A Summary of Biomedical Aspects of Mood Disorders

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INTRODUCTION

Historical Background

The severe disorders of mood or effect are among the most common of the major psychiatric syndromes. Lifetime expectancy rates for such disorders are between 3 and 8% of the general population (Silverman, 1968; Slater & Cowie, 1971). Only a minority are treated by psychiatrists or in psychiatric hospitals and about 70% of prescriptions for antidepressants are written by nonpsychiatrist physicians (Hollister, 1978). These and other modern medical treatments of severe mood disorders have contributed to a virtual revolution in the theory and practice of

modern psychiatry since the introduction of mood-altering drugs three decades ago (Hollister, 1978; Baldessarini, 1977a, 1977b, 1980). These agents include lithium salts (1949), the antimanic and antipsychotic (neuroleptic) agents such as chlorpromazine (1952), the monoamine oxidase (MAO) inhibitors (1952), and the tricyclic or heterocyclic (imipramine-like) antidepressant agents (1957)(Baldessarini, 1977b). In addition, electroconvulsive therapy (ECT) continues to have a place in the treatment of very severe and acute mood disorders, especially life-threatening forms of depression (Fink, 1979).

The development of these modern medical therapies has had several important effects. First, these agents have provided relatively simple, specific, effective, and safe forms of treatment with a profound impact on current patterns of medical practice, for example, many depressed or

hypomanic patients can be managed adequately in outpatient facilities to avoid prolonged, expensive, and disruptive hospitalization which were formerly common. Second, partial understanding of the pharmacology of the new psychotropic drugs has led to imaginative hypotheses concerning the pathophysiology or etiology of severe mood disorders. These, in turn, have encouraged a revolution in experimental psychiatry in which the hypotheses have been tested in clinical research. Many of the earlier hypotheses have been found wanting or simplistic, nevertheless, they have led to increased understanding of the diagnosis, biology, and treatment of mood disorders and to newer research that represents a third level of development. This level is the focus of the present summary as it promises to have practical clinical benefits now and in the near future.

Diagnosis and Terminology

For the purposes of orientation, a few comments on psychiatric nosology and the nature of theorizing in biological psychiatry may be helpful. The diagnosis of the severe mood disorders is complicated by a number of sometimes confusing terms and associated concepts. The first important step was that of Kraepelin a century ago who boldly lumped a bewildering series of syndromes into the two major categories: manic-depressive illness (MDI) and dementia praecox (schizophrenia). The first syndrome (MDI) included all of the severe mood disorders (mania and melancholia), with or without an intermittent pattern of excitement alternating with depression (Winokur et al., 1970; Kraeplin, 1921). The MDI concept survives today as a generic term for severe mood disorders. Recent diagnostic schemes have led to several

ways of subdividing depressions. Most systems recognize some illnesses that are relatively minor ("neurotic," "reactive") and others currently referred to in the 1980 diagnostic Manual of the American Psychiatric Association as "major." The latter include severe depressions (with or without episodes of mania) marked by striking biologic signs and symptoms (such as loss of energy, libido, sleep, appetite, and intestinal function—all, typically, with some degree of diurnal rhythmicity), a tendency to remit and reoccur spontaneously, and apparent relative autonomy from life-events or stresses. Often (but not always) other psychiatric or medical illnesses are not present and there is a relatively high incidence of similar disorders among close family members. These characteristics have supported the use of such terms as "endogenous," "endogenomorphic," "vital," "psychotic," or "melancholic" depressions.

It is this subgroup of severe idiopathic illnesses that is most likely to respond favorably to modern medical treatments.

The apparently biological, vital, endogenous or autonomous and severe forms of depression must be differentiated from patterns of illness and demoralization that are commonly encountered in serious medical disorders, especially chronic infections, tumors, hepatic or renal failure, brain syndromes, intoxications, and metabolic or endocrine disorders (especially of the thyroid, parathyroid, and adrenal glands). In addition, a concept has arisen from a research need to define relatively homogeneous groups of depressed patients with “primary” depressions, that is, mood disorders without additional complicating medical or other psychiatric disorders (Fink, 1979). Clinically, the value of this concept (except as a reminder to consider fresh cases of mood

disorders with a medical differential diagnostic approach) is somewhat limited since some cases of "secondary" depression have striking endogenomorphic or vital characteristics and respond well to antidepressants.

Yet another diagnostic dimension that is useful clinically and in research derives from the concept of "bipolar" vs. "monopolar" mood disorders introduced by Leonhard (1962) as a way of subdividing MDI syndromes into those without a strong past and family history of psychotic or manic episodes. For etymologic consistency, the latter term has been changed to "unipolar" in the United States. The bipolar (BP/UP) dichotomy is now considered to represent recurrent alternations of mood from normal euthymia into depression or into excited, manic, dysphoric, or psychotic states, vs. recurrent depression alone. It is recognized that some BP patients move from

depression into mania (the so-called “switch process”) only on exposure to antidepressant drugs or ECT (Bunney et al., 1972),and that still others (so-called BP-Type II disorder) manifest mild, spontaneous *sub*clinical euphoria or hyperactivity alternating with clinical depression (Fieve et al., 1976). Since the evaluation and management of these two main subgroups of MDI (BP vs. UP) are dissimilar, and since their understanding can now be enriched by a consideration of recent genetic and biochemical findings, these will be summarized.

First, however, it may help orientation to reiterate that a major thrust of psychiatric research in severe mood disorders over the past 30 years has been to define biological characteristics of MDI patients that are diagnostically useful, which can help to optimize treatment, and which might even point the way

toward the pathophysiology or even the causes of these idiopathic conditions. While there has been considerable progress toward a biologically and clinically robust diagnostic scheme, and in understanding some characteristics that can help to guide treatment, search for primary causes has been unsuccessful so far. Indeed, virtually all of the biological characteristics of MDI patients that have been defined are “state-dependent” (that is, they disappear with recovery) and not stable biological traits or markers of a possible heritable defect (Gershon, 1978).Thus, while such state-dependent biological alterations can be most useful for diagnosis and for guiding therapy, from a theoretical perspective they may merely be concomitant variations or secondary changes within the MDI syndrome.

GENETICS

Family and genetic studies support both the search for biological explanations of MDI and for improved biomedical diagnostic and therapeutic evaluations of MDI patients. This approach indicates a strong genetic contribution in MDI generally, and provides especially strong support for the BP/UP distinction.[1] Thus, as a general rule, family histories of severe mood disorders (manic or depressive) tend to be stronger among first-degree relatives of BP patients. Recent family studies indicate that rates of mood disorders among first-degree relatives of BP cases are about twice those of relatives of UP depressives (Cadoret et al., 1971; Winokur, 1978) (Table 1) These morbid risk rates for UP depression are, in turn, at least two or three times above those of the general population, in which clinically significant mood disorders occur in about 3 to 5% of men and perhaps 6 to 8% of women over a lifetime (Slater

& Cowie, 1971; Winokur, 1978), although published prevalence rates of mood disorders have varied widely with diagnostic criteria and methods of ascertainment (Silverman, 1968). Studies by Winokur and his colleagues in the US Midwest indicated that risk rates exceeded 25% if a sibling and one parent were affected and exceeded 40% if a sibling and both parents had MDI (Tsuang, 1975); rates among close relatives tended to rise when the proband or index case had a UP depression of relatively early age of onset (below 40 years), and especially high morbid risk rates were found among relatives of BP or UP cases of the same sex (Winokur, 1971; 1978). In UP depression, female probands with an early onset tended to have an excess of female relatives with depressions, while male probands tended to have an excess of relatives not only with mood disorders, but also of male relatives with

sociopathic traits or alcoholism (Fieve et al., 1976). These various details can be diagnostically helpful in evaluating cases of mood disorder.

The Polarity Hypothesis

The early work of Leonhard that led to the current BP/UP concept was based mainly on the observation of an excess of psychosis in the family backgrounds of BP cases (Leonhard et al., 1962). There are now several additional studies that can be added to Leonhard's which support the conclusion that there is a more than threefold excess in rates of affective psychosis among first-degree relatives of BP over UP patients (Von Trostorff, 1968; Winokur, 1978)(Table 1). Leonhard also suggested that there may be familial differences in personality types in which close relatives of BP patients seem to have an excess of excited or hypomanic traits, while

relatives of UP patients may have more depressive traits (Leonhard et al., 1962).

Table 1. Family History in Bipolar (BP)and Unipolar (UP) Manic-Depressive Illness (MDI)

Illness in the 1° Relatives	*Rates in Relatives by Diagnosis in Index case*		
	BP	UP	(Ratio)
Mood disorder [a]	19	13	(1.5)
Mania or affective psychosis [b]	9.3	2.7	(3.4)
Bipolar MDI [c]	6.8	0.4	(17)
Unipolar MDI [c]	8.3	6.0	(1.4)

a Cadoret et al., 1970 & Winokur, 1978

b Leonhard et al., 1962; Von Trostorff, 1968; Winokur, 1978

c Gershon, 1978

Data are pooled from the reports and reviews cited. Note, for comparison, that a control population had only a 5.5% rate of mood disorders among first degree (1°) relatives, compared with 10% for relatives of index cases with MDI (Gershon et al., 1976). Since the rates of mood disorders vary markedly among studies, comparisons above are best made between columns, as is indicated by the BP:UP ratios. Note also that about half (40 to 70%) of mood disorders among relatives of BP index cases are *depression* only. (Mendlewicz, 1977)

Not only do psychoses appear more frequently among close relatives of patients with BP-MDI, but severe psychiatric syndromes tend to "run true" in families. Thus, while the morbid risk of severe

mood disorders (in a large series of hundreds of cases and family members evaluated "blindly" by Winokur and his colleagues [1978]) among relatives of MDI patients (UP or BP) was 10%, such illness appeared among only 3% of relatives of schizophrenic index cases—a rate that is similar to the value of 5.5% for relatives of normal subjects. Another clinically important point derived from follow-up studies is that the BP/UP distinction remains clinically robust over time. For example, the rates of altered diagnosis were only 3 to 5% whether comparisons were made after only a month of follow-up, or between a first and a second episode of illness, or after more than 10 years of follow-up.

While not specifically a genetic point, there are also compelling data that describe the natural history of recurrent manic-depressive illnesses from long-term follow-up studies (Grof et al.,

1974; Zis et al., 1980). For either BP or UP-MDI, the mean cycle-length *decreases* approximately logarithmically, from about three years from the initial episode, to about a year after the fourth or fifth, and to less than a year after the sixth or seventh. Put in other terms, the risk or recurrence within two years is about 50% in a 50 to 60-year-old UP, or a 40 to 50-year-old BP patient, but only about 20 to 30% for those in their twenties. That is, the risk of relapse in MDI (BP or UP) tends to *increase* with age.

Twin and Adoption Studies

A second important class of genetic data is derived from twin studies. Table 2 summarizes data from nine modern studies reviewed by several authors,[2] which indicate much higher concordance rates between identical (monozygote, MZ) twins than between fraternal

(dizygote, DZ) twins. In addition, the MZ/DZ ratio tends to be higher for BP illness than for UP cases. These data not only provide additional support for inherited contributions to risk for both BP and UP illness, but also suggest that this contribution may be stronger in BP-MDI (or that UP-MDI is a more heterogeneous cluster of syndromes).

Table 2. Twin Concordance Rates in MDI

	Concordance Rates by Index Diagnosis (%)	
Group	BP	UP
DZ	14	11
MZ	72	40
MZ: DZ Ratio	5.1	3.6

Data are pooled from reviews of nine published reports (Price, 1968; Zerbin-Rudin, 1969; Allen, 1976; Winokur, 1978). Overall concordance rates for MDI, irrespective of polarity are 68% and 19% for MZ and DZ twin pairs, respectively (MZ: DZ ratio = 3.6) (Winokur, 1978).The groups above include over 100 twin pairs. Among the rare instances (12 pairs) of MZ twins reared separately, the concordance rate for MDI was 75 per cent (Price, 1968).

A third important genetic technique that is aimed at separating contributions of environmental factors, learning, or experience

(the “nature vs. nurture” issue) is the adoption method. One of the few available studies of this type in MDI is that of Mendlewicz and Rainer (1977). They found a marked excess of mood disorders among the *biological* parents of the adopted proband cases (31% prevalence) over the adopting parents (12%). In contrast, adoptive and biological parents control adoptees without MDI, or parents of offspring with a chronic neurological disorder, had similarly low prevalence rates for MDI (6 to 10%), close to those expected in the general population, while the parents of *non*-adoptive manic-depressives had an expected high rate of MDI (26%). When all psychiatric diagnoses were included, the rates were 40% vs. 16% for biological vs. adopting parents of MDI index cases. Another study (Cadoret, 1978) found a 38% prevalence of primary depressions among a small number of adoptees, a biological parent of whom

had such a disorder, compared with only 7% among a larger number of adoptees without such a parental history of mood disorder. Still other preliminary data from a study of Danish adoptees(Kety et al., 1980) indicates a 6.5-fold excess of suicides among biological over adoptive relatives of 70 depressed adoptees. Again, strong support is provided by these several approaches for a familial, and probably an inherited contribution to the risk of MDI.

AMINE HYPOTHESES

The next question that arises is what the nature of the genetic contribution to risk of MDI might be. In short, this is not known, although the genetic data just reviewed encourage the search for biological as well as putative developmental or psychosocial factors in MDI. The most prominent of the hypotheses that have been considered over

the past two decades have implicated altered function of one or more monoamines acting as synaptic neurotransmitters at nerve terminals in the central nervous system (CNS). About the earliest formulations of such amine-based hypotheses concerning the biology of mood disorders were made by Everett and Tolman (1959) and by Jacobsen in 1959, although clinical studies of amine metabolism in MDI patients had been carried out by Weil-Malherbe (1967) even earlier in that decade. The most often mentioned amines have been the catecholamine norepinephrine (NE) (Schildkraut, 1970) or the indoleamine serotonin (5-hydroxytryptamine, 5-HT)(VanPragg, 1978) In addition, there have been considerations of altered function of acetylcholine (ACh)(Janowski et al., 1974) as well as of the catecholamine dopamine (DA)(Sjostrom & Roos, 1972), a transmitter in its own right as well as the

immediate precursor of NE. All of these substances are known to be synthesized, stored in, and released from specific neuronal fibers in the brain, spinal cord, or peripheral nervous system. These systems have been well-characterized and their detailed biology is reviewed elsewhere.[3]

They are especially well-suited, theoretically, to involvement in mood disorders. Thus, the CNS monoamine systems are widely and diffusely distributed and appear to subserve tonic background activities that occur over a long time base and include regulation of autonomic functions, arousal, sleep, sex and aggression, movement, diurnal cycles, and hypothalamic-pituitary function.

The Pharmacologic Basis of Amine Hypotheses

Support for this class of hypotheses derives mainly from the analysis of the differential actions

of drugs on behavior in experimental animals and mood in patients or other human subjects. This pharmacologic literature is large and complex[4] and the essence of it is summarized in Table 3. The main idea that arises from these observations is that treatments which deplete, inhibit the synthesis of, or block the actions of monoamines (notably, the catecholamines, CAs) tend to induce depression in susceptible subjects (Goodwin et al., 1972), or at least to induce sedation, behavioral underarousal, or antiautonomic effects; treatments that increase the availability or actions of the CAs have stimulating or arousing actions. The effects of increasing or decreasing the actions of 5HT or ACh tend to be opposite to those of NE or DA. That is, enhanced 5HT or ACh effects tend to be similar to diminished CA effects. This reciprocal tendency may seem confusing since most of the available

metabolic support for amine hypotheses in MDI, while suggesting a deficiency of CAs or an excess of ACh function, also suggests a deficiency of 5HT in depression. Perhaps the most reasonable way in which to consider such ideas is to suspect that any single-amine hypothesis that would account for the entire complex of signs and symptoms in MDI is almost certainly oversimplified, while altered function of individual amine systems might contribute to specific features of the syndrome. For example, it is not unreasonable to suppose that increased function of DA might lead to mania or psychosis (Melter & Stahl, 1976), while a lack of DA might lead to anhedonia and psychomotor retardation; that a deficiency of NE might lead to anergy and anhedonia too, or that its excess might contribute to agitation or mania; a lack of 5HT might also contribute to agitation and insomnia; that an excess of ACh might add to psychomotor

retardation and depressed mood; and that dysfunction in any of these systems might contribute to altered biorhythms that are now increasingly documented in MDI.

Table 3. Effects of Drugs on the Metabolism of Amines in the CNS

Type of drug	*Drug*	*Action*	*Behavioral effects*
Precursors	L-Dopa	DA increased	Agitation
	Tryptophan (TRY)	5-HT increased	Sedative usually, antimanic (?)
	Choline or lecithin	ACh increased	Depressant (?), antimanic (?)
Inhibitors of synthesis	α-Me-*p*-Tyrosine (AMPT)	Blocks tyrosine hydroxylase, lowers CA levels	Sedative, antihypertensive
	α-Me-dopa (Aldomet)	Blocks decarboxylase	Sedative, antihypertensive, depressant
	Disulfiram, fusaric acid	Block ß-hydroxylase, lower NE, raise DA	Little effect, some depression, some excitement on withdrawal
	p-Cl-Phenylalanine (PCPA)	Blocks tryptophan hydroxylase, lower 5-HT	Aggression, hypersexuality, insomnia
Decrease retention	α-Me-dopa*	False transmitter replaces endogenous CA	Sedative, antihypertensive, depressant
	Reserpine,* tetrabenazine	Block storage in vesicles, lower amine	Sedative, depressant, antihypertensive

		levels	
Alter membrane crossing	Amphetamines	Increase release, decrease reuptake (some MAO-inhibition)	Stimulant, anorexic, psychotogenic
	Cocaine	Decreases reuptake	Stimulant, euphoriant
	Heterocyclic antidepressants	Mainly block reuptake (weak MAO-inhibition), increase sensitivity of 5-HT, and a-NE receptors and decrease that of ß-NE receptors	Antidepressant
	Lithium salts	Decrease release of NE and DA	Antimanic, mood-stabilizing
Block receptors	Neuroleptics	Mainly DA-receptor-blockade	Antimanic, antipsychotic sedative
	Methysergide	Mainly indoleamine-receptor-blockade	Weakly antimanic (?), anti-depressant (?)
	Atropine	Blocks muscarinic receptors	Intoxicant
Inhibitors of catabolism	MAO-inhibitors	Block MAO, increase amine levels	Antidepressant, euphoriant

Polyphenols (e.g. butylgallate)	Block COMT	Little effect or toxic
Physostigmine	Block cholinesterase	Depressant (?), antimanic (?)

Abbreviations and symbols used: DA: dopamine; NE: norepinephrine; CA: catecholamine; SHT: serotonin; 5HTP: 5-hydroxytryptophan; Me: methyl; MAO: monoamine oxidase; COMT: catechol-O-methyltransferase.

*Note that depression associated with antihypertensive (anticatecholamine) agents is a problem in clinical practice. About 15% of patients on reserpine (especially those with a past history of MDI) reportedly become significantly depressed (timing is *unpredictable*).

It is important to realize that this way of developing biological hypotheses in psychiatric research has been dominant in the past 20 years. Despite the attractiveness and seeming rationality of this inductive approach, it suffers from potentially fallacious logic when applied to pathophysiology or etiology. Thus, a typical proposition is that if anti-depressant treatments tend to increase the function of NE or 5HT[5] (see Table 4), and antimanic treatments tend to diminish the function of CAs (Baldessarini, 1980), then their opposite might reflect the

pathophysiology of the illness under treatment. While such notions might be heuristic or experimentally testable, they may be no more logical than to assume a penicillin deficiency state in general paresis (even though the drug helps the illness), or a renal tubular defect in congestive heart failure (even though thiazide diuretics remove edema). Moreover, they are based on a still very incomplete understanding of the actions of mood-altering agents.

Table 4. Actions of Heterocyclic Antidepressants

Acute (hours)

- Block uptake of NE or 5HT[a]
- Reduce turnover of NE or 5HT[b]
- Reduce firing rates of NE or 5HT
- Block 5HT, ACh (muscarinic), NE (α_1), and histamine ($H_1 >> H_2$) receptors[c]

Later (weeks)

- Block uptake of NE or 5HT
- Return of NE turnover and firing rates[b]
- Decrease NE (β) and NE ($\alpha 2$, presynaptic) receptor sensitivity[d]
- Increase NE release[e] (α_2 effect?)
- Increase $5HT_2$ and NE (α_1) receptor sensitivity[f]

a Not true of certain experimental antidepressants, notably iprindole, while some receptor changes can occur with iprindole. (Glowinski J, Baldessarini RJ, 1966)

b Schildkraut JJ, Roffman M, Orsulak PJ, et al, 1976

c Fuxe K, Ogren S-O, Agnati L, et al., 1977; Snyder SH, Yamamura H, 1977; U'Prichard D, Greenberg DA, Sheen PP, et al., 1978; Richelson E, 1979

d Crews FT, Smith CB, 1978; Vetulani J, Stawarz RJ, Dingel JV, et al., 1976

e Crews FT, Smith CB, 1978

f Wang RY, Aghajanian GK, 1980;

One additional curious effect of the amine hypotheses has been their interaction with the

process of developing potential new mood-altering agents. In general, there have been remarkably few fundamentally new medical treatments for MDI since the somewhat fortuitous clinical discovery of the antidepressant effects of MAO inhibitors (MAOIs) and imipramine, or of the antimanic actions of lithium salts and chlorpromazine—all prior to 1960 (Baldessarini, 1977b). A partial understanding of the actions of these agents focused attention on their interactions with the monoamines (Table 4), and may have contributed to screening tests that have led to ever-larger numbers of similar agents, as well as a possibly excessively narrow focus on such amines in the pathophysiology of MDI. Most of the newer antidepressants have been discovered by screening compounds for blocking actions against CA-uptake (e.g., amoxapine, trimipramine, maprotiline, mianserin, nomifensin,

viloxazine, and metabolites of clomipramine), 5HT-uptake (e.g., clomipramine, femoxetine, trazodone, and zimelidine), or MAO activity (e.g., chlorgyline) (Pinder, 1980; Zis & Goodwin, 1979). Iprindole may be a notable exception, although its efficacy in severe endogenous depressions is not well established (Zis & Goodwin, 1979).

The attempt to test the amine hypotheses of MDI in clinical experiments has led to much work using several clever clinical research strategies that are summarized in Table 5. Most of this work has involved tests of a CA or a 5HT hypothesis.[6]

Table 5. Clinical Strategies to Test Amine Hypotheses in MDI

1. Interpretation of differential drug responses (improvement vs. worsening)*
2. Precursor loading (tryptophan, 5-hydroxytryptophan, dopa)*
3. Metabolite excretion vs. clinical state or treatment (esp. urinary 5-hydroxy-indoleacetic acid [5HIAA] or 3-methoxy-4-hydroxy-phenethylene-glycol [MHPG])
4. CSF metabolites (basal or after probenecid to block removal) vs. diagnostic or clinical state (5HIAA, MHPG,

vanillylmandelic acid [VMA], or homovanillic acid [HVA])

5. Neuroendocrine responses that may be secondary to altered amine function (cortisol or ACTH, growth hormone, prolactin)
6. Postmortem levels of brain metabolites (DA, NE, 5HT, MHPG, HVA, 5HIAA), esp. in suicides
7. Enzyme activities (brain, plasma, platelets, rbc) (tyrosine hydroxylase, dopamine-β-oxidase [DBH], MAO, catechol-O-methyltransferase [COMT])

*As in Table 3.

Comments on Amine Hypotheses

Overall, the *clinical* research evidence favoring amine deficiency or excess hypotheses in MDI is weak. The effects of experimental pharmacologic interventions (Table 3, excluding accepted standard treatments with heterocyclic antidepressants (HCAs), MAOIs, Li^+, and neuroleptics) do not provide compelling support. For example, loading patients with amino acids that are precursors of amines[7] or trials of inhibitors of amine synthesis[8] are both known to alter amine turnover in human CNS, based on studies of CSF metabolites (Post & Goodwin,

1978).

Yet, they have not provided a useful antidepressant or antimanic treatment to date. Stimulants such as amphetamines provide a most interesting *model* of MDI as intoxication in stimulant abusers results in lithium-sensitive euphoria (Angrist B. Gershon S, 1979), followed by agitation and paranoid psychosis (as in mania), followed by depression ("crashing").[9] Nevertheless, their effects in clinical depression are, at best, transitory in most cases, and they worsen agitation in many cases.[10] In mania, stimulants or DA agonists can even induce a paradoxical beneficial effect.[11] Interesting preliminary suggestions of benefits have recently been obtained with the 5HT agonist fenfluramine in mania and depression (Murphy et al., 1978a) and the DA agonist piribedil in depression (Post & Goodwin, 1978), and with the NE-α agonist

clonidine (Jouvent et al., 1980) and anticholinesterase physostigmine (Janowsky et al., 1973), as well as the ACh precursor choline (or lecithin) in mania (Davis & Berger, 1978; Lipinski, 1980). These observations have arisen directly from attempts to test amine hypotheses. It is also important to realize that certain antihypertensive (antisympathetic, or anti-NE) agents such as reserpine and α-methyl-dopa (Aldomet) are associated with clinically significant depression (Goodwin et al., 1972; Garver & Davis, 1979).

In metabolic tests of amine hypotheses, the CAs (Table 6) and serotonin (Table 7) are, by far, the most extensively evaluated. Data for Tables 6 and 7 were obtained from previous reviews concerning CAs,[12] 5HT,[13] or both.[14] As these tables illustrate, the data supporting a deficiency of CAs or 5HT in depression and the opposite in mania are, frankly, meager and inconsistent. One

of the few repeatedly observed relationships is a fall in urinary MHPG with depression and its return to normal values with recovery (Schildkraut, 1978) or switch into mania (Bunney et al., 1972). There are also suggestions that low MHPG may be more characteristic (or more easily observed) in BP depression (Schildkraut, 1978). There are several reports of attempts to predict responses to specific types of heterocyclic antidepressants (HCAs) from initial values of urinary MHPG excretion. The idea has been that low MHPG may predict responsiveness to drugs with relatively strong effects on NE neurons (desipramine or imipramine), whereas higher values may predict responsiveness to HCAs more selective for 5HT systems (clomipramine or amitriptyline) (Goodwin et al., 1978).

Table 6. Clinical Guidance Concerning a Catecholamine Hypothesis

	Measure	*Available Studies (N)*	*Proportion Supportive*	*Comments*
1.	Postmortem Regional Brain Chemistry			
	A. NE	3	33%	
	B. DA	3	33%	
	C. HVA	1		Regions inconsistent; one study found HVA higher.
2.	Urinary MHPG			
	A. All depressed	11	82%	Most studies are from three labs with small N and much overlap in small decreases among Dx groups and controls.
	B. BP vs. UP	3	100%	All three found BP 30% lower; two also found depressed schizoaffectives (?BP) lower than UP (36%), but these differences are similar to interlab differences in same Dx groups.

	C. To predict TCA response	9	67%	Most studies dealt with few variables, with small mean N = 12; two other studies unable to draw conclusions due to high response rates or high MHPG variance.
3.	CSF Metabolites (Depression)			
	A. [MHPG]	5	40%	Poor correlation with urine MHPG; cannot use probenecid for MHPG; probably unchanged in mania but not adequately studied.
	B. [MHPG]	1	0%	
	C. [VMA]: Basal	12	67%	UP tend to have lower VMA; with probenecid, not all significantly lower; suggest sub-groups.
	Probenecid	9	67%	
4.	CSF Metabolites (Mania)			
	Basal	6	0%	All studies found low or normal VMA; one found increased rise of VMA
	Probenecid	3	33%	
5.	Enzyme Activities			

A.	Platelet MAO	7	14%	Four studies suggest *low* MAO: in BP two found lower, one higher than UP.
B.	RBC COMT	5	20%	Two studies found *low* COMT; another suggested better response to HCA with lower COMT.
C.	Plasma DBH	6	20%	One study found low DBH (in UP cases).

(*)Note that the illustrative summaries in Tables 6, 7, and 8 are not exhaustive reviews of every study reported; abbreviations are explained in Table 3.

Table 7. Clinical Evidence Concerning a Serotonin Hypothesis in MDI

Measure	*Available Studies (N)*	*Proportion Supportive*	*Comments*
1. Postmortem Regional Brain Chemistry			
A. 5HT	7	51%	Only 10% mean decrease in most studies.
B. 5HIAA	5	40%	Only 15% mean decrease, but very inconsistent among CNS regions.
2. [5HT] or [TRY] in Plasma or CSF	5	20%	Small changes, highly inconsistent.
3. CSF [5HIAA] in Depressions			
A. Basal	15	47%	Up to 70% decrease in four studies; trend to decrease in 12, but increases in two studies; *subgroup* suggested.
B. Probenecid	9	67%	Up to 60% less accumulation.
4. CSF [5HIAA] in Mania			

	A. Basal	3	67%	Decreased in *UP* only
	B Probenecid	3	33%	Decreased in *BP* only; these results contradictory, but 3/6 do suggest ca. 30% decrease in UP + BP series.
6.	Effects of TCAs on CSF [5HIAA]	8	100%	All find decreases of 10-49% in basal and 31% less rise after probenecid.
7.	TRY or 5HTP as Antidepressant	10	40%	Only one double-blind pos. study but 40% suggest some possible benefits alone or with HCA, MAOI or ECT; CSF 5HIAA does rise.
8.	PCPA as Antimanic (blocks 5HT synthesis)	1	0%	Not effective in mania; effects in depression poorly evaluated.

However, these ideas are based on the study, to date, of a total of only 71 low MHPG cases and 53 with high MHPG; and at least four recent studies have failed to support the predictions (Spiker et al., 1980) or produced equivocal results

(Hollister et al., 1980). Furthermore, the marked interindividual and interlaboratory variance in MHPG assays suggests that this approach may not lead readily to practical routine clinical methods (Hollister et al., 1978). Indeed, the diurnal variance (ratio of standard error to mean) in MHPG excretion is about 30%-40% in normals and MDI patients, while the mean difference between controls and BP or UP depressed cases is only about 20%-40% (Wehr et al., 1980). Other recent findings, furthermore, cast doubt on the idea that urinary MHPG levels may selectively reflect NE metabolism in the CNS in that much of MHPG is converted to VMA, and 20% or less of urinary MHPG may derive from central NE metabolism (Blombery et al., 1980).

Among studies of indoleamine metabolism, some encouragement has come from studies of cerebrospinal fluid (CSF) levels of the main 5HT

metabolite, 5HIAA (Table 7).[15] These results suggest that a *subgroup* may be defined by low 5HIAA levels among MDI cases. These patients may be either UP or BP and are not readily separable by other clinical characteristics. One intriguing proposal emerging from the work of Asberg, Van Praag, Maas, and Goodwin and their colleagues is that low CSF levels of 5HIAA may correspond with normal levels of urinary MHPG (serotonin deficiency, or in Maas' terminology, "Type-B" depression), and correlate with selective responsiveness to 5HT-enhancing agents such as precursor amino acids or clomipramine or amitriptyline (Goodwin et al., 1978; Maas, 1975). Conversely, normal CSF levels of 5HIAA and low urinary MHPG (NE deficiency or "Type A") may define a group of endogenous depressions who respond selectively to drugs that selectively enhance NE transmission (e.g., desipramine,

imipramine)— an effect that may be predicted by an acute activating effect of a test dose of *d*-amphetamine (Corsini et al., 1977). The proportion of low to normal CSF 5HIAA cases (Types B:A) is about 1:4, based on limited available data (Goodwin et al., 1978). Unfortunately, this approach may not be practical for routine clinical application, due again to the variance of the MHPG measurement, as well as the variance in 5HIAA values (ca. 30%, or about the same as the mean difference between levels in HCA-responsive vs. nonresponsive depressed patients), as well as the impracticality of routine lumbar punctures (Post & Goodwin, 1978).

Urinary assays of 5HIAA have been found not to be a useful alternative (Murphy et al., 1978a; 1978b). In addition, there is a suspicion that much of the apparent bimodality of distribution of CSF levels of 5HIAA may be due to the inexact

matching of groups by sex (males tend to have lower values) (Post & Goodwin, 1978). If a biologically and clinically meaningful subgroup can be defined by such an approach (regardless of applicability to clinical practice), much more study will be required. One other result of studies of CSF metabolites is that there is now strong agreement (all of eight studies) that HCA treatment regularly leads to decreases of 5HIAA) (Post & Goodwin, 1978)., a result that accords well in theory with recent evidence that HCAs increase sensitivity of central 5HT receptors (Wang & Aghajanian, 1980) (Table 4). There is also weak evidence that ECT may also lower CSF levels of 5HIAA (Post & Goodwin, 1978), and MAOIs, of course, directly prevent formation of this deaminated metabolite.

NEUROENDOCRINE FINDINGS

It has been known or suspected for many years

that the regulation of hormone metabolism is altered in severe psychiatric illnesses. More recently, several specific abnormalities have been described that are apparently characteristic of MDI.[16] Some of these have been studied in the context of seeking metabolic signs of putative abnormalities of amine functions in the limbic system and hypothalamus that may lead to dyscontrol of the release of hormones from the anterior pituitary. This approach has also encouraged clinical investigators to evaluate pathophysiologic features of MDI for their own sake, and without the necessity of testing a preconceived body of theory. Simultaneously, there has also been increased interest in the clinical utility of endocrine measurements as laboratory tests to aid in diagnosis and treatment of patients. Several of the well-evaluated or still preliminary endocrine findings in MDI are

summarized in Table 8, based on the reviews already cited[17] and studies cited below.

Table 8. Neuroendocrine Responses in MDI

Hormone		*Change*	*UP vs. BP*	*Data Quality*
Cortisol				
Basal		increase	BP = UP	good
Rise with ACTH		increase	?	good
Brain cortisol		decrease	?	weak
DST:	depressed	breakthrough	BP ≥ UP (?)	very good
	manic or euthymic	suppressed	—	good
ACTH level		(?)	(?)	poor
Growth Hormone				
Basal		none	—	fair
Stimulated (by insulin or CA agonists)*		decrease	UP > BP	good
TSH				
Basal		none	—	fair
TRF-Stimulated:	depressed	decrease	1° UP ≥ BP (?)	fair
	manic	decrease	—	fair
Prolactin				
Basal:	mean	decrease or no change	BP > UP	fair
	rhythm	diminished	BP = UP	weak
Dopa	(decrease)	normal	—	weak
Morphine	(increase)	less	BP = UP	fair

		(?)	
Luteinizing Hormone			
Basal	small decrease	UP = BP	weak
Testosterone			
Basal	none	—	weak

(*)amphetamines, dopa, clonidine, desipramine have all been used as NE agonists. See text for references.

The Hypothalamic-Pituitary-Adrenal Axis

It has been known for more than a decade that severe depression is associated with excessive secretion of cortisol from the adrenal cortex. Sachar and others applied the technique of 24-hour sampling of blood through an indwelling venous catheter to permit detection of "spikes" of release of cortisol and evaluation of their diurnal rhythm (Sachar et al., 1973). This approach revealed that spikes were higher and more frequent, and that the normal day-night rhythm was less obvious in depression. Although this markedly increased release of cortisol was at first

thought to reflect psychotic disorganization in severe MDI (Sachar, 1976; Sachar et al., 1973), Carroll and colleagues found that similarly agitated and disorganized schizophrenic subjects failed to show a similar high output of cortisol (Carroll, 1976; Carroll et al., 1976). More recently his group and several others have virtually abandoned the use of simple measures of cortisol level in plasma or urine in favor of a *dexamethasone suppression test* (DST), which has recently been established as a relatively simple diagnostic test of great specificity and power, comparable to, or exceeding in clinical utility, many laboratory tests that are considered standard in clinical pathology and medical practice (Carroll, 1981; *Lancet*, 1980).

The DST has been standardized as follows (Carroll, 1981): The synthetic glucocorticoid is given in an oral dose of 1.0 mg at bedtime on day

one. On day *two,* plasma samples are collected at 4:00 and 11:00 PM for inpatients, or sometimes for simplicity and convenience for outpatients, at 4:00 only. Normally, adrenal function is strongly suppressed by dexamethasone through hypothalamic-pituitary mechanisms that inhibit release of ACTH for up to 48 hours. In endogenous depressions, the suppressing effect is incomplete and short-lived. A criterion of 5 μg/dl (50 ng/ml) has been established as a cut-off, *above* which the DST is said to be *positive.* The use of the afternoon and evening samples can detect about 98% of all positive results, while the afternoon sample, by itself, finds about 79%. While the test is highly selective for primary endogenous depressions (few false positive results), it confirms the diagnosis in only about 60% of cases. Only about 4% of normal persons have a false positive DST result. While the test detects UP and BP cases,

rates of positive DST are somewhat higher in BP cases and a family history of a major mood disorder can increase the rate of positive tests to 80-90% (Carroll et al., 1981; Schlesser et al., 1980). Perhaps the greatest power of the DST lies in *negative* results, which almost certainly *exclude* the diagnosis of MDI.

The DST effect in depression is not due to abnormal metabolism of dexamethasone, nor is it related in an important way to age (age accounts for only 2% of the variance) (Carroll, 1981). While there had been suggestions that severity of depression may contribute to changes of a positive DST, this is now thought not to be an important factor. Thus, groups of patients with primary vs. secondary depressions of well-matched severity were clearly distinguished by DST. In addition, the correlation between severity of depression as assessed by standardized rating scales and 4:00

PM cortisol levels the day after a dose of dexamethasone is reportedly very weak (r = +0.20). The use of DST under standardized conditions similar to those outlined above has recently been well replicated in several American and European psychiatric centers in studies involving nearly 1,000 depressed patients.[18]

Potential problems in applying the DST can occur (Carroll, 1981) during pregnancy, the use of high doses of estrogens (ordinary menopausal replacement therapy and the use of contraceptive steroids are not a problem), Cushing's disease, corticosteroid therapy, uncontrolled diabetes, use of reserpine or narcotics, severe weight loss, serious medical illness, and some organic mental syndromes. Ordinary doses of antidepressants, lithium salts, and neuroleptics seem not to produce problems, while high doses of benzodiazepines and use of sedatives and

anticonvulsants (induce hepatic drug- and steroid-metabolizing enzymes) can all produce spurious results.

While theory indicates that the DST phenomenon in depression is due to dyscontrol of ACTH release, there has been little direct evaluation of plasma ACTH in depression. It is also suspected that NE and 5HT play important roles in the control of ACTH release at the level of the limbic system and hypothalamus. Nevertheless, the precise role of monoamines in the control of ACTH in man remains unclear due to some pharmacologic effects in primates or man that seem *not* to fit models derived from laboratory animals indicating an inhibitory control of corticotropin (ACTH) releasing factor (CRF, a peptide hormone produced in hypothalamus) by NE-α or DA effects, and facilitation of CRF release by 5HT (Ettigi & Brown, 1977).

The DST phenomenon is clearly state-dependent as cortisol levels tend to fall with treatment and recovery, and they are not elevated in mania. There have, as yet, been few studies attempting to correlate the DST with other biological measurements in depression, but several are currently under way. Also, provocative preliminary attempts to use DST as a predictor of response to HCAs or of risk of relapsing (Goldberg, 1980) have so far been somewhat inconsistent and require further study (Carroll, 1981).

Other Neuroendocrine Response

Other endocrinologic characteristics of depressed patients are much less well evaluated than is cortisol and the DST, although their highlights are summarized in Table 8. Growth hormone (GH) is known to be released by NE-α, DA and 5HT agonists, but again comparisons

between lower animals and primates or man are uncertain (Ettigi & Brown, 1977). Several laboratories have reported that while basal levels of GH are normal in depression, their response to a variety of NE agonists is low (Carroll, 1981). These state-dependent differences do seem to differentiate primary endogenous depressed from neurotic patients and normals, but so far do not differentiate UP from BP MDI; mania has not been evaluated adequately. GH responses to NE agonists yielding plasma levels below 4 ng/ml are reported to differentiate primary from secondary depressions fairly well in nearly a dozen studies, although low values have been found in about one-third of normals or patients with secondary depressions. Nevertheless, a high value can rule out endogenous primary depression in 70% to 90% of cases. Among the problems associated with GH response tests in depression are

invalidation by the HCAs, and spurious results by the mere insertion of a venous catheter, or if the patient falls asleep during a test (Carroll, 1981).

While most thyroid function tests are in the normal range in MDI, several laboratories have reported diminished elevations of thyroid stimulating hormone (TSH) by intravenous injections of thyrotropin (TSH) releasing hormone (the peptide, TRH) in severe depression, and possibly also in mania (Prange et al., 1977). Release of TRH from the hypothalamus may be stimulated by NE and DA and inhibited by 5HT but not by Ach (Ettigi & Brown, 1977). Results are conflicting, or very preliminary, whether the TRH-TSH test may help to differentiate UP from BP cases (TSH responses may be slightly more blunted in UP-MDI) (Bjorum & Kirkegaard, 1979), or to separate mania and schizoaffective illness (which may be closely related to. if not

synonymous with, MDI) from chronic schizophrenia, which reportedly has normal TSH responses to TRH (Extein et al., 1980). To some extent the TSH response may be confounded by interactions of high cortisol levels (Carroll, 1981). A potentially important recent observation is that the blunted TSH response to TRH in primary UP depression may, to some extent, represent a *trait,* as it persisted following recovery in 69% of a small group of patients (Asnis et al., 1980).

Release of prolactin (PL) is known to be inhibited by DA, and facilitated by 5HT (Ettigi & Brown, 1977) as well as opiates (Gold et al., 1980a). While there are few studies of PL in depression, there are recent suggestions that BP depressed patients may have somewhat lower basal plasma levels of PL and a blunted release during sleep (Mendlewicz et al., 1980), and that depressed patients generally may have a blunted

PL release in response to infusion of an opiate (Gold et al., 1980a).

NEUROPHYSIOLOGICAL FINDINGS

Patients with MDI have altered sleep EEG patterns, as might be anticipated in view of classic alterations in sleep behavior. It was reported by Kupfer in the early 1970s that key features in severe depression are a shortened latency between first falling asleep and the start of the first period of rapid-eye-movement (REM) or "dreaming" phases of sleep, and increased REM activity throughout the night (Kupfer & Foster, 1972). These characteristics can now be used successfully to differentiate primary endogenous depressions from secondary depressions associated with other medical or psychiatric illnesses, or from other forms of insomnia, in over 80% of cases . [19]This observation has been

replicated by several investigators and appears to rest on solid ground. Some typical values for changes in REM latency are summarized in Table 9.

Table 9. REM Sleep Latency in Psychiatric Disorders

Diagnosis	*REM Latency* (Min ± SEM)
Controls	109 ± 12
Schizophrenics	95 ± 12
Neurotics	87 ± 5
UP-MDI	45 ± 5*
BP-MDI	43 ± 6*

Severe depression was associated with latency as short as 18 min. Schizoaffective cases were indistinguishable from MDI.

From Kupfer et al. 1972; 1978

(*)Significant

This test does not seem to differentiate UP from BP MDI. It is not yet adequately evaluated in mania (technically very difficult), but is clearly state-dependent and to some degree reflects the severity of depression. It has been reported that ACh agonists can mimic the changes found in

depression (shorten REM latency in normals) (Gillin et al., 1979). Other pharmacologic observations include indications that initial REM latency per se does not help to predict responsiveness to antidepressant therapy. On the other hand, Kupfer and colleagues found that the degree of prolongation or suppression of REM onset during the first two nights following test doses of a HCA predicted the clinical response to a month of treatment (Kupfer et al., 1976) and correlated significantly with plasma levels of the drug, but poorly with urinary MHPG excretion (Kupfer et al., 1979). Further studies are under way in which several metabolic and hormonal variables are evaluated along with sleep EEG patterns.

These studies on the tendency for REM sleep to be increased in depression, and for antidepressants to suppress or delay REM

sleep[20] lead to the hypothesis that REM-suppression or other sleep-altering effects of antidepressant treatments may be an important clue to their mechanism of action (Vogel et al., 1980). These concepts have been given further support by recent provocative claims of antidepressant effects of selective deprivation of REM sleep by deliberately awakening patients (Vogel et al., 1980) or, more paradoxically, by brief partial deprivation of all phases of sleep (Schilgen & Tolle, 1980).

One other EEG characteristic that has been suggested by Buchsbaum and his colleagues as capable of differentiating UP from BP cases of MDI is the pattern of response of EEG potentials evoked by sensory stimuli of increasing intensity (the average evoked response, AER test) (Buschbaum et al., 1973). BP cases are said to tend to increase EEG amplitudes with increasing

stimulus intensity (“augmenters”), while UP cases have an opposite response, at least at strong stimulus intensity (“reducers”). This test has not yet been widely evaluated by other investigators and its significance and possible utility remain unclear. In general, EEG and sleep EEG techniques are not readily available in clinical practice, but for those with access to clinical or research sleep laboratories, the REM latency test can be helpful in evaluating complex or confusing cases.

OTHER APPROACHES

There is now a large literature and clinical experience with the use of chemical assays of blood levels of HCAs to aid in providing optimal treatment regimens for depressed patients. These can be quite helpful in the management of patients with atypical responses (no response or toxicity) or at high risk of intoxication (especially the

elderly or cardiacs). In general, blood levels of the parent compound and its major metabolite above 100 ng/ml are associated with favorable antidepressant effects, while levels above 500 ng/ml present high risk of intoxication. This topic has been reviewed elsewhere recently (Baldessarini, 1979b). One additional use of blood drug assays is to predict individual requirements for a TCA. Thus, several groups have found, for example, very high correlations ($r > + 0.90$) between plasma levels of antidepressant 24 hours after a single test dose and those found after several weeks of treatment of the same patient with a therapeutic dose.[21]

An additional biological measurement that can be helpful in defining an effective dose of an antidepressant is the criterion of inhibiting blood platelet MAO activity by > 80%, during treatment with phenelzine (Nardil) (Murphy et al., 1977;

Robinson et al., 1978). The observed correlations between strong inhibition of platelet MAO and optimal clinical antidepressant effects have encouraged use of larger doses of phenelzine (45 to 90 mg/day) than were common in the past (Robinson et al., 1978). Whether similar correlations will hold up for other MAOIs is not certain. Some preliminary data suggest that this approach may be feasible with isocarboxazid (Marplan), but probably not with tranylcypromine (Parnate), as the latter produced strong MAO inhibition at clinically ineffective doses (Giller & Lieb, 1980).

Surprisingly few studies have aimed at evaluating CA hypotheses by measuring cardiovascular responses to infusions of NE agonists, and the few which have been done have, inconsistently, suggested lesser (Prange et al., 1967) or greater (Friedman, 1978) responses in

depressed patients than in normals; the possible influence of prior antidepressant treatment in these studies is unknown. There are several intriguing recent reports of altered indices of CA receptor function in blood cells in MDI as well. These include reports of diminished binding of ^{3}H-dihydroalprenolol (which labels β receptors), or of responses of isoproterenol-sensitive (β - receptors) adenylate cyclase in platelets or leucocytes from depressed or manic patients (Pandey & Dysken et al., 1979; Extein et al., 1979). These changes are believed to be state-dependent and not to be artifacts of drug treatment (Extein et al., 1979). In addition, the binding ^{3}H-imipramine to platelet membranes is reportedly diminished in MDI, although the significance of this form of "receptor" labeling is not yet clear (Briley et al., 1980). Still other uses for blood cells have also been reported. There have been repeated

suggestions that erythrocytes (rbc) from BP-MDI patients are dissimilar to UP or normal subjects in their ability to transport monovalent cations, notably Li^{+}, in that a high ratio of rbc:plasma Li^{+} concentration might predict clinical responses to lithium therapy (Ramsey et al., 1976; Cooper et al., 1976), or that defective Na^{+}/Li^{+}exchange processes may be inherited characteristics of MDI patients and their first-degree relatives (enduring traits) (Pandey & Dorus et al., 1979). Unfortunately, these leads have not held up well to critical attempts at replication.[22] One other lead concerning altered electrolyte metabolism in MDI is the suggestion made by Coppen and his colleagues in the 1960s that "residual" or intracellular levels of sodium may be increased (Coppen, 1965).

Another emerging strategy in biological research in MDI is to measure a variety of

physiological and biochemical changes in patients as a function of time of day, as it has long been recognized that altered diurnal rhythmicity is a hallmark of the syndrome. Wehr, Goodwin and colleagues have been using this approach intensively and found recently that depression is associated with temporal *delays* in the diurnal peak (acrophase) of body temperature, motor activity, and MHPG excretion.

These peaks are delayed by perhaps 1.5 hours in depression, and even longer (about two hours) in mania (Wehr et al., 1980). They suggest that dyscontrol of diurnal rhythms may be an essential feature of the pathophysiology of MDI and that mania and depression may not be biological "opposites." In addition, recent experimental therapeutic interventions aimed at altering the timing of sleep and activity in depressed patients[23] may be effective by their interactions

with altered regulation of diurnal bodily rhythms (Wehr et al., 1979).

For the future, there is a new class of technical advances which will almost certainly have a profound impact on research and clinical evaluations of the CNS in psychiatric and neurological illnesses. These include improved methods of evaluating cerebral flow in man, which are beginning to suggest regionally selective decreases in depression (Matthew et al., 1980). Thus far, computer-assisted x-ray tomography (CT scanning) of the brain has not been fruitful in MDI, but still newer scanning methods are just starting to emerge. These include methods for evaluating regional differences in the rate of glucose utilization, the application of positron-emission tomography (PET), and the use of nuclear magnetic resonance (NMR) scanning methods (Phelps et al., 1980). These new techniques

promise to revolutionize the clinical investigation of the abnormal structure and function of the intact human brain.

CONCLUSIONS

For the present, it is clear from the material reviewed above that there have been remarkable advances in the application of biomedical methods to the evaluation of patients with severe manic-depressive illnesses. There has been a trend to move away from attempts to support or refute biological hypotheses derived inductively from a partial understanding of the effects of psychotropic drugs, toward a more neutral and descriptive approach. This approach has provided powerful and compelling support for genetic and metabolic characterization of the MDI syndrome and of its unipolar and bipolar variants. A summary of these characteristics is provided in

Table 10. In addition, biological strategies have helped considerably to sharpen our ability to provide more nearly optimal application of available, though imperfect, antidepressant, anti-manic, and mood-stabilizing medical therapies as improved treatments are being sought, as will be discussed further in a future issue of this Journal.

Table 10. Clinical Features of BP/UP MDI

Feature	*BP*	*UP*
Mania, hypomania	+ + + +	0
Family History of psychosis or mania	+ + +	+
Mood switches (spont. or Rx-induced)	+ + + +	0
Median onset (yrs)	26	40
≥ 5 episodes (%)	18	6
F/M sex ratio	1.4	1.9
Psychomotor retardation	+ +	+
Hypersomnia	+ +	+
Insomnia	+ + +	+ + +
Diurnal changes	+ + +	+ +
Agitation	+	+ + +
Anger in depression	+	+ + +
Somatic or neurotic sx	+	+ + +
Reduced REM latency	+ +	+ +
DST nonsuppression	+ + +	+ +
Low urinary MHPG	+	±
Li as antidepressant	+	±?
Prophylaxis	Li	TCAs
Average evoked EEG response	augmentation (?)	reduction (?)

A general criticism of the field is that the practical application of some of the better clinical tests has been remarkably slow. Some (notably the DST and blood antidepressant assays) are adequately developed for routine clinical use. Other endocrine measures and the REM-latency test can be applied almost routinely in advanced treatment and teaching centers. It is also remarkable that more cross-validation among tests and clinical data in the *same patients* at the same time has not been undertaken.

SUMMARY

Severe mood disorders are among the most common major psychiatric disorders in medical practice, with risk rates of about 5 per cent. Theory and management of manic-depressive illnesses (MDI) has virtually been revolutionized with the development of psychopharmacology

since 1950. Effective short-term and preventive treatment of depression is afforded by heterocyclic and experimental antidepressants as well as monoamineoxidase inhibitors; neuroleptic agents are highly effective in mania and lithium salts are especially useful in long-term management of MDI. The action mechanisms of these agents have become increasingly rich and complex in recent years, with much current focus on their ability to alter catecholamine and indoleamine receptors in brain tissue; late effects are typically dissimilar to immediate actions. Theories concerning the pathophysiology of MDI have in the past been heavily, perhaps unduly, influenced by such partial understanding of drug actions. The resulting *inductive* approach to formulation and testing of hypotheses has enriched psychiatric research and supported progress in pharmacology. Nevertheless, searches

for direct metabolic support for amine hypotheses of MDI in clinical studies have led to an ambiguous and inconclusive literature. Recent trends in MDI research have moved beyond the testing of amine hypotheses to enrich the clinical descriptive, diagnostic, genetic, endocrinologic and neurophysiologic understanding of the syndromes of MDI. These approaches have led to compelling support of bipolar and unipolar subtypes of MDI, to diagnostic laboratory tests at least as robust as those used in general medicine, and to unprecedented enlightenment in the clinical management of manic and depressed patients. These developments represent the most substantial contributions of a biomedical approach to psychiatry to date, and support the clinical and scientific value of the approach.

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