THE ASSOCIATIONS BETWEEN PSYCHIATRIC AND ENDOCRINAL DISORDERS

T H E S I S

Submitted in partial fulfilment of
the Master Degree (Neuropsychiatry)

BY

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1981

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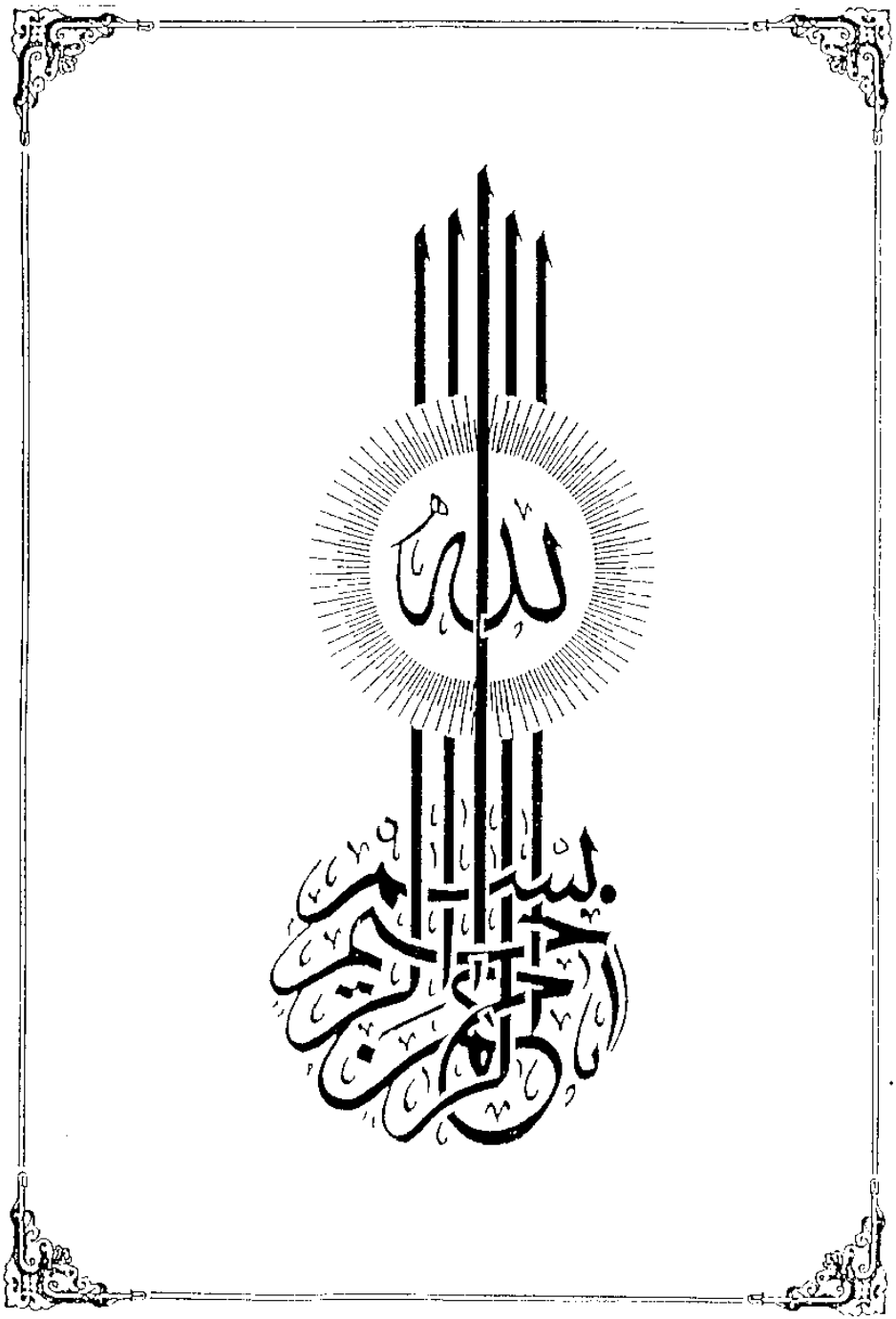
ACKNOWLEDGMENT

I wish to start this work by expressing my deepest gratitude to prof. Dr. AHMED OKASHA , Chairman of Psychiatric Department, Ain Shams University, for his constant guidance, generous help and encouragment.

I wish also to express my cordial appreciation and thankfulness to Dr. MOHAMED ANWAR ETRIBI , Assistant Professor of Neurology and Psychiatry, Ain Shams University, for his kind support, valuable advice, help and encouragment all through the work.

And finally, I also wish to thank all my superiors and collaegues in Behman Hospital for their generous help and consideration.



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THE DEVELOPMENT OF PSYCHOENDOCRINOLOGY

Since antiquity the humours of the body have played a large and mysterious role in people's perception of their own being.

From ancient times the belief has persisted that they have an influence on temperament and mental health. The belief that their actions somehow depend on the phases of the moon has also continued well into modern times.

With the passing of centuries, it is as though a circle has been completed concerning the relation of humours and mental function. We are again recognising their importance in mental life but with the difference that many mysterious "juices" have now become chemically identified substances with exactly defined effects on specific parts of the brain. Humours transfer the nervous impulse , if only at the synapses, and today we know what was suspected for decades, that the effects of many humours are tied to biological phases, to a four weak cycle, and to cycles that depend on exposure to light. Great mysteries have been unveiled. But what remains to be discovered about hormones and neurotransmitters in the brain is still a mystery, a mystery as great as that of the old body humours.

Contemporary endocrinology has began about one hundred and fifty years ago, yet it was only in 1908 that the term endocrinological psychiatry "psychiatrie endocrinienne" was introduced by the french psychiatrist Laignel-Lavastine. Since then,

endocrinological psychiatry has been understood to be the science of psychiatric disturbances in endocrine patients and endocrine disturbances in psychiatric patients.

The first phase of endocrinological psychiatry however, had started long before 1908. It reached its climax in the second and third decades of this century and had ramifications up until the fourth and fifth when the systematic research of the second phase was already going on.

In its first phase, endocrinological psychiatry comprised both wild unscientific speculation inherited from the past and useful psychopathological descriptions of individual endocrine patients. The french literature was particularly rich in these at that time. Individual observations , however, were often too hastily generalised. One reason there are so few lasting results from this first phase of endocrinological psychiatry lies in the overestimation of the notion of specific disease entities. Characteristic psychiatric disturbances were sought in specific endocrine disorders and characteristic endocrine disturbances in specific mental illnesses. Even when they were not found, belief in their existence was nevertheless maintained. The psychiatric disturbances in hypofunction of the adrenal cortex for example, were for a long time presented as being quite characteristic of this disease. It was not noticed that they also largely correspond to the psychiatric disturbances in hyperfunction of the adrenal cortex.

The transition from the first phase of psychiatric - endocrinological research (that of individual observations and speculation) to a second phase of systematic clinical research, took place in the 30's . This second phase of clinical research has produced precise knowledge which will be discussed in the first part of this work.

For the time being, this phase of clinical research in endocrinological psychiatry has come to an end. One would like to speak of a third phase but it is more correct to say that psychiatric-endocrinological research has now become a modest part of major brain research using modern refined methods. In the second phase, the clinician was in the forefront. His experience with his patients established new knowledge. Today he has been superseded by the basic researcher working fulltime in a laboratory with vast technical resources.

The transition to brain research began with the finding that hormones are also formed in the brain and manifest certain effects on brain function. At the same time it was found that hormones and neurotransmitters are interrelated. When the importance of the latter in mental functions was recognised, interest in the significance of hormones in this field accordingly started to focus on their relation to neurotransmitters. Contemporary brain research has extended its field of study from that of pathological processes in respect to interwined nervous and endocrine functions to the study of the normal relations of these two systems.

However, just as clinical questions and experience were originally the main motivating forces for brain research, so also in the future only observation of patients will put many of the findings of brain research in proper perspective, and it will remain the clinicians task to seft critically the high-flown and speculative ideas of the brain researcher for clinical significance.

PHYSIOLOGY OF NEUROENDOCRINE RELATIONSHIPS.

The nervous and the neuroendocrine systems are the principal mediators of physiologic adaptation to environmental stress. Generally speaking, neural reactions are faster than hormonal effects, the former being involved in immediate responses while the latter serve in haemostatic adaptation (Federman , 1981)

There are three types of neuroendocrine interaction :

1 - The hypothalamic regulation of pituitary function .
2 - The neural control of endocrine secretion .
3 - The combination of neural and endocrinal responses to stimuli .

The first and second interactions will be discussed in the following pages, while the third which involves the autonomic nervous system will be beyond the scope of this work .

(1) The hypothalamic regulation in pituitary function :

a) Anterior pituitary function :

There is general agreement (Guillemin, 1977) that connections between the hypothalamus and the anterior pituitary are not provided through tracts but rather through a vascular link in the form of a system of portal vessels , this hypothalamico-hypophyseal portal system was first proposed by Harris in 1955 .

This proposition was based on a number of observations :

1 - Transplantation of the pituitary in peripheral organs causes failure of secretion of pituitary hormones, while its transplantation in the vicinity of the median eminence of the hypothalamus causes resumption of the normal secretion (Guillemin, 1971) .
2 - Section of the pituitary stalk as a means of severing hypothalamo-pituitary relationships causes temporary

reduction in the secretion of the anterior pituitary , which returns to normal with the regeneration of the cut portal vessels (Harris, 1955) .

3. Local destruction of the median eminence of the hypothalamus inhibits completely the release of ACTH that usually follows exposure to any stressful stimulus . (Guillemin , 1980) .

Consequently, Harris and others postulated that pituitary function is regulated by tropic and inhibitory factors secreted by the hypothalamus , some of these factors have been identified chemically and synthesized and are now called Releasing hormones (Schally et al.,1978) .
These factors or hormones are small polypeptides that are relatively species non specific(Brooks and Koizumi,1980). Some inhibit release but most of those definitely identified cause release of hormones from the anterior pituitary (Reichlin ,1976) .

(1) Corticotropin Releasing Factor C.R.F. :

The first of these compounds to be investigated in detail was C.R.F. This substance has now been extracted from the pituitary stalk and median eminence .
It has some of the effects of Alpha Melanocytes Stimulating Hormone (MSH) . Vasopressin in high concentrations can mimic its action in causing ACTH liberation from the anterior lobe (Harris , George , 1969) .
CRF is liberated from the hypothalamus under conditions of stress and there is a diurnal variation in its output. It is not definitely known whether ACTH or corticosteroids act on the hypothalamus to control CRF release although this has been suggested frequently (Schally , 1973) .

(2) Thyrotropin Releasing Factor TRF or TRH :

This compound releases TSH (Thyrotropin) from the anterior pituitary . It is most highly concentrated in the

median eminence and certain nuclei of the hypothalamus , but it has been found in other regions of the C.N.S. (Reichlin ,1976) .
TRF is liberated under various conditions of stress but exposure to cold is a specific stimulus for its release . Thyroxine increase is known to inhibit TSH release at the pituitary level ,but whether it affects TRF production at the hypothalamic level has not yet been clarified .

(3) Growth hormone release (GRF,GIF) :

The material that promotes growth hormone release from the anterior pituitary is called GRF or Somatotropin releasing factor(SRF) , while the material that inhibits growth hormone release is GIF, Somatotropin release inhibitory factor (SIF) or Somatostatin .
Insulin induced hypoglycaemia and Arginine infusions are standard and reliable clinical tests for the growth hormone (Brooks and Koizumi,1980)releasing function of the brain and anterior pituitary .
GRF is also influenced by thyroid hormone , glucocorticoid and estrogen levels in the blood .
Growth hormone induces formation of Somatomedin from peripheral tissues mainly the liver , which is involved in the production of growth ,
It has been suggested that Somatomedin rather than growth hormone itself exert the feedback control on the hypothalamus or hypophysis to prevent excessive growth hormone production.

(4) Control of prolactin release (PIF& PRF) :

The chemical nature of PIF & PRF is unknown (Schally,1973) but PIF is found in high concentrations in the median eminence . PIF inhibits prolactin secretion from the anterior pituitary. Its concentration in the hypothalamus is reduced by suckling and increased by tranquillizers.
Dopamine increases PIF levels in hypophyseal portal blood

thus reducing prolactin levels in man and other animals .
PIF may be inhibited by estrogens as the latter increase prolactin release from the anterior pituitary .

(5) Gonadotropin- releasing factors, (GnRF) :

Follicle stimulating hormone - releasing factor (FRF or FRH) and Luteinizing hormone - releasing factor (LRF or LRH) .
FRF is thought to initiate cyclic changes on the ovaries and production of estrogens therefrom by causing a release of FSH from the anterior lobe .
Subsequent discharge of LRF liberates LH, which produces ovulation and development of the corpus luteum .
Ovulation requires both FSH and LH and thus a combined FRF and LRF action .
Acyclic change in the LRF content of the median eminence has been demonstrated, it is highest during proestrus and diestrus , low throughout estrus . LRF concentrations are particularly high in the median eminence at the time of puberty .
Estrogens and progesterone have multiple negative feedback effects, that block FSH & LH release (Yen,1977) .
This blocking action on release occurs in the basal medial region of the hypothalamus as well as in the pituitary gland.
FSH and LH can also inhibit their own release through inhibitory feedback effects on the brain .

(6) Control of Melanocyte Stimulating Hormone :

The hypothalamus plays a role in the release of MSH from the pars intermedia . " Visual Stimuli " cause the release of MSH and the chromatophore adjustments that occur in fish and amphibia . MSH can affect many body functios , but its importance to mammals is unknown (Kastin et al ,1974) .
Releasing factors are involved in regulation of all MSH functions . There are MSH releasing factors (MRF) and MSH release inhibitory factors (MIF) in both amphibia and mammals .

In considering the control of chromatophores and melanophores, the existence of melatonin in high concentrations in the pineal gland should not be ignored. It has been suggested that melatonin acts on MIF secretion (Rust and Meyer, 1969).
Very complex reciprocal reactions must occur involving the hypothalamus as well as other structures in the nervous system, in forming the complex patterns of skin coloration that are visually controlled (Fingermann, 1970).

(7) Posterior pituitary function :

As early as 1924, Abel demonstrated the presence of vasopressin not only in the posterior lobe of the pituitary, but also in the tuber cinereum of the hypothalamus.
In the 1930's, Scharrer, Roussy and Mosinger postulated on the basis of histologic work that the neurons of the supraoptic and paraventricular nuclei have a secretory or endocrine role (Brooks and Koizumi, 1980).

Bargmann and his associates, in the late 1940,s accummulated morphologic evidence indicating that neurons of the hypothalamus synthesize vasopressin and oxytocin.
These compounds are transported down the fibres of the nerve endings of the neurohypophysis from which they are secreted into the blood stream.
The neurons in the supraoptic and paraventricular nuclei possess both nervous and endocrine properties. They possess resting potentials of the same order of magnitude found in other neurons (Koizumi and Yamashita, 1972).
Action potentials originating in the soma of these nuclei are conducted along axons down the stalk to the pituitary gland and release hormone from their endings (Dyball and Koizumi, 1969).
ADH is secreted mainly by the cells of the supraoptic nuclei while oxytocin by those of the paraventricular nuclei. Activity of the cells of the latter nuclei is much affected by

by excitatory and inhibitory influences not only from the hypothalamus but also from other regions of the nervous system . It is well known that psychic stimuli greatly modify milk ejection . Emotional disturbances affect lactation in women as well as the milk ejection reflexes of many species of animals (Brooks and Koizumi , 1980) .

Neurophysins :

Oxytocin and vasopressin are loosely bound to a carrier protein called neurophysin . This material is identified by histochemical and immunochemical markers .
There appear to be two neurophysins , one binding oxytocin and the other vasopressin . These can be secreted independently in response to physiologic stimuli (Zimmerman,1976).
Thus there is nicotine-stimulated neurophysin (NSN) associated with vasopressin and oestrogen-stimulated neurophysin (ESN) associated with oxytocin (Rabinson, 1980) .

(2) Neural control of endocrine function.

1) Neuroendocrine Transduction : (Johnson , 1982)

This is the process of conversion of electrical stimuli into chemical secretion . It occurs in the autonomic nervous system where secretion of acetylcholine from preganglionic sympathetic fibres directly onto chromaffin cells causes release of catecholamines . It also occurs in the central nervous system , where special neuroendocrine cells present in areas of the hypothalamus , secrete releasing or inhibiting hormones that control pituitary function .