. E. Brown-Sequard, the famous French Physician and one of the founders of endocrinology. In 1889 he injected himself with animal testicular extract. A man in his seventies, he reported that he got back his youthful vigour, appearance and sexual appetite. Whatever be the fallacy of his experiment, it led to a tremendous boost in clinical medicine (Wolmen 1975). It needs to be made clear that these observers and experimenters were not aware of the nature of the chemical secreted by these ductless glands. In 1902 Bayliss and Starling got an inklng of the nature of the secretion of these glands and in 1905 Sterling named it “Hormone” (the Greek word Hormein means “I arouse” or “I excite”).

During the early years of the present century much research and publication centred round the possibility of endocrine involvement in some mental disorders. These research activities encouraged the use of hormones in the treatment of mental disorders. Among the works on endocrinological psychiatry of historical prominence were the studies of M. Laignel-Lavestine of France (1908). Serious experimentations with humans, however, began around 1920. The well-known experiments by G. Maranon of Spain (1887-1960) may be considered the beginning of experimental psychoendocrinology of man. He conducted experiment on the effect of adrenaline injection on emotions and on other reactions in man. These experiments received wide attention and prompted extensive work in this area throughout Europe and America. Taking the cues from the works of W. B. Cannon on the effects of emotion on the sympathetic nervous system, Hans Selye, in 1936, investigated on the activation of the Pituitary adrenal cortical system in stress. His studies profoundly influenced psychoendocrinological research as they directed attention to the sensitivity and responsiveness of hormonal secretion to psychological stimulation. Inspired by Selye’s concept of stress, some pioneering workers in India took up the studies in this area in the mid-twenties. Nandi and Banerjee (1958) reported on adrenocortical functions in some mental diseases by methods which were considered up-to-date at the time but finer methods, e.g. radiimmunoassay were still unavailable to them. It is, however, noteworthy that their findings...
were mostly corroborated by later studies using the radioimmunoassay.

This area of research was the initial springboard of the work of Max Reiss (1900-1970). Early in his scientific career Reiss could recognize the intimate link between the brain and the endocrine system and perceived, as implication for psychiatry. Since 1939 he had been concentrating his whole attention on the role of endocrines on mental health. It is he who applied the name psychoendocrinology to this area of research. Reiss was instrumental in organizing the Psychoendocrine association which held its first symposium in Zurich in 1957 and in the following year, the first book bearing the title Psychoendocrinology was published under his editorship. In 1969 an international organization, with Max Reiss as its first President, was formed in Milan, Italy, under the name International Society of Psychoendocrinology. Its membership indicates the wide spectrum of specialties with which Psychoendocrinology is associated as a field of research. Workers in the area of endocrinology, psychiatry, psychology, biochemistry, pharmacology and neurophysiology are actively involved in the activities of this society. In the same year a journal named "Hormones and Behaviour" was also launched. Modern research, as it reveals with increasing precision the interaction between the nervous and endocrine systems, provides scientific basis and framework for the exploration and interpretation of the endocrine-behaviour relationship. Moreover, the improved methods of measurement of hormones in body fluids and tissues as well as the identification and synthesis of several key hormones particularly the hypothalamic releasing factors, have greatly aided and broadened psychoendocrine research.

The scope of psychoendocrine research is wide and ever expanding. Among the topics vigorously pursued at present are: (a) the effects of various forms of stress on the endocrine system (b) interaction between hormones, neurotransmitters and psychoactive drugs (c) Hormonal factors in sexual behaviour, emotions, aggressive behaviour, learning and memory functions (d) hormonal correlates of mental illness and the use of hormones in the treatment of mental and behavioural disorders (e) hormonal regulation of homeostatic mechanism and biological drives.

New insights on behaviour endocrine functions are being derived from studies on the early influences on ontogenesis of behaviour and brain development and on the effects of early experience on endocrine functions in adult life (Wolmen 1975).

To understand the properties and functions of hormones we must take note of its long evolutionary history from earliest living matter to the Homo-sapiens. It is generally conceded that the factors involved in the first appearance of the various hormones is largely a matter of conjecture. It is, however, known that hormones are one of the mechanisms for chemical regulations which are found in living things at all stages of development. Perhaps chemical regulators including hormones appeared first as metabolic by-products. Many important features of the vertebrate endocrine system were present in the primitive jawless vertebrates and these features were presumably present in their fossil ancestors that lived more than five million years ago. The evolution of the endocrine system in the more advanced vertebrates has involved both the appearance of new hormones and the further evolution of some of those already present in their primitive ancestors.

That hormones are one of the principal co-determinants of behaviour have been brought home by the classical experiments done on nonhuman primates about two decades ago. It was shown that parental hormones play a crucial role not only in the anatomical differentiation of the species but also in the modulation of the behaviour.
specific for its male or female members (Ehrhardt 1975).

If androgen is present at a critical time of differentiation, the exposed animal will exhibit more male-like behaviour when stimulated with androgen in adulthood. If androgen is not present, the probability increases that female behaviour will occur after exposure to female sex hormones of the genetic sex i.e. it can be produced experimentally, contrary to the animal's genetic sex. The clinical replica of this condition is the Adrenogenital syndrome (AGS) - a condition in which the adrenal glands have a genetically determined defect in their function from foetal life on. The genetic defect prevents the adrenal cortex from synthesizing cortisol but releases too much of a male sex hormone which is androgenic in biological action. The most prominent results of prenatal androgens on behaviour in genetic females as studied by Ehrhardt and Baker on a group of 27 patients cluster round three things: activity and aggression, marriage and materialism, and gender role. In all these spheres of behaviour and adjustment they were significantly different from the control females. It has long been generally believed by psychiatrists and other clinicians that stress plays a role in the metabolism and development of body tissues, and this concept of the physiology and pathology of stress (1950) has made this belief more popular and widespread in the scientific fraternity. Psychosocial stress, properly speaking stress as a consequence of psychosocial stimuli, has been the subject of modern research in psychoneuroendocrinology. Many innovations and precisions brought about by workers in this area have added much to our knowledge of the relationship between stress and psychopathology. In the past experimental designs relied on situational criteria of emotional states with the assumption that all subjects would experience similar emotional arousal in a given stressful situation. It soon became apparent that this was not a safe assumption in view of the wide range of individual differences in their response to the same stressful situation. Methodological refinements have brought quantitative and objective estimates of emotional states of subjects under study. They have cleared up some of the puzzles of previous research findings and have extended the studies beyond signs of emotionality to include an evaluation of the style and effectiveness of psychological defence mechanisms. Present knowledge of the excellent assay methods of hormones has made it possible to apply psychoneuroendocrine approaches to the experimental study of a range of issues in psychiatric theory - e.g. the study of neurotic, psychotic and psychosomatic processes including the role of developmental and social factors in such processes.

Some of the most intriguing leads emerging from this approach include the possibility that hormone levels may reflect certain neurotic processes. A number of observations have been reported that suggest that marked psychologically induced hormonal changes can occur in certain subjects in the absence of overt signs or even subjective awareness of emotional reaction. Research on the neurohumor and observations on the possibility that they may provide psychophysiological support for the concept of neurotic repression of affect or at least reflect unconscious processes would seem to deserve careful consideration (Mason 1975). Time is not far when the stream of psychoneuroendocrine research will augment the stream of psychoanalytic research and will enrich the field of psychiatry. The pioneering work of Knapp and his associates in refining methodological approaches for the collection and utilization of psychoanalytical data in psychosomatic research has already provided some useful guidelines for further work along these lines (Ibid). Recent reports from clinical
fields have elaborated this concept. Henry and Stephen (1977) are of the opinion that psychosocial stress may be involved in the pathogenesis of several psychosomatic disorders. In idiopathic hirsutism, a condition which is often accompanied by severe mental agony, hyperactivity of the endocrine system seems to be of pathogenic significance as shown by the elevation of the level of adrenal androgens above a critical value for the induction of hair growth of the masculine type. Incidentally, the stress concept has been discussed not only in relation to the disorder itself, but also with respect to the mechanism of action of one of the most effective therapies namely ECT. Such treatment acts, indeed, as a stressor on the endocrine system, the Hypothalamo-Pituitary-Adrenal System in particular. This mechanism is, however, of no apparent therapeutic significance in depression. It is now clear that psychoendocrinology provides us with an experimental approach with which we may evaluate at a new level of insight, the possibility that a number of illnesses may represent not local or regional diseases but disorders of the integrative machinery according to the time-honoured clinical formulations of psychosomatic medicine. While the relationships between stressful life situations and onset of illness have long been recognized, psychoendocrine approaches now provide us with new leverage in getting at the bodily mechanisms that play a mediating role between the psychosocial input and diseased tissue. Now let us focus our attention to the relationship between the endocrine system and certain clinical conditions. Though this relationship has not yet been clarified and many blind spots in our knowledge still remain, the known facts are sufficient to elucidate some of the mysteries of mental disorders. The nature of the illness, their diagnosis and the mode of action of some of the remedial measures (psychoactive drugs) have all been encompassed and enlightened by research findings in this area.

In a relatively high percentage (more than 10-20%) of patients with either hypo or hyperadrenocorticism severe mental disturbances occur episodically or, more seldom, persistently. Confusional states (predominantly in Addisonian crisis), paranoid delusions and affective disorders - commonly of a depressed type - can be observed. In spite of the overall similarity between the hypo and hyperfunction of the adrenal gland, the frequency distribution of the various psychopathological syndromes do show some remarkable differences. Depression is more common in Cushing's syndrome than in Addison's disease (Whybrow and Hurwitz 1976). It is not surprising that similar mental abnormalities may appear as consequence of long term therapy with high dose of cortisol and most other glucocorticoids used for therapeutic purposes. There is, however, ground to conclude that an optimum level of glucocorticoids is a requirement for normal mood and mentation. Marked deviations from this hormonal optimum tend to be associated with mental abnormalities predominantly in the emotional sphere, with depression of a varying degree as the most prominent feature. This leads us to the exploration of other endocrine abnormalities in depression which may clarify some of the neurochemical abnormalities of aetiological and diagnostic significance.

The relationship between endocrine function and depressive illness has been studied extensively and a plethora of data can now be adduced to establish its importance in the understanding of the pathophysiology of this illness. But the crux of the problem is that many of these findings require additional study before definitive conclusions can be based on them.

It has, however, gained wide acceptance that adrenal functions change remarkably
in depression. There is flattening of the diurnal rhythm and elevation of the cortisol levels particularly at those times when cortisol is normally the lowest. There is also an increase in the secretory episodes. An altered 24 hour rhythm of serum prolactin has also been reported. The thyroid stimulating hormone (TSH) response to the thyroid releasing hormone (TRH) is reduced in a significant percentage of depressed patients.

There are several reports (which require replication studies) about reduced luteinizing hormone (LH) response to Luteinizing hormone-releasing hormone (LHRH) in postmenopausal depressed women and hyperresponsiveness of the LH response to LHRH in some secondary depressed men.

It has been postulated that a central neurotransmitter defect is at the heart of the depressive syndrome. The deficit is believed to involve different types of neurotransmitters. If there are in fact different underlying abnormalities in depression, they should be reflected in the different clinical symptom complexes. It is of some interest, therefore, that there is increasing evidence that primary depressive illness differs from secondary depressive illness in a number of areas. It appears that hypercortisolism, abnormal dexamethasone suppression response, failure of the TSH response to TRH and other cases of hypothalamic dysfunction have been reported in secondary depression.

Melatonin shows a marked diurnal rhythm. One of the core characteristics of depressive illness is also an alteration in diurnal rhythm. Hence melatonin has been studied by workers enthusiastically. But the current view is that the existence of an altered rhythm of cortisol in depressed patients does not necessarily imply that there is an alteration of melatonin. Recent studies have shown that the factors controlling melatonin and adrenal rhythm differ.

The technique that appears to be the most promising in the investigation of neurotransmitter theory of depression is a pharmacoeendocrine strategy. In this method, agents which specifically alter neurotransmitter functioning are employed to study the endocrine changes. An example of this approach is the recent investigation in which the effect of lithium on endocrine function has been examined. It has been suggested that lithium acts to limit changes in receptors, particularly by preventing the super sensitivity of dopamine receptors. These ideas are derived from animal experiments. The best results are expected from studies on human controls and depressed patients. The progress of research lies in this direction (Brown et al 1981).

It has been found that rapid intravenous administration of TRH to otherwise untreated unipolar depressed female patients caused a rapid though brief and partial improvement in depressive symptoms (Prange et al 1975). Some workers have found similar response in the bipolar form of the disorder also. The frequent though not invariably, improvement in depressive symptoms produced by TRH may not be its most valuable contribution to the understanding of depressive disorders. There is broad agreement that in depressed patients hypothalamic dysfunction causes a deficit of THS. This in turn results in increased negative feedback on the pituitary gland from elevated thyroid hormone. In one of our studies (Boral et al 1980) we found that there was deficiency of both T3 and T4 in a sample of depressives comprising both males and females. The deficiency was more marked in the female cases.

These findings may lead us to believe that in depression hypothalamic TRH ac-
Activity is diminished and this in turn leads to a paucity of releasable TSH. In depression there is also a deficiency of the growth hormone response to insulin induced hypoglycemia. Somatotropin Release Inhibiting Factor (SRIF), of course, inhibits the release of growth hormone. Recently it has also been shown to inhibit TRH induced release of TSH: it is reasonable to suggest, therefore, that in depression there is increased activity of SRIF. This suggestion is consistent with what is known about the behavioural effect of this substance on experimental animals. Further light may be thrown on this issue by the study of SRIF injected animal as a pharmacological model of depression.

As a footnote to this discussion of the relationship between depressive state and hypothalamo-pituitary-thyroid dysfunction, I would like to emphasise its clinical significance. In continuation of what I have said about the experimental use of TRH in depression, it may be added that Takahashi et al (1975) made clinical trial of TRH with imipramine in severe relapsing cases of depression. Though TRH had no advantage over imipramine there was no doubt that it was more effective than placebo. Those who are enthusiastic about its use as a therapeutic agent, believe that studies of the mechanism of action of TRH and of its endogenous metabolism will identify a sub-group of depressives in which its use will be more appropriate. The use of thyroxine in some cases of refractory depressive is now too common to bear repetition.

The knowledge of the Hypothalamo-Pituitary-Adrenocortical System (HAPS) dysfunction in depression has found its clinical utility in the development of a laboratory procedure to positively identify the type of depression in the inpatient and even in outpatient setting. I am alluding to the Dexamethasone Suppression Test (DST). The test has already become so well-known that I take the liberty to skip the description of the test procedure. The mechanism of action of DST has not yet been fully elucidated. It is, however, known that under normal condition Corticotropin Releasing Factor (CRF) of the hypothalamus increases the secretion of cortisol. The negative feedback of high level of cortisol on the CRF is supposed to act through noradrenergic neurons which inhibit the CRF and the rest of the chain reaction occur. In depression noradrenergic neuronal activity is diminished. As a result, its inhibiting action on CRF is also diminished and CRF secretion becomes uninhibited which leads to increased ACTH and Cortisol. When Dexamethasone is injected into a depressed patient, it fails to suppress the CRF-ACTH axis as the noradrenergic neurons no longer perform their usual duty of inhibiting the CRF. Carroll et al (1980) have extensively worked on the DST for the evaluation of depression. Abnormal test results were found in about half of the patients with clinical diagnosis of endogenous depression, compared to 2% of the patients with non-endogenous depression. The predictive value of an abnormal test result for the diagnosis of endogenous depression was 95%. The test can be performed easily in an outpatient setting and requires only a single blood sample. The high specificity and the simplicity of the test make it useful as part of the routine diagnostic evaluation of depressed patients.

The attention of the Psychiatrists has recently been drawn to Prolactin, a hormone secreted by the Pituitary, under control of the hypothalamus, for its tremendous potential as an index of hypothalamic activity during psychiatric illness. It has already found its use is the study of mechanism of action of psychoactive drugs. It is known that all the antipsychotic drugs currently in use increase prolactin level. This effect is believed to be a consequence of their dopa-
mine-blocking properties which are directly proportional to their clinical potency. In clinical psychiatry, this knowledge can be used to detect drug compliance in psychiatric patients, since normal levels of prolactin would imply either that the patient is not taking his antipsychotic drugs or that they are not getting into the blood. Since Prolactin may be an indicator of central dopaminergic activity, it has been used to understand the chemical pathology in a variety of clinical disorders where central monoamine abnormalities have been suspected. In schizophrenics, the basal prolactin is normal (Meltzer and Fang 1976). Rotrosen et al (1976) gave prolactin suppression test to 17 patients who fulfilled the Feighner's criteria for schizophrenia and reported hypo responsiveness to apomorphine compared with the control group. Tamminger et al (1977) had also reported hyporesponsive prolactin responses in chronic schizophrenic patients following suppression with both apomorphine and L-dopa. The difference in the prolactin responses between the schizophrenic patients and the controls were interpreted as indicating a central abnormality of dopaminergic activity. Studies on prolactin response in depression, Parkinson's disease and Huntington's Chorea show that hypothalamic dopamine mechanisms may be present in those disorders. Prolactin changes in grand mal seizures are quite interesting. Timble et al, (1980) have reported that measuring prolactin 20 minutes after a grand mal seizure may establish the diagnosis of epilepsy where it is in doubt, especially where hysteria is suspected. If this report is replicated and easy method of estimation is made available, it will certainly be a useful tool in the hands of the clinicians.

**Concluding Remarks**

The latest developments in psychoendocrine research have opened up possibilities that substances called neuropeptides act in the central nervous system and in the hypothalamus to modulate the release of hypothalamic releasing or inhibiting hormones. Bolus (1980) made observations which indicate that peptides like endorphins and enkephalins interact with the CNS in a multiple way and thereby serve behavioural adaptation. Additionally, subtle derangements in physiological mechanisms regulating β-endorphin homeostasis may be the aetiological basis of certain mental disorders.

It has been postulated that accumulation of β-Endorphin might explain the catatonic form of schizophrenic psychosis. Animal experimentation with α-type endorphins and human study with amphetamine toxicity give rise to the possibility that an excess of α-type endorphins may be responsible for the paranoid form of schizophrenia (Wied, 1978). The pathogenesis of schizophrenic psychosis is supposed to be based on the disorder of endorphin balance. If this supposition is established by further studies, schizophrenic psychosis may be considered as neuroendocrine disease and treated like other hormonal disorders.

It has now become evident that the brain is a major endocrine organ both as a source of neurally active peptides and as a target of peptides of pituitary origin. Neuropeptides or fragments of these molecules affect learning, memory, motivational, attentional, sexual and sleep processes. In short, they serve as transmitters of more or less specific brain processes. The biologic substrate of these processes is the limbic system.

This is a major departure from the traditional view of physiologists and may be a prelude to yet another revolution in psychiatry. We should not be content to be mere witness to this revolution. Let us participate in that revolution.
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