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A Psycho-Neuro-Endocrine Framework for Depression: A Clinically Eclectic Approach

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For quite some time the factors underlying the etiology of clinical depression have remained elusive. However, many provocative studies have been conducted that have elucidated some of the central features of the clinical picture. Our current understanding provides us with the notion that many factors are superimposed upon the neural architecture which enter into a dynamic interplay in the orchestration of the complex phenomenon associated with the behavioral and arousal changes exhibited by depressed patients. The objective of the present paper is to emphasize the importance of establishing a framework which considers the various factors acting in the manifestations of the disorder. I will give consideration to a host of neuropsychiatric ramifications which include (1) biobehavioral configurations; (2) genetic and familial studies with both human and nonhuman primates; (3) the analysis of sleep; (4) neuro-psychopharmacology; and (5) neural circuit mechanisms acting on differentiated axes in the psychoneuroendocrine apparatus. An attempt is made to framework depression and hence bring forth a modicum of understanding to this multifactorial disease which is neither wholly endogenous or wholly exogenous—but rather one whose comprehension necessitates an inevitable union between the biological and psychological concomitants.

The way individuals perceive their world can interfere with behavioral function when those views or cognitive maps are inaccurate or idiosyncratic. Mislearning is often at the root of many personality limitations that can then result in inadequate management of one's world. It should be clear, however, that many learned maladaptive behavioral patterns occur concomitantly with constitutional variables and illnesses. Recent evidence suggests that a confluence of both biological and psychological factors are provocative in predisposing individuals to be less resistant to the traumatic and potentially anxiety-provoking events that are often associated with the origin and symptomatology of depression.

Despite the fact that in reality no state can be classified as purely endogenous, some forms of depression may be grounded in constitutional factors while other forms may be psychosocially determined. Surely it would be desirable to sort out more cogently the influences of constitutional traits, life

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experiences, and the symptoms that can be identified in illness. And at this point there should not be any debate that the psychological effects of life events can be translated into their neurophysiological substrates—and therefore must interact with neurochemical and physiological mechanisms of CNS function to produce their final effects in the psychoneuroendocrine pathways that regulate mood. Unfortunately, though, there has been an incomplete recognition of the crucial interplay between psychological, neurological, and endocrinological factors that serve as potential precipitants in the etiology of depression. Current nomenclature leaves much room for personal interpretation depending on respective psychiatric or psychological allegiances.

A problem for most theories of depression is that they are oversimplified. Their formulators enthusiastically hope that they have found the one set of common denominators that determine all the others. According to dynamic psychologists, for example, symptoms exhibited by the patient can be viewed as reactions to intrapsychic conflicting forces. Consequently these professionals will usually suggest psychotherapy as the exclusive mode of treatment. The well documented fact that many of these patients undergo various forms of psychotherapy for many years without any significant amelioration of the depressive signs lends credence to the rejection of this unidimensional approach (Klerman, 1983). Even with the current integration of psychoneuroendocrinological principles we cannot parenthetically state that the biological and psychological components of depression are easily sorted out, but rather that they coexist in a conditional relationship, one inextricably related to the other. Whichever end of the nature/nurture debate each of these theories rest upon, most share the common fault of relying too heavily on one group of factors to the exclusion of the others.

For the sociologist, depression is the result of an abberant social structure that deprives individuals with certain roles from control over their own destiny. For the existentialist, depression supervenes when the individual discovers that his or her world has lost its meaning and purpose (Becker, 1964). The behavioralist regards depression as a set of maladaptive behavioral responses (Ferster, 1965; Lazarus, 1968). Finally the biological psychiatrist conceptualizes depression as the behavioral product of a genetically vulnerable CNS which is deficient in biogenic amines (Bunney and Davis, 1965; Coppen, 1967; Schildkraut, 1965). Unfortunately each theoretical framework has its own therapeutic modality which tends to be rather limited when administered alone. These therapeutic approaches range from psychoanalysis to behavioral therapy, from social activism to chemotherapy and electroconvulsive shock therapy (ECT).

Amidst all the discussion about which factors contribute the greatest influence in precipitating depression, abundant speculation has surrounded the issue of whether biological aberrations, which predispose persons to illness, are the result or the cause of psychological changes. Certainly the

evidence being presented is not totally unambiguous. I am strongly opposed to the psychiatric division of depression into the endogenous and exogenous subtypes, because I have found that the deeper one explores into the past history of a previously diagnosed endogenously depressed patient, the more likely one could identify a traumatic event which had triggered the depression. Alternately, the rudiments of an exogenous depression can often be located long before the time of the identified traumatic event.

It is true that semantic controversies such as medical versus psychosocial, organic versus functional, hereditary versus environmental, and endogenous versus exogenous only serve to cloud psychiatric thinking. However, whether the affective state is depression of the ubiquitous type, which involves emotional responses to everyday adaptation to stress, frustration and loss, or is a chronic state of deep rejection, these conditions establish the dimensions of illness when there is observed the concomitants of disruption of vegetative and psychomotor functions.

As many of the problems suggest it is now necessary and appropriate to construct a clinically meaningful orientation that will provide greater cohesion between previously separate and at times antagonistic disciplines. It is my present objective to discuss the various lines of evidence which taken together constitute a psycho-neuro-endocrine framework that will provide a more comprehensive clinical approach from which the psychiatrist or psychologist can systematically identify symptom constellations and subsequently employ eclectic treatment configurations when confronting the depressed patient. Three primary benefits accrue immediately by subscribing to this approach. First, it would serve to avoid the nosological and semantic disputes that obscure the impressive advances achieved in this area of mental illness. Additionally, depression would be approached in the broader context thereby prohibiting the disciplinary fragmentation that has occurred for so long in psychiatry. Finally, the practical application of this framework prescribes a biopsychiatric modality to treating the depressed patient. Here, appropriately indicated forms of psychotherapy are coupled with the administration of chemotherapeutic agents such as the tricyclic antidepressants. This mode of treatment is comprehensive in that the psychotherapy addresses the refractory maladaptive living patterns which develop during the course of the illness while the drugs work to compensate for neurotransmitter and hormonal perturbations and can therefore elevate mood and be instrumental in bringing the patient to the point where psychotherapy or community rehabilitation can begin. The primary evidence supporting this synthesis will be derived from the psychoendocrine theories of depression which include the results from studies that were conducted to elucidate the relationships between neurochemistry and neuro-circuit mechanisms acting within the hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-thyroid (HPT), and more recently the pineal-hypothalamic-pituitary-adrenal axis of interaction.

Further, consideration will be given to behavioral studies on both human and nonhuman primates, polysomnographic sleep analysis, and genetic and hereditary studies.

At the onset, one caveat must be levied against this approach. Despite the temptation to consider any framework definitively comprehensive, in a broader sense, advances are occurring very rapidly whose findings contribute to a greater clarity toward a more comprehensive delineation of the link between neuropeptides and/or neurotransmitters in behavior. In many instances the open door approach of maintaining a flexible and dynamically changing framework provides a crucial role, often at the interface between medical science and our ability to understand and to diagnose and treat disorders.

Major Depression as Illness

According to the *DSM III*, major depression is considered a major affective disorder, being one that presents a disturbance of mood. In these disorders it is paramount to distinguish between those illnesses whose characteristic episodes are the result of some underlying organic aberration and illnesses which are bona-fide psychiatric disorders. Thus, only by excluding an organic etiology can the attending specialist make the diagnosis of major depression.

In the past, diagnosis was complicated by the fact that the depressive symptoms are often expressed primarily in overt behaviors, cognition, and subjective feelings. And although it is misleading to assume that a consensus exists about clinical boundaries of depressive types, the *DSM III*, *RDC*, and other disease classification schemes represent practical and effective tools by which the mental health specialist can now commence the evaluation of the patient with a suspected depressive form.

As codified in the *DSM III*, the core features of depression include dysphoria with anhedonia, changes in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, abulia, fatigue, thoughts of death, or suicidal ideation or suicidal attempts. It is important to point out that despite the advances afforded by using the *DSM III* and other diagnostic criteria, there are severe limitations. For the most part the nosology of the depressive illnesses is often the expression of a dualistic and reductionistic philosophy for which the mind/brain dichotomy is central. This philosophy is predicated on the precept that certain events are psychological or determined by psychological cause while others are physical and enjoy relative freedom from psychic influences. This concept brings forth an awareness that the brain is somehow dissociated from mind. In cogently addressing this construct MacKay's (1982) "comprehensive realism" recrystalizes the necessary nexus between mind/brain considerations—"the view that man is a unity with logically complementary mental and physical aspects, must be held together if we are

to do justice to all the facts of our experience" (p. 293). He describes, "mind as acting not on but in the brain, and conscious agency as embodied in, rather than interactive with, the special re-entrant pattern of cerebral information flow that continually and actively revises its own programme, and so becomes its own arbiter" (p. 293).

The above points are especially useful when thinking about depression as they illustrate the futility of looking for one to one cause and effect relationships rather than emphasizing the dynamic interplay among neural circuit mechanisms, endocrine function, and behavioral state configurations. Furthermore, the strict professional allegiances, which tend to preclude cross disciplinary validation, only serve to exascerbate problems since by exclusively recognizing differences one tends to ignore relationships.

By virtue of the difficulties in codifying the depressive forms it should now be customary to support diagnostic decisions by integrating information derived from the *DSM III*, family and genetic history, laboratory tests, and the analysis of sleep. Further, certain technical and medical exclusion criteria must be considered before any group of facts is considered definitive for depression.

Biobehavioral Configurations

Whereas most of the psychiatric literature is dominated with considering behavioral changes as secondary to changes in biogenic amines, other studies are available which suggest that the opposite case may be appropriately hypothesized: that social variables can indeed evoke major changes in brain amines (Barchas and Freedman, 1963). Hence biochemical defects can also be secondary to developmental and interpersonal events.

Attempting to assess the place of life events in the onset of depression, Thomson and Hendrie (1972) found that diagnosed endogenous depressives had experienced as much stress as reactive depressives. Given that life events precede the onset of many depressions at a rate greater than in controls, how important is the causative effect? If we apply the epidemiological concept of relative risk—which is the ratio of the rate of disease among those exposed to a causative factor to the rate of those not exposed—we find that the ratio is 6:1 for the risk of developing depression in the six months after the more stressful classes of events (Paykel, 1978).

Taken together the studies that have tried to assess the etiological and nosological significance of psychological stress give rise to three primary points of view: (1) that the relationship between stress and depression is coincidental (Cadoret, Winokur, Dorzab, and Baker, 1972; Hudgens, Morrison, and Barchha, 1967; Morrison, Hudgens, and Barchha, 1968); (2) that stress is produced by the depressive illness. In effect, individuals predisposed to affective illness display abnormal reactivity to normative stress, thus the

so-called precipitating stressful event actually represents the prodromal manifestations of the illness; (3) that stress does play a role in precipitating the depressive illness (Leff, Roatch, and Bunney, 1970; Paykel et al., 1969; Thomson and Hendrie, 1972), usually in individuals who are genetically or developmentally predisposed to such illness.

As the debate continues about potential relationships between stress and the onset of depression, it seems likely that a multiplicity of factors work in concert via a common final pathway to elicit the CNS changes which contribute in establishing behavioral states and mood. Some biological factors that have been implicated include the parameters of genetic vulnerability, physiological stressors such as hyperthyroidism, viral infection and others that can exert detrimental effects on diencephalic function. The developmental and interpersonal factors include childhood experiences, personality configurations, psychological defense mechanisms, and the reaction patterns leading to greater vulnerability to stress such as reactions to object loss and learned helplessness.

In the psychoanalytic tradition, depression represents the introjection of hostility resulting from the loss of an ambivalently loved object (Abraham, 1960; Freud, 1917), or a reaction to separation from a significant object of attachment (Bowlby, 1960; Robertson and Bowlby, 1952; Spitz, 1942). That the separation from a loved object could have depressionogenic consequences was first emphasized by Freud in the paper "Mourning and Melancholia" (1917). The dissolution of interpersonal attachment bonds results in significant loss of reinforcement and induces a behavioral state that may be associated with helplessness and the degeneration of behavior.

The above concepts as they relate to depression have been validated by numerous studies with human and nonhuman primates and, together with our expanding knowledge of neuroendocrinology, may help to establish conceptual bridges with biological models of depression. Bowden and McKinney (1972) and Young, Suomi, Harlow, and McKinney (1973) demonstrated with Rhesus monkeys that separation and other forms of deprivation can induce syndromes that mimic human depression, not only behaviorally but physiologically and biochemically. In fact, the same symptoms that have been produced in monkeys by means of norepinephrine depletion have been produced in them by separation from an attachment figure (Suomi, 1975). These primates also exhibited alterations in sleep pattern and cortisol elevation.

More recently, ego psychology approaches have shifted focus to helplessness, lowered self esteem (Bibring, 1965) and negative cognitive set (Beck, 1967). The well-known learned helplessness model can be related to psychosomatic effects of ulcer production. If dogs are given a series of electric shocks with no opportunity to escape, then subsequent experience with an opportunity to escape will find the dogs very slow in relearning. In effect they have given

up and are convinced that there is nothing they can do to affect their environment (Seligman and Maier, 1976). Weiss, Glazer, and Pohorecky (1976) showed that there are clear physiological consequences of shocking rats without allowing them to escape. These rats have more gastric ulcerations (indicating stress) and also have depleted levels of norepinephrine. Similarly, in humans, traumatic life experiences can cause people to react by constructing a wall about themselves which further facilitates an intellectual and emotional regression that serves to distort one's perception and to feel that situations are rendered hopeless. Inevitably this process can lead to the development of chronic maladaptive behavioral patterns (low self esteem) thereby intensifying the patient's inability to function in essential operational modes and to assume responsibility for his/her destiny. Transporting the person into a narrow conceptual world, the erection of powerful defenses occurs for fear that some similar disaster could be forthcoming. If left untreated the patient's chances for gaining self insight and resuming behavioral function remains highly remote. Furthermore, with the strong conviction that depression could ensue, the patient might be actively contributing to its onset. This type of forecasting is dangerous in that it establishes expectations that make validation almost a personal imperative. As is often evident in cases of low self insight and the subjection to self-fulfilling prophecies the common denominator of the depression might predominantly be determined by such rigid action patterns. Hence, in first approaching these patients the emphasis must be placed upon the need to become self controlling instead of self frustrating.

Familial and Genetic Studies

Much has been learned about the genetic basis of the affective disorders from inheritance patterns that were examined for the purpose of separating the effects of nature and nurture. If depression has strong genetic components then it should be feasible to statistically demonstrate that relatives of patients with strongly biological depression are more likely to have similar maladies compared with the population at large. A great deal of research has been done in the area of twin studies and was designed to capitalize on the fact that monozygotic or identical twins come from the same fertilized egg and are therefore genetic carbon copies of each other. The probability of inheriting a disorder reaches its maximum in the case of identical twins. If one identical twin has manic-depressive psychosis the incidence that his or her co-twin will suffer is between 50% and 80% (Wender and Klein, 1981). In nonidentical or fraternal twins the probability is approximately 10%—still higher than the 4% seen in the normal population.

In another study (Cadoret, 1978) a group of adoptees were raised by parents who did not show signs of affective disorder but whose biological parents were in fact diagnosed as endogenously depressed. The results indi-

cated that there was a higher prevalence of illness in those adoptees whose biological parents were depressed in comparison to those who were not.

In a more speculative study (Weitkamp, Stancer, Persad, Flood, and Gittornsen, 1981) it was found that a deviated human leukocyte antigen (HLA) on chromosome 6, clusters within families, indicating that it was genetically transmitted. This pattern deviates from the normal pattern of random Mendelian inheritance and is interesting because families that presented the deviated HLA pattern also had an increased frequency of depressive disorders. It is quite conceivable that a gene involved in transmitting depression and those for HLA are in close proximity or linked in such a way that they are inherited together, thus conferring upon the recipient an increased predisposition for depressive illness. When we reflect upon these findings it is obvious that a genetic factor in the depressive disposition has been demonstrated beyond a reasonable doubt.

Polysomnographic Sleep Analysis

The EEG patterns from depressed patients have been shown to be clearly differentiated from those exhibited by persons suffering from normal insomnia (Chen, 1979; Kupfer, Coble, McPortland, and Ulrich, 1978; Sachar, 1981). Some of the more salient aspects of sleep dysfunction in depression include: prolonged sleep latency, multiple awakenings, early morning awakenings, decreased delta sleep, and an increased REM period with a decreased REM latency. REM latency is the most specific finding for depression since the other features are found to occur in a variety of other nonaffective conditions. Therefore, like the dexamethasone test, the REM latency test is beginning to prove useful in the diagnosis of this disease (Akiskal, Lemmi, Yerevanian, King, and Belluomini, 1982; Kupfer et al., 1978; Rush, Giles, Roffwarg, and Parker, 1982).

Biogenic Amine Theory

For quite some time the primary theory of depression underscored the cerebral deficiency of brain biogenic amines (Schildkraut and Kety, 1967). In effect this theory predicted insufficient neurotransmitter at certain synapses hence prohibiting normal postsynaptic activity (Curzon, 1967). In particular, these deficiencies might be due to reduced neurotransmitter production, excessive neurotransmitter turnover by monoamine oxidase (MAO), or perhaps by a decreased response sensitivity of the postsynaptic receptor (Bunney and Davis, 1965).

Some early support for the biogenic amine theory came from the clinical observation that approximately 15% of the patients taking the antihypertensive medication, reserpine, were found to have depressive episodes (Goodwin

and Bunney, 1971). It is strongly believed that reserpine depletes the neurotransmitters norepinephrine and serotonin. Other evidence for this theory that has also had great significance for biochemical pharmacology and the theory of mental illness was that iproniazid, a monoamine oxidase inhibitor (MAOI), which was originally used as an antitubercular agent, induced a mood elevation in tuberculosis patients (Sourkes, 1976). The depletion of another monoamine, 2-phenyl-ethylamine (PEA), has recently been proposed (Sabelli et al., 1983) as another piece of the puzzle in further delineating biological marker systems for depression. Hence drugs that serve to decrease monoamines in the CNS tend to precipitate depressive symptomatology, while drugs which increase central monoamines tend to have an antidepressant effect.

Catecholamines

Studies that discuss deficiencies of norepinephrine in depression now also include information on the urinary excretion of the main norepinephrine metabolite, 3-methoxy-4-hydroxy-phenylglycol (MHPG) (Glowinski, Kopin, and Axelrod, 1965). It has been shown (Markku, Farouk, and Potter, 1982) that there is a high correlation (greater than .83) between the MHPG excretion rates and the production of brain norepinephrine. In addition to low levels of MHPG being used as a biological marker for depression, MHPG levels can be used as an index of therapeutic efficacy for antidepressant drugs. With Imipramine administration, concomitant with the amelioration of the depressive symptoms, an increase in urine MHPG levels followed, thus indicating that this drug might be normalizing a norepinephrine imbalance (Rosenbaum et al., 1980).

The somatic dysregulation that results in changes of the homeostatic and circadian mechanisms, symptomatic of depression, can be partly explained in terms of the role of norepinephrine in the noradrenergic-locus coeruleus system (NE-LC). This neural substrate, located within the dorsorostral pontine tegmentum, calibrates neuronal discharge rates which ascribe the different stages of the sleep-waking cycle and therefore mediate corresponding levels of cortical and behavioral arousal. Aston-Jones and Bloom (1981) demonstrated in rats that sensory evoked responses in the NE-LC vary in intensity as a function of behavioral state. One predominant feature of the system is the phasic alterations, in discharge, which could serve to facilitate transitions between global CNS modes and behavioral states. Indeed the punctuated derangement of arousal and behavioral patterns observed in depression could parallel changes in the normal discharge rates subsequent to neurochemical perturbations. Hypothetically this system might be an active constituent of the psychoneuroendocrine hardware and whose idiosyncratic functioning—either primary or secondary to changes in norepinephrine and

depression—could account for some of the salient arousal and sleep disturbances observed in depressive illness.

Serotonin

The main serotonin metabolite in cerebral spinal fluid (CSF), 5-HIAA, has been shown to be abnormally low in depressed patients (Ashcroft et al., 1966; Coppen, 1971). Meltzer, Arora, Baber, and Tricou (1981) have developed an assay for determining the uptake of serotonin into blood platelets. They contend that the serotonin deficiency evidenced in depression may be partly due to a reduction in the uptake sites for serotonin on the cell surface of blood platelets. In some patients the total number of uptake sites can be as much as 30-40% below average. Like norepinephrine, serotonin serves an integral role in the regulation of arousal and behavioral states. Consequently, somatic dysregulation can be anticipated when there exists a departure from the normal CNS levels of this and other biogenic amines.

2-Phenylethylamine (PEA) and Phenylacetic Acid (PAA)

Sabelli et al. (1983) have recently brought forth a still investigational but rather intriguing biochemical marker system for depression. 2-phenylethylamine (PEA) is a metabolite of phenylalanine and phenylacetic acid (PAA) is a metabolite of PEA. Sabelli has proposed that brain PEA modulates alertness, wakefullness, and excitement, performing as an endogenous amphetamine. In fact PEA closely resembles the amphetamine chemical structure and thus far is the only neuroamine to exert amphetamine-like affects on behavior and brain electrophysiology. Thus a CNS deficiency or decrease in turnover of PEA, perhaps in concert with alterations in serotonin and catecholamines, may be causally related to depression. Conversely, an excess of PEA may underlie some forms of mania.

Although the proportion of urinary PAA that comes from brain PEA as well as how much PEA is normally present is still unknown, assays on more than 500 patients and controls have been able to correlate PAA levels with affective states. The results of these assays were consistent in showing decreased urinary PAA levels in a large majority of patients with unipolar or bipolar depression, higher values in normals, and even higher in manic subjects. As seen with urinary MHPG levels, effective antidepressant therapy raises PAA values to those that are seen in normal subjects. Sabelli has also found that some depressed patients respond well to exogenous phenylalanine supplementation. At this point, however, the PAA assay is not yet definitive for depression but certainly proves to be another provocative area of active research in biological psychiatry.

Components of the Psychoneuroendocrine Apparatus

A prominant hormonal abnormality in depressed patients is an increase in activity in the hypothalamic-pituitary-adrenal (HPA) axis, as manifested by elevated urinary free cortisol (Carroll, Curtis, and Mendels, 1976) and a loss of dexamethasone suppression (Carroll, Curtis, Davies, Mendels, and Sugerman, 1976; Sachar, Hellman, et al., 1973). Hypercortisolism is demonstrated via the overnight DST (Carroll, 1980) and the 24 hour urinary excretion of free cortisol (UFC) (Carroll, Curtis, Davies, et al., 1976). The DST is an important test in that it can differentiate clinical depression from other dysphoric conditions to a diagnostic specificity of 98% (Carroll, Feinberg, et al., 1981) for depression with melancholia, hence the test is rarely positive in nonmelancholic dysphoric states. Both ACTH and CRF, and therefore cortisol levels, are variable according to a circadian rhythm (Berson and Yallow, 1968), the derangement of which can be either primary or secondary to psychic anxiety factors (David-Nelson and Brodish, 1969). In addition to its diagnostic importance, the DST can be used to measure treatment response in that it returns to normal with recovery (Carroll, 1982; Yerevanian et al., 1983). This normalization of cortisol is consistent with the normalization of other proposed depressive markers such as urinary MHPG and phenylethylamine. These multivariate correlations suggest that various contributing factors of depression participate in concert along common or related pathways in the psychoneuroendocrine apparatus. Also significant are the correlations between plasma cortisol values and the CSF monoamine metabolites, MHPG and 5-HIAA (Agren and Wide, 1982) and concurrent normal to high levels of both CSF MHPG and CSF 5-HIAA are necessary for a depressed patient to manifest a pathological DST. Additionally, cortisol hypersecretion in depression might be thought of as dependent on an interactive balance between CNS noradrenergic and serotonergic functions. The decreased or attenuated noradrenergic inhibition of hypothalamic CRF secretion, secondary to low levels in monoamines, is known to result in an escalation of ACTH activity and so a resultant hypersecretion of adrenal cortisol (Sachar, 1975). Other studies that supported the regulation of ACTH secretion by monoaminergic function utilized drugs that deplete biogenic amines. The administration of either reserpine or alpha-methyl-para-tyrosine, or the destruction of noradrenergic or serotonergic nerve fibers elicit ACTH release with a subsequent cortisol hypersecretion (Fuxe, Corrodi, Hokfelt, and Jonsson, 1970).

In past clinical experience patients with hypothyroidism often presented depressive symptomatology. Though less well studied for genetic and treatment response variables, a thyroid function dysregulation, acting in the hypothalamic-pituitary-thyroid (HPT) axis, is expressed as an impaired or absent thyrotropin response to thyroid releasing hormone (TRH) and appears to be a concomitant of depression (Schlach, Gonzales-Barcena, Kastin,

Achally, and Lee, 1972). TSH response to TRH tends to be decreased or delayed during depression (Prange, Wilson, Lara, Alltop, and Breese, 1972; Yamaguchi, Hatotani, Nomura, and Ushijima, 1977). Baseline plasma cortisol and peak TSH values in TRH tests (Loosen and Prange, 1980; Loosen, Prange, and Wilson, 1978) revealed significant negative correlations in normals as well as in depressed patients. Glucocorticoids are able to blunt the TSH response to TRH (Otsuki, Dakoda, and Baba, 1973; Re, Kourides, Ridgway, Weintraub, and Maloof, 1976) and a similar action may be evident in Cushing's syndrome. Wybrow and Prange (1981) described an interaction between thyroid and catecholamine receptors that could elicit alterations in the activity of the sympathetic nervous system. Ultimately sympathetic changes, such as those present in depression, can influence the release of thyroid hormones T3 and T4 (Melander, Westergren, Ericson, and Sundler, 1977) indicating that sympathetic tone is intimately related to thyroid function. Other reports have discussed abnormalities of growth hormone (GH) secretion (Gruen, Sachar, Altman, and Sassin, 1975; Sachar, Altman, Gruen, Halpern, and Sassin, 1974). Several investigations have shown diminished GH release in depressed patients after insulin hypoglycemia (Sachar, Finkelstein, and Hellman, 1971) and in a study by Sachar, Altman, et al. (1974) a suppression of GH and LH responses was noted in depressed postmenopausal women.

Recently, a pineal-hypothalamic-pituitary-adrenal axis (PHPA) has been proposed (Wetterberg, 1983) in lieu of the findings that patients with depression secrete low levels of nocturnal serum melatonin. Normally melatonin is secreted according to circadian control with low levels in serum during the day and maximum levels occurring at night. This nocturnal hyposecretion of pineal melatonin, with melatonin normally exerting an inhibitory action on hypothalamic CRF, is consistent with the findings that patients with an abnormal DST have lower melatonin levels than patients with a normal DST (Beck-Friis et al., 1981).

Taken together the above aggregate systems—the HPA, HPT, and PHPA—represent points of contact between the nervous and endocrine systems, and in conjunction with behavioral and cognitive state integration, create permutations in the psychoneuroendocrine mechanisms that regulate states of consciousness, emotional behavior, instinctive drives and autonomic function.

Biopsychiatric Treatment

At this point I have considered some points of evidence which could serve as an indictment for the integration of three sets of variables acting in depression at chemical, experiential, and behavioral levels, such that the functional impairment in one system could result in functional shifts in one or more of the other systems, all of which contribute in determining affective states. Such an indictment mandates as a precondition to treating these

patients, the scrupulous delineation of both biological and psychical parameters. Therefore, the premise of any comprehensive treatment scheme must address the various levels at which a disease becomes manifest.

For quite some time in the field of psychiatry it has been standard practice to classify treatments for affective disorders categorically into somatic treatments and psychological treatments. Somatic treatments are those which change the functioning or structure of the CNS which in turn acts to hopefully attenuate depression. Some examples include the tricyclic antidepressants, MAOIs, and electro-convulsive shock therapy (ECT). As we turn to the psychotherapies the situation becomes very complicated by virtue of the great number of psychotherapeutic forms which now number approximately 200. For brevity these therapies can be classified into the individual psychotherapies that include psychoanalysis, interpersonal and cognitive behavioral therapies, and the group psychotherapies which inlcude milieu therapy, family and couples therapy and social skills therapy. Although the volume of evidence for the efficacy of psychotherapy is less than that for the drug treatments, in clinical practice, the majority of patients receive some form of psychotherapy (Keller et al., 1982).

In major depression there always exists some level of interference of social-occupational functions. And in some extreme cases the individual is completely unable to function in all instrumental modes. It is imperative to recognize at the onset that the depressive episodes can arise both with and without psychosocially manifested precipitants. In many of the cases there is a chronic course with considerable residual symptomatic and social impairment. These residual patterns represent a nonspecific postmelancholic manifestation of the illness and can be a period which is prolonged both by the patient's difficulty in recovering his or her role and by the fear of facing the world. Following a depressive episode, and despite the apparent amelioration of the depressive signs, persistent maladaptive social patterns usually prohibit a smooth reintegration back into the family and social milieu. In lieu of these residual behavioral and thinking patterns, combined therapy of drugs and psychotherapy seems essential. The drugs are often effective in mitigating the somatic signs of neuroendocrine dysregulation while the psychotherapy addresses the refractory living maladjustments. Together these modalities are often effective in expediting behavioral reconstruction and neuroendocrine normalization.

A number of studies have demonstrated that optimal outcomes are achieved with combination drug and psychotherapy, while both treatments individually are better than controls (Klerman, DiMascio, Weissman, Prusoff, and Paykel, 1974). Weissman et al. (1979) reviewed evidence for the efficacy of drugs and psychotherapy in comparison to both of these treatments alone. The results of the analysis supported the efficacy of psychotherpy or drugs alone as compared to the control group. In another study (Paykel, DiMascio,

and Klerman, 1976) it was found that combined treatment was synergistic in its effect on social adjustment and therefore greater than the effect of either treatment alone. Weissman et al. (1979), utilizing the combined therapy approach, showed again the efficacy of both amitryptiline and psychotherapy in overall symptom reduction. Amitryptiline had its effect mainly on somatic signs such as sleep changes, general somatic complaints and appetite. The effects of psychotherapy were mainly on depressive mood, suicidal ideation, guilt, and low self esteem. In a study by Prusoff, Weissman, Klerman, and Rounsaville (1980) it was interesting to discover that a differential response was identified to psychotherapy and drug treatment depending on the subtype of depressive illness—endogenous or situational depression. The results specified that patients diagnosed as either endogenous or situationally depressed responded to combined therapy; those diagnosed as strictly endogenously depressed did not respond to interpersonal psychotherapy alone; finally, situationally depressed patients responded to either interpersonal psychotherapy or to tricyclic antidepressant drugs alone. A Boston-New Haven study (Klerman et al., 1974) which found a psychotherapeutic effect only in patients who remained free of somatic complaints, best supports the hypothesis that drugs have a positive effect on the patient in that the somatic symptom relief produced more readily by drugs, rendered the patient more accessible to psychotherapy, thereby expediting the period required for behavioral reconstruction.

Resynthesis

As illustrated in my investigation of the available evidence, there is a necessity for the individual mental health professional to make an assertive departure from strict disciplinary allegiances and begin to integrate information from the various facets of study that have made significant contributions to our understanding of depressive illness. In clinical psychology and psychiatry—as in other areas of medicine—the primary objective is to serve the patient. Certainly the present capability to achieve multi-variate biobehavioral correlations can be instrumental in providing patients with diagnostic and treatment regimens that are more comprehensive, in addition to being operationalized more systematically when placed within the framework of a multidisciplinary approach. On the other hand, one disclaimer must be made in defense of the current proliferation of new and exciting data being derived from the pursuits of basic and clinical research. New findings should act to revise and expand the psycho-neuro-endocrine framework for depression. Hence there is no quanta of information that can act as the totality of understanding—rather, the present framework can be thought of as a dynamically changing construction. With these points in mind it is paramount that we not become preoccupied with the notion of absolute determinism, but

rather that we remain open-minded to the progressive delineation of putative relationships between mind and behavior.

Working at Columbia University, Eric Kandel has contended that life experiences work by acting on the brain—and quite likely on the connections between nerve cells (Kandel, 1979). Hence disturbances which are environmentally produced could become manifest from discrete changes in genetic expression. On the other hand, disturbances which are known to be inherited could represent the behavioral residues of alterations in genetic structure. The premise of the latter argument is based on the facts that certain psychiatric dispositions have been shown to strongly relate to an individual's genetic constitution and are therefore inheritable. Acting independently, or in concert, these changes should have profound effects on the dynamics of synaptic modulation and so give rise to complex variations in behavioral and arousal states (Kandel, Krasne, Strumwasser, and Truman, 1979).

Although many have tried to resolve the dilemmas created by the nature/nurture debate, this long protracted controversy has remained tenaciously refractory to erosion. The precepts inherent in such determinisms often preclude the comprehension of mind and behavior as the interactive and communicating continuum necessary to appreciate the essence of our unity. Until recently the complexity of trying to unravel neural circuit wiring diagrams has presented a major obstacle to understanding functional brain mass changes that accompany the various permutations of behavioral response to simple and complex stimuli. Working with the 20,000 nerve cell *Aplysia*, Kandel has been responsible for unmasking some of this mystery. In studying certain characteristic nerve circuit changes concomitant with various types of learning (e.g., habituation, sensitization, classical conditioning), he has been able to map functional circuit units that exhibit neural plasticity to changing stimuli (Kandel, 1981). This synaptic 'connectionism' affords an organism the behavioral repertoire which is necessary for adaptive responses to continuing environmental perturbations.

And while there are many constraints from making the giant leap from a small organism like *Aplysia* to a human brain, with its some 20 billion nerve cells, we should keep in mind the salient fact that humans, unlike *Aplysia*, are capable of a multiplicity of complex biological and behavioral functions. Since a high degree of neural specialization creates immense competition along the synaptic networks, it is highly adaptive that there exist a remarkable degree of circuit redundancy. Hence, although we must remain cautious, it is hoped that archaic organisms like the sea snail, *Aplysia*, might provide us with valuable insights into the dynamic interaction between brain architecture and life experience.

Through the evidence in this paper I have tried to address the intimate relationship between behavioral states and neuroendocrine functioning in the brain. Education on this information must be widely disseminated in order to

enhance the potential for greater cohesion and consensual agreement between the various schools that approach the depressive patient. Additionally, the endorsed approach can perhaps serve to improve successful indentification and biopsychiatric treatment for the patient suffering from depression, as well as provide researchers of mental illness with valuable clues about mind and behavior.

The brain and nervous system both contain sites for the action of steroid hormones which evoke particular permutations in the psychoneuroendocrine apparatus and therefore facilitate the occurrence of discrete behavioral states. Just what changes are necessary to elicit the various nuances of behavior are not yet understood. Nevertheless, evidence has strongly suggested that the effects of hormone action, with simultaneous regulation by biogenic amines, are coordinated with each other and together contribute to the functional and structural integrity of the CNS mechanisms that regulate behavior. In 1980 Sperry (personal communication, 1984) restated his view that "The physical brain process is not causally complete without including the subjective mental properties . . . . Mind does actually move matter in the brain." In the future more professionals will subscribe to the recognition of depression as a distinct disease entity with aspects of the mind acting within the brain, juxtapositioned to a confluence of neuroendocrine events acting along the various pathways of the neural circuitry. Whether the depression is manifested by a situation whose stress exceeds the individual's ability to cope, or from metabolic aberrations in central monoamine mechanisms, such factors participate in a complex interplay exerting their effects via a common final pathway.

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