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Advances in Psychopharmacology

Predicting and Improving Treatment Response

Edited by
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Advances in Psychopharmacology: Predicting and Improving Treatment Response

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INTRODUCTION

IMPROVING AND PREDICTING RESPONSE TO PSYCHOTROPIC MEDICATIONS

The current generation of widely effective psychotropic drugs were developed — often fortuitously and always empirically — during the decade following World War II. Most of the subsequent 25 years have been spent in generating and testing theories on the etiology of the major mental disturbances, based in large part on their response to these agents. Pharmacology provided both the impetus and the principal lines of evidence for the dopamine hypothesis of schizophrenia and the noradrenergic and indoleaminergic hypotheses of mania and depression.

Only in recent years have a few groups of investigators admitted a degree of scientific nihilism in this search for etiologies and focused their explorations on a far more pragmatic concern — how to predict which subgroup of patients with a particular psychiatric diagnosis will respond to a particular pharmacological agent. Researchers had neglected clinicians and clinical research issues for so long that few, if any, groups were looking for ways to predict response or improve response rate.

Admittedly the stability of a given predictor is, over a period of time, obfuscated by changing diet, concurrent medications, compliance, etc. However, the potential rewards of finding accurate predictors have become increasingly obvious. First, there is a variable latency period prior to behavioral response, and nearly a month at therapeutic blood levels must pass before nonresponse can be categorically ascertained in patients treated with neuroleptics, lithium, and antidepressants. Accordingly, accurate predictors of which patient will not respond would obviate ultimately ineffective drug trials that, by delaying effective treatment, would cost patients continued suffering, incapacitation, hospitalization expenses, and risk of harm to themselves or others. Second, 10 to 50% of patients with primary psychiatric illness who "respond" during open trials of psychotropic drugs would have responded equally well to placebo or recovered spontaneously. Growing awareness of and concern about iatrogenic morbidity of psychotropic drugs underscores the importance of selecting those patients in whom a trial of active drug would either be unnecessary or ineffective. Studies should ideally correlate predictor variables with drug response as assessed in the same patient during an adequate double-blind placebo-crossover trial of the agent in question. Response should be ascertained by such a design, with a control group receiving only placebo (without a control group proposed, "predictors" of lithium response utilizing such behavioral measurements as the MMPI or SCL-90 may merely describe those patients with a better natural course if left untreated or those responding to placebo). Third, a corollary to prediction of therapeutic response would be the prediction of side effects (e.g., which patients on neuroleptics might be especially likely to develop tardive dyskinesia, or which manic patients on lithium might develop nephro- or neurotoxicity). Prevention (or minimizing) of side effects and maximizing therapeutic efficacy are increasingly possible in clinical settings.

Drug trials in which a possible predictor is to be assessed must utilize valid and reliable procedures to assess a clinically significant response and must administer the drug for an adequate duration (e.g., 1 month for most neuroleptics or thymoleptics) and at adequate dosages (e.g., 150 to 300 mg/day for most tricyclics) commonly accepted as an "adequate" trial. Ideally, any such study should be monitored not only by dosage but also by blood levels in order to assure adequate absorption and compliance (e.g., HPLC or mass spectrometric assay of tricyclic antidepressants, the radioreceptor assay for neuroleptics, platelet MAO level for monoamine oxidase inhibitors, and atomic absorption or plasma emission spectroscopy for lithium).

The ideal predictor of response should be readily available and rapidly and inexpensively quantifiable, either before the patient begins treatment, or early (day 1 to 5) in the course of treatment. Symptom-descriptive predictors of a behavioral response run particular risk of being redundant reiterations rather than true predictors; and when these are correlated with response to an open trial, they run particular risk of predicting the type of person responding to placebo or remitting spontaneously.

We shall present data using neuroendocrine testing (including the Dexamethasone Suppression and TRH tests), the RBC/Serum ratio of lithium ion, Lithium Efflux, Platelet Serotonin Transporter, and the cranial CT scan as predictors of response to antidepressants, lithium, and major tranquilizers, respectively. Before we begin with this exercise we will focus on reducing heterogeneity in diagnostic groups. Improved medical and psychiatric diagnosis by themselves reduce diagnostic heterogeneity and improve response of psychopharmacological treatment. Knowing how to make a psychiatric diagnosis (still to this day a diagnosis of exclusion) demands a rigorous process which will be reviewed at great length. Thereafter we will focus on the major medications used in general practice, family practice, and psychiatry from the point of view of who should receive this medication and how we can optimize response.

Psychiatrists have traditionally relied on the clinical interview to make diagnostic and treatment decisions. As is true in other branches of medicine, a careful and complete history is of utmost importance in evaluating the patient with psychiatric complaints. Over the last 10 to 15 years, however, the importance of clinical laboratory and diagnostic testing has increased greatly. The psychiatrist of the 1980s and beyond will need to become familiar with the recent developments in these areas in order to provide the safest and most efficacious treatment possible for his or her patients.

There are several reasons for the burgeoning field of diagnostic and laboratory testing. Psychotropic drugs for the treatment of major depression, bipolar illness, schizophrenia, and anxiety disorders are relatively effective and specific. Because of this, the need for accurate diagnosis is increased. A number of tests are available which allow physicians more certainty in clinical diagnosis, in the need for medication, and even in the choice of a particular agent. The response rate to some medications can be greatly improved if blood levels are monitored and dosages tailored for the individual patient. With the increased use of drug treatment comes the increased prevalence of side effects. Lithium-induced thyroid and renal dysfunction emphasizes the need for periodic medical evaluation; tardive dyskinesia highlights the importance of accurate diagnosis before exposing patients to the risk of potentially irreversible damage. Psychiatry is now returning to its position as the subspecialty of medicine, and there is much interest in the overlap between "medical" and "psychiatric" disorders, and the subsequent questions in differential diagnosis. An example is the interplay between thyroid function and affective disorders. Finally, after years of neglect by psychiatrists, substance abuse is being recognized as an important disease complex and confounding factor in psychiatric diagnosis. Advances such as GC/MS and radioimmunoassay procedures for detection and quantification of low drug levels help the physician recognize and treat the substance abuser who may present with an affective or psychiatric syndrome. It is our hope that this book will be a useful manual to physicians who are trying to reduce the risk and maximize the benefits when prescribing psychopharmacological treatments.

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A Phi Beta Kappa, Dr. Gold was awarded the American Psychiatric Association Foundation's Fund Annual Prize for his research in opiate addiction (1981—82). Dr. Gold was the senior author on the discovery paper reporting the invention of the first effective non-opiate treatment for narcotics addicts in the history of medicine (Patent No. 4,312,878). He also received the 1982 Presidential Award from the National Association of Private Psychiatric Hospitals for his leadership in research and discoveries which have led to the understanding, treatment, and prevention of mental illness.

Dr. Gold is a member of several professional organizations, including the American Psychiatric Association, the Society of Neuroscience and the American Association for the Advancement of Science. He is also co-editor of the *Psychiatry Letter, Advances In Alcohol and Substance Abuse* and the *International Journal of Psychiatry in Medicine,* and serves on the review board of several prestigious medical journals, including *The Journal of the American Medical Association* and *The American Psychiatric Association Journal.*

Dr. Gold has lectured throughout the United States, and Eastern and Western Europe. He has authored or co-authored more than 200 papers, mainly dealing with three areas of research interest: identification and treatment of drug abuse in the work setting; development and use of biological measures in psychiatric diagnosis and treatment, and the use of drug therapy in the treatment of patients with depression. Dr. Gold teaches and lectures at universities throughout the United States and Europe. He has lectured in England, Germany, Austria, Sweden, France and the Netherlands in addition to lectures at Yale, Harvard, Brown, Columbia, Cornell, Emory and other universities. Dr. Gold, in addition to this research and clinical work, maintains an active schedule of public service lectures to prevent drug abuse. Dr. Gold has spoken at high schools throughout the New York-New Jersey-Connecticut metropolitan area and appeared on national television shows such as Phil Donahue, John Davidson, PM Magazine, Today Show, Good Morning America, and Dick Cavett, on the subject of drug abuse and its prevention. Dr. Gold is the founder and Medical Director of 800-Cocaine, the nation's first national cocaine Hotline. 800-Cocaine provides factual information about cocaine and its effects to cocaine users, parents, and concerned loved ones. Dr. Gold and 800-Cocaine have been covered on ABC, NBC, and CBS network television and radio as well as United Press, Associated Press, and Time Magazine.

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Among other awards, he has received the A. E. Bennett Award from the Society of Biological Psychiatry for outstanding clinical research in psychobiology and the Curt P. Richter award from the International Society of Psychoneuroendocrinology.

He is board certified in Psychiatry. He has presented over 30 lectures at national or international meetings and has produced more than 70 publications in clinical psychobiologic research. His current major research interests include biological predictors of psychotropic drug response and the influence of calcium and calcitropic hormones on bipolar affective disorder.

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TABLE OF CONTENTS

CONCLUSION

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Chapter 1

PSYCHIATRIC DIAGNOSIS: THE STATE OF THE ART

Robert Moreines, Irl Extein, and Mark S. Gold

TABLE OF CONTENTS

I. DSM III

Psychiatrists have spent a great deal of time characterizing, describing, and diagnosing patients. This process has evolved to the point that many psychiatrists now believe that these diagnoses mean something. We will look at the diagnostic process and try to relate it to practical consideration, like predicting treatment response rate and identifying or reducing relapse.

A. Introduction

DSM III,[1] the *Diagnostic and Statistical Manual of Mental Disorders,* third edition, has been developed by an American Psychiatric Association task force of leading clinicians and researchers under the chairmanship of Dr. Robert Spitzer. It is an achievement of great scholarship and thoughtfulness which brings more consistency and comprehensiveness to the classification of mental disorders. The project involved a good deal of debate and compromise in order to devise a system that was acceptable to clinicians of diverse backgrounds and techniques of treatment. Most important, the Manual introduces to general practice a rigorous approach to diagnosis previously limited to research in descriptive psychiatry. Starting with the Feighner criteria[2] proposed by the Washington University group and continuing with the *Research Diagnostic Criteria* (RDC),[3] there had been developed specific criteria for the standardization of diagnosis and the progressive identification of more homogeneous subgroups of patients. At the very least, DSM III facilitates the communication of information and enables clinicians to incorporate research gains into their treatment strategies of individual patients.

B. Reliability

One of the primary goals in the development of DSM III was to improve the accuracy and consistency of diagnosis; to increase interclinician reliability. In a recent review of the area of classification in psychiatry, Spitzer and Williams[4] note there are important sources of variance between practitioners in diagnosing patients. The first is *information variance,*[4] a lack of the necessary data with which to make a diagnosis. In listing specific inclusion criteria, the Manual provides a catalogue of the information needed. As the clinician becomes increasingly familiar with the criteria through usage and by reviewing the criteria between subsequent interviews, he can direct his inquiry into key areas of behavior that distinguish among categories in the differential diagnosis.

A second source of error is *interpretation variance*[4] in evaluating the information available. While increasing sensitivity is acquired through experience, a familiarization with the diagnostic system can be of help here also. An anticipation of associated symptoms will enhance skill in recognizing their presence.

The final source of unreliability has been found to be the most important; it is *criteria variance*[4] the basis on which a clinician assesses the data to make a diagnosis. Specified inclusion criteria prevent idiosyncratic categorization. Furthermore the inclusion of a glossary of technical terms, instructions for the use of the Manual, decision trees, and discussion of pertinent issues in differential diagnosis all help to minimize errors in this area. In experimental field trials,[5] interrater agreement in diagnosis was much higher using DSM III than it had been using previous diagnostic systems.

An illustration of the advances made over DSM II[6] in the area of reliability can be seen in the approach to schizophrenia. Historically, there has been great variation in the frequency with which different groups of clinicians have made the diagnosis.[7] Today it is recognized that many patients previously labeled by American psychiatrists as schizophrenic in past decades most likely suffered bipolar illness or personality disorders.[7] Conceptualizations of schizophrenia had been vague and overinclusive.

In DSM II schizophrenia was described as follows: "This large category includes a group of disorders manifested by characteristic disturbances of thinking, mood and behavior. Disturbances in thinking are marked by alteration of concept formation which *may* lead to misinterpretation of reality and *sometimes* to delusions and hallucinations, which frequently appear psychologically self protective. Corollary mood changes include ambivalent, constricted and inappropriate emotional responsiveness and loss of empathy with others. Behavior may be withdrawn, regressive and bizarre."

There was a further discussion of a number of subtypes distinguished by prominent symptoms; paranoid, catatonic, hebephrenic, simple, and undifferentiated. There was also an additional category, latent schizophrenia, which included patients *without* psychosis; they were thought to have an attenuated or incipient form of the illness.

In DSM III, schizophrenia is much more clearly and narrowly defined.[8] (See Table 1 for a listing of the criteria). Most important, the presence of psychosis is required. A number of different types of disturbances of thinking are then specified which exemplify the severity and quality of thought disorder characteristic of this illness. Two additional criteria

1. continuous signs of the illness for 6 months
2. deterioration of functioning in work, social relations, or self care

capture the pervasive effects of the illness. The onset must be before age 45, which distinguishes schizophrenia from other late onset psychotic disorders without the same course or familial inheritance. Finally, affective disorders, organic mental disorder, and mental retardation must all be excluded.

These stringent criteria have created a much more homogeneous diagnostic category. Other similar psychotic conditions, which have different prognosis, course, family history, symptomatology, and response to treatment have been excluded (paranoid disorder, schizophreniform disorders, brief reactive psychosis, and schizoaffective disorder).[8] The required exclusion of an affective disorder prevents the past excess of considering manic episodes accompanied by Schneider's first rank symptoms as schizophrenia.[9] The diagnosis of schizophrenia is now more meaningful and, accordingly, the rate has been changed to approximately 0.5%. This makes it a relatively rare illness, with addiction to heroin equaling schizophrenia and addiction to all narcotics dwarfing schizophrenia.

C. Validity

One of the most important considerations in the development of this diagnostic system has been the validity of the disorders described. Validity of the syndromes was addressed in two ways. If pathophysiology was known, it was included in the definition of the disorder, as in multi-infarct dementia or alcohol amnesic syndrome. In all other cases, no assumption of etiology was made. It was hoped that this would provide for a universal acceptability among the divergent sub-groups of psychiatric clinicians. In this latter group of disorders, where the etiology is unknown, diagnostic classes were defined by shared signs and symptoms. Validity of these syndromes was corroborated in more indirect fashion by field studies and review of the scientific literature. Spitzer and Williams[4] have described the different types of validity and their relative power and meaningfulness.

Descriptive validity was the basic requirement for inclusion in the Manual. A disorder has descriptive validity if the defining criteria (1) form a cluster that can be distinguished from the characteristics of other disorders and (2) coexist together at a rate greater than chance. Many mathematical approaches have been used to try to define more homogeneous subtypes of disorders at this level of validity. It is assumed that, if descriptive validity is possessed, the higher order validities also exist.

Prediction validity involves the ability to describe course and, most important, response

Table 1
DIAGNOSTIC CRITERIA FOR A SCHIZOPHRENIC DISORDER

A. At least one of the following during a phase of the illness.
   1. Bizarre delusions (content is patently absurd and has no possible basis in fact), such as delusions of being controlled, thought broadcasting, thought insertion, or thought withdrawal
   2. Somatic, grandiose, religious, nihilistic, or other delusions without persecutory or jealous content
   3. Delusions with persecutory or jealous content if accompanied by hallucinations of any type
   4. Auditory hallucinations in which either a voice keeps up a running commentary on the individual's behavior or thoughts, or two or more voices converse with each other
   5. Auditory hallucinations on several occasions with content of more than one or two words, having no apparent relation to depression or elation
   6. Incoherence, marked loosening of associations, markedly illogical thinking, or marked poverty of content of speech if associated with at least one of the following:
      a. blunted, flat, or inappropriate affect
      b. delusions or hallucinations
      c. catatonic or other grossly disorganized behavior

B. Deterioration from a previous level of functioning in such areas as work, social relations, and self-care

C. Duration — continuous signs of the illness for at least 6 months at some time during the person's life, with some signs of illness at present. The 6-month period must include an active phase during which there were symptoms from A, with or without a prodromal or residual phase, as defined below

   Prodromal phase — a clear deterioration in functioning before the active phase of the illness not due to a disturbance in mood or to a Substance Use Disorder and involving at least two of the symptoms noted below

   Residual phase — persistence, following the active phase of the illness, of at least two of the symptoms noted below, not due to a disturbance in mood or to a Substance Use Disorder

   Prodromal or Residual Symptoms
   1. Social isolation or withdrawal
   2. Marked impairment in role functioning as wage-earner, student, or homemaker
   3. Markedly peculiar behavior (e.g., collecting garbage, talking to self in public, or hoarding food)
   4. Marked impairment of personal hygiene and grooming
   5. Blunted, flat, or inappropriate affect
   6. Digressive, vague, overelaborate, circumstantial, or metaphorical speech
   7. Odd or bizarre ideation, or magical thinking, e.g., superstitiousness, clairvoyance, telepathy, "sixth sense," "others can feel my feelings," overvalued ideas, ideas of reference
   8. Unusual perceptual experiences, e.g., recurrent illusions, sensing the presence of a force or person not actually present

   Examples — 6 months of prodromal symptoms with 1 week of symptoms from A; no prodromal symptoms with 6 months of symptoms from A; no prodromal symptoms with 2 weeks of symptoms from A and 6 months of residual symptoms; 6 months of symptoms from A, apparently followed by several years of complete remission, with 1 week of symptoms in A in current episode

D. The full depressive or manic syndrome (criteria A and B or major depressive or manic episode), if present, developed after any psychotic symptoms, or was brief in duration relative to the duration of the psychotic symptoms in A

E. Onset of prodromal or active phase of the illness before age 45

F. Not due to any organic mental disorder or mental retardation

to treatment. *Construct validity* entails knowledge of the etiology and pathophysiology of the disorder. These two definitive measures of validity are demonstrated by studies of follow-up, familial patterns and genetics, associated laboratory measures, and response to medications.[10]

As knowledge is gained, diagnostic categories are further refined and subdivided to describe more homogeneous disease entities. For example, a subgroup of patients will be found who respond to a specific medication or who have an underlying biochemical or physiologic abnormality, or a demonstrable familial inheritance. This data can then be incorporated into the defining criteria of a disorder and researchers can work backwards to develop a purer constellation of associated features and further understanding of etiology. Unfortunately, the current state of the treatment of mental disorders suffers from a lack of

specific knowledge of the underlying processes of pathophysiology. Diagnosis and pathophysiology are interrelated, a heterogeneous diagnostic system makes finding a biochemical pathology unlikely. In the absence of a biologically valid disease entity, a more indirect means of classifying syndromes is the predominant one utilized in the Manual. This shortcoming, and one of the failures in modern psychiatry, is the lack of specificity in the pharmacological treatment as indicated by diagnosis. Specific diagnoses, once made, do not often result in specific therapy.

D. Multiaxial System

DSM III strives to encourage a comprehensive approach to the individual patient. A multiaxial assessment requires the clinician to attend to the array of factors that contribute to the final expression in symptomatology that a disorder takes in an individual. The DSM III is the first multiaxial diagnostic system with a five-axis review added to the diagnostic process. Axis 1 disorders are the clinical syndromes for which psychiatric evaluation and treatment are indicated. Axis 2 diagnoses are personality (character) disorders and developmental disorders; they can also, at times, be the focus of treatment. While other axes exist, the overwhelming focus of the DSM III is on Axes 1 and 2. Axis 3 is reserved for any physical, neurological, endocrinological, vitamin deficiency, or other known illness to be mentioned. Axis 4 is the axis for estimating severity of associated environmental stressors. Axis 5 allows for a social, occupational, and leisure time rating to determine highest level of functioning in the past year. Thus, a patient with the primary diagnosis on Axis 1 of schizophrenia or affective disorder can be given other diagnoses or qualifications such as the presence of personality traits or disorder, physical illness, psychosocial stress, and highest level of adaptive functioning. This more complete and individualized conceptualization will help shape a more specific and appropriate treatment approach.

The DSM III recognizes that the first step in psychiatric diagnosis is an accurate recognition of certain phenomena by observation and history. To us this means a 10- to 14-day medication and drug-free comprehensive neuropsychiatric evaluation. The second step is the use of psychiatric terminology to label on a tentative basis the likely psychiatric syndrome. The third step is a "systematic ruling in or out" of competing or other possible disorders which could (and do) produce a similar clinical syndrome. We believe that distinguishing among this latter group of disorders requires intense evaluation and thought. No patient should be given a psychiatric diagnosis and stigma (not to mention inappropriate treatment and disruption of family and work) because the psychiatrist failed to rule out B12 or Folate deficiency (or other common mimickers) on the basis of "clinical experience". Too many cases of typical onset, typical course, typical secondary impairment, typical predisposition, and even the typical family history exist which turned out to be primarily medical problems *and* reversible. One cannot justify the "clinical interview alone" approach of many psychiatrists.

DSM III also incorporates a hierarchical approach in the consideration of data. A number of known organic disturbances: medical illness, physiologic processes like dementia, toxic substance abuse, and mental retardation all may have associated cognitive, mood, and personality disorders. Diagnosis of these known pathophysiology processes always takes priority in assigning an individual to a diagnostic category; all of the Axis 1 conditions have as an inclusion criterion "not due to any organic mental disorder". Unfortunately, the vigor with which competing viable diagnoses are ruled out is not addressed, and psychiatrists and other physicians misdiagnose the patient's complaints as primary (psychiatric) and prescribe the wrong treatment for many secondary syndromes. Axis 3 is almost an afterthought and is generally ignored by most clinicians. Unfortunately most psychiatrists have not retained a "black bag" in their office.

The DSM III diagnostic criteria for cocaine intoxication is a prime example of the inadequate attention given to medical diagnosis. An examination of the criteria demonstrates

how little help they are and how they contribute to the relative neglect of this increasingly more common and serious problem.

The criteria include:

1. Recent use of cocaine (pharmaceutical or by prescription; how would anyone really know; or are these people reliable historians?)
2. Two of the following: psychomotor agitation, elation, grandiosity, loquacity, hypervigilance. (These are true of many users who are intoxicated; true of most people who are happy or had something positive happen to them; also caused by caffeine and numerous other possibilities.)
3. Two of the following: tachycardia, pupilary dilation, chills or perspiration, elevated blood pressure, nausea, and vomiting. (All are dose-related and duration-related effects that can also be caused by fever, caffeine, atropine, and hundreds of other possibilities.)
4. Maladaptive behavior (incredible).
5. Not due to any other physical or mental disorder (which physical disorders; how do you rule them out or rule this in?)

The diagnostic criteria for cocaine intoxication given by the AMA manual specifies cocaine levels in blood and/or urine.[11] The only additional facts that matter are whether the person came to treatment *before* spouse, bank, employer, friend, professional society forced him/her. Since all drug and alcohol use is unhealthy (though some people have more acute or visible consequences than others) and no drug use is totally without problems, the existing DSM III system for drug abuse diagnosis is bankrupt.

E. Homogeneous Groupings

The decision of the task force to group together major disorders that share a common predominant dysfunction has enhanced consistency over prior classification schemes.[8] All the disorders of mood, for example, are contained in a single category. In DSM II, major affective disorder was classified with the functional psychoses, dysthymic disorder with the neuroses, and cyclothymic disorder with the personality disorders. Similarly, anxiety disorders have been grouped together in DSM III. These decisions are based on the current literature: family studies, prognosis, and somatic treatment response all support this orientation. Furthermore, this organization acknowledges the fact that a description of the cross-sectional psychopathology is an unreliable criterion when used alone. As Pope and Lipinski[7] have demonstrated, a particular episode of manic psychosis can be indistinguishable from an acute schizophrenic episode or any other psychosis but still retain the other features shared with bipolar illness (see Table 2). It is primarily an affective disorder, not a psychosis. All of these efforts ought to stimulate clinicians to carefully look at the syndrome over time and gather all available data regarding past personal and family history. It is dangerous to cross-sectionally diagnose an acute illness and treat the illness in a day or two.

On the other hand, the DSM III has taken a rather conservative approach in limiting the number of subcategories recognized. Perhaps the authors are attempting to redress past excesses, as in the prior over-inclusion of disorders within schizophrenia. Perhaps it is a reflection of their sense of responsibility to provide a relatively permanent classification system that led its authors to eschew the inclusion of biochemical parameters that have not yet "stood the test of time". Perhaps their concern is with creating too unwieldy a system for general usage (after all, the chairperson of the task force was a co-author of the Research Diagnostic Criteria[3] (RDC) which includes seven subtypes of major depression).

For example, there is no discussion of the special significance of certain symptoms or signs or certain combinations of behaviors across axes which may constitute disorder on the basis of common medication response. The coexistence of major depressive disorder and

Table 2
DIAGNOSTIC CRITERIA FOR A MANIC EPISODE

A. One or more distinct periods with a predominantly elevated, expansive, or irritable mood. The elevated or irritable mood must be a prominent part of the illness and relatively persistent, although it may alternate or intermingle with depressive mood.

B. Duration of at least 1 week (or any duration if hospitalization is necessary), during which, for most of the time, at least 3 of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a significant degree:
   1. Increase in activity (either socially, at work, or sexually) or physical restlessness
   2. More talkative than usual or pressure to keep talking
   3. Flight of ideas or subjective experience that thoughts are racing
   4. Inflated self-esteem (grandiosity, which may be delusional)
   5. Decreased need for sleep
   6. Distractibility, i.e., attention is too easily drawn to unimportant or irrelevant external stimuli
   7. Excessive involvement in activities that have a high potential for painful consequences, which is not recognized, e.g., buying sprees, sexual indiscretions, foolish business investments, reckless driving

C. Neither of the following dominate the clinical picture when an affective syndrome (i.e., criteria A and B above) is not present, that is, before it developed or after it has remitted:
   1. Preoccupation with a mood-incongruent delusion or hallucination (see definition below)
   2. Bizarre behavior

D. Not superimposed on either Schizophrenia, Schizophreniform Disorder, or a Paranoid Disorder.

E. Not due to any Organic Mental Disorder, such as Substance Intoxication.

Mood-incongruent Psychotic Features — either (A) or (B):

A. Delusions or hallucinations whose content does not involve themes of either inflated worth, power, knowledge, identity, or special relationship to a deity or famous person. Included are such symptoms as persecutory delusions, thought insertion, and delusions of being controlled, whose content has no apparent relationship to any of the themes noted above

B. Any of the following catatonic symptoms: stupor, mutism, negativism, posturing

obsessive-compulsive anxiety disorder indicates potential maximal benefit from use of a serotonergic antidepressant. An important diagnosis for this group of patients could be "serotonin agent responder". Depressive disorder following long-term narcotic addiction might respond to manipulation of endorphins. Panic anxiety disorder coexisting with the physical condition, mitral valve prolapse, would suggest addition of propranolol to the standard treatment with monoamine oxidase inhibitor or tricyclic antidepressant.

The DSM III is a major advance over prior diagnostic systems, but it does not go far enough for the medical psychiatrist or the medical practitioner who is interested in a close diagnosis-medication response relationship. We should like to offer some further diagnostic subdivisions which may yield more homogeneous subgroups and help the clinician determine indicated pharmacotherapy and attain maximal treatment response. After years of debate, it is likely that some of them will find their way into DSM IV.

F. Schizotypal Personality Disorder

The approach to the so-called "spectrum disorders", more subtle abnormalities of thinking and behavior found in the families of schizophrenic patients, occupies a central place in current thinking about the boundaries between major categories of illness. To the credit of DSM III, two syndromes were identified, schizotypal and borderline, and are now considered as personality disorders (see Table 3). This represents an important correction of past excesses in viewing them as milder forms or precursors of schizophrenia. The previous organization reflected an optimism that grew out of breakthroughs of that period. The neuroleptic medications were hoped to have a relatively greater curative power. Clinicians took researchers literally when they described antipsychotic response. When the major variable in response is state hospital census, response can be clearly demonstrated; however, when psychiatric

Table 3
DIAGNOSTIC CRITERIA FOR SCHIZOTYPAL PERSONALITY DISORDER

The following are characteristic of the individual's current and long-term functioning, are not limited to episodes of illness, and cause either significant impairment in social or occupational functioning or subjective distress.

A. At least four of the following:
   1. Magical thinking; e.g., superstitiousness, clairvoyance, telepathy, "6th sense," "others can feel my feelings" (in children and adolescents, bizarre fantasies or preoccupations)
   2. Ideas of reference
   3. Social isolation; e.g., no close friends or confidants, social contacts limited to essential everyday tasks
   4. Recurrent illusions, sensing the presence of a force or person not actually present (e.g., "I felt as if my dead mother were in the room with me"), depersonalization, or derealization not associated with panic attacks
   5. Odd speech (without loosening of associations or incoherence), e.g., speech that is digressive, vague, overelaborate, circumstantial, metaphorical
   6. Inadequate rapport in face-to-face interaction due to constricted or inappropriate affect; e.g., aloof, cold
   7. Suspiciousness or paranoid ideation
   8. Undue social anxiety or hypersensitivety to real or imagined criticism

symptoms or psychological function are carefully analyzed, response in many (not most) areas can be demonstrated, but even here it is often not complete. In addition, theories of deranged family interactions were thought to have greater etiological significance and to be remediable through psychotherapeutic techniques. And the genetic findings offered the possibility of identifying patients at risk who could conceivably benefit from primary preventative efforts. We feel that the current separation of schizotypal personality disorder from schizophrenia is an important gain in the prevention of making of casual associations and the blurring of important distinctions. However, all of these diagnoses are hopelessly vague and irrelevant, as the Hinkley trial demonstrated.

G. Borderline Personality Disorder

In contrast to schizotypal personality disorder, which possesses an inherent relative homogeneity, the borderline syndrome seems to include many different types of patients. Part of the problem relates to varying usages of the term.[12] In DSM III, the borderline personality disorder is defined phenomenologically, and a number of studies have demonstrated syndromal validity for the cluster of symptoms[13,14] (see Table 4). Nevertheless, it seems to be a personality disorder that exists at a different level of abstraction from all the others. In fact, in the psychoanalytic literature, it connotes a level of ego organization to be contrasted with the more fragmented psychotic and more integrated neurotic patients. Even in the phenomenological usage, borderline symptoms can be associated with any of the other personality disorders or affective disorders purely as a measure of severity of disturbed behavior.[12] For example, many untreated patients with cyclothymic disorder meet criteria for borderline personality; after successfully being treated with lithium they no longer do.[15] It would not be expected of a character disorder to remit so promptly with medication. In DSM III, personality disorders are described as enduring patterns which are generally reconizable by adolescence and continue throughout most of adult life.[1]

We believe it was an important advance to classify cyclothymic disorder as an affective disorder (it was previously defined as a personality disorder). Similarly a number of authors have suggested that there are other affective disorders that could be carved out from the borderline syndrome.[16-18] More precise subtyping would lead to more efficacious treatment strategies.

One method of conceptualizing the borderline syndrome that holds promise for a more precise approach to these patients is that offered by Stone.[16] It reconciles the psychoanalytic

Table 4
DIAGNOSTIC CRITERIA FOR BORDERLINE PERSONALITY DISORDER

The following are characteristic of the individual's current and long-term functioning, are not limited to episodes of illness, and cause either significant impairment in social or occupational functioning or subjective distress

A. At least five of the following are required:
   1. Impulsivity or unpredictability in a least two areas that are potentially self-damaging; e.g., spending, sex, gambling, substance use, shoplifting, overeating, physically self-damaging acts
   2. A pattern of unstable and intense interpersonal relationships; e.g., marked shifts of attitude, idealization, devaluation, manipulation (consistently using others for one's own ends)
   3. Inappropriate, intense anger or lack of control of anger; e.g., frequent displays of temper, constant anger
   4. Identity disturbance manifested by uncertainty about several issues relating to identity such as self-image, gender identity, long-term goals or career choice, friendship patterns, values, and loyalties; e.g., "Who am I?", "I feel like I am my sister when I am good"
   5. Affective instability: marked shifts from normal mood to depression, irritability, or anxiety, usually lasting a few hours and only rarely more than a few days, with a return to normal mood
   6. Intolerance of being alone; e.g., frantic efforts to avoid being alone, depressed when alone
   7. Physically self-damaging acts; e.g., suicidal gestures, self-mutilation, recurrent accidents, or physical fights
   8. Chronic feelings of emptiness or boredom

B. If under 18, does not meet the criteria for Identity Disorder.

and phenomenologic approaches and distinguishes three major subcategories within the borderline level of functioning. One is schizotypal, primarily a disorder of cognition, and its relationship to schizophrenia has already been noted. A second is a spectrum of disorders related to the major affective disorders and sharing a disturbance of mood. This would include cyclothymic and dysthymic disorder as well as a number of other syndromes that authors have described as subaffective or atypical depressions. A third category is a residual one including the severe character disorders (with or without affective symptoms) and the organic brain dysfunctions which lead to the lability and impulsivity so prominent among the borderline characteristics. This scheme provides a consistency of level of abstraction and follows the historic trend of separating the affective psychoses from schizophrenia. Schizotypal and the affective borderline disorders would bear similar relationship to schizophrenia and major affective disorders respectively; genetic, phenomenologic, and treatment response data are all consistent with this approach. The final category would be a residual one, with purely a descriptive and behavioral definition at this time. It would be expected that further understanding of etiology would lead to further subtypes in this last category as well.

The results of the DSM III field trial[14] examining the validity of the two borderline syndromes — unstable (eventually the DSM III borderline) and schizotypal — actually gives some support to this type of formulation. First, over 50% of the "borderline" patients met criteria for both schizotypal and unstable personality disorder. This suggests inclusion of both within a class at a higher level of abstraction. If the sample of total borderline patients was analyzed for five clusters, there were the following three additional dimensions: affective, paranoid, and schizoid. Thus an alternative organization might be a larger group of "borderline patients" with subsets: (1) schizotypal, (2) affective, (3) impulsive/labile, (4) schizoid, and (5) paranoid (in fact quite similar to Stone).

1. Borderline Affective Disorders

Liebowitz and Klein[17] have described a syndrome, hysteroid dysphoria, which they feel is selectively responsive to MAOI and can be viewed as a subtype of atypical depression. (A controversy remains over the validity of this syndrome; Spitzer and Williams[19] were

unable to verify syndromal validity in field trials and thus it was not included in DSM III). In a pilot study, Liebowitz and Klein[17] demonstrated a high degree of overlap between hysteroid dysphoria and borderline personality disorder. They provide further evidence for conceptualizing the borderline symptoms as state dependent and measures of severity; during treatment with MAOI, symptoms became significantly attenuated.

While this study is limited by its size, it exemplifies a thoughtful and promising design. Rather than meeting the criteria of syndromal descriptive validity, it meets the validity measure of medication response. Starting from a list of criteria for a syndrome, it sought to validate it by response to a specific medication treatment.

A recent study by Carroll et al.[20] found a high incidence of major depressive episodes as diagnosed by RDC[3] (13/21—62%) superimposed on a population of hospitalized patients with the *primary* admitting diagnosis of borderline personality disorder. Moreover there was also a high incidence of abnormal Dexamethasone Suppression Test (DST) (13/21—62%; although not the same 13 patients). This finding suggests the importance of *carefully* assessing the borderline patient, especially when requiring hospitalization, for symptoms of affective disorder. This is particularly significant because the difficult style of these patients causes countertransference obstacles in the clinician; moreover these patients present with a confusing combination of complaints which they may express in hystrionic manner. Carroll also notes that there was a relatively high false positive DST rate (5/21), as compared with studies in other nonaffective control populations.[21] He believes this may reflect in part the difficulty in diagnosing depression in this population, even when RDC or DSM III criteria are specifically considered.[16] The patients with positive DST who meet RDC criteria for major depression would be expected to respond to antidepressants; however this study did not include rigorous medication trials.

Akiskal[18,22-24] and his associates have done a great deal of thoughtful research in teasing apart affective syndromes from the characterological disorders. They have combined careful assessment of phenomenology, longitudinal follow-up, family studies, physiological measures, and pharmacological response. Their work provides compelling evidence in favor of the shift in category of cyclothymic disorder from the personality to the affective disorders (see Table 5). It also suggests the existence of subgroups of affective disorder within the borderline personality syndrome and demonstrates reversal of these "character traits" with treatment of the underlying affective disorder.

2. Cyclothymic Disorder

In a study of cyclothymic disorder,[24] Akiskal et al. demonstrated a family history positive for affective disorder in these patients similar to bipolar patients and significantly different from a control group with personality disorder. They observed nearly one third of the cyclothymic group to suffer a full blown depression or manic episode during a 2- to 3-year follow-up. And they found equal incidence of tricyclic antidepressant induced hypomania in bipolar and cyclothymic groups.

It should be noted that they provide an exemplary approach to assessing symptoms. Not only did most of the cyclothymic patients carry diagnoses across the spectrum of character disorders, but many of the control patients with personality disorder complained of "highs" and "lows". If these latter reports of mood shift were not associated with substantiated changes in behavior, these patients were described "pseudocyclothymic" and not included in the cyclothymic group. Finally in an open trial,[24] 9/15 cyclothymic patients who had failed in 2 to 4 years of previous treatment showed a dramatic response to lithium.

3. Other Affective Subtypes

In a recent study of 100 patients diagnosed as borderline personality disorder, Akiskal[15] and his co-workers provided stronger evidence for the heterogeneity of the group. On

Table 5
DIAGNOSTIC CRITERIA FOR CYCLOTHYMIC DISORDER

A. During the past 2 years, numerous periods during which some symptoms characteristic of both the depressive and the manic syndromes were present, but were not of sufficient severity and duration to meet the criteria for a major depressive or manic episode

B. The depressive periods and hypomanic periods may be separated by periods of normal mood lasting as long as months at a time, they may be intermixed, or they may alternate

C. During depressive periods there is depressed mood or loss of interest or pleasure in all, or almost all, usual activities and pastimes, and at least three of the following:

1. Insomnia or hypersomnia
2. Low energy or chronic fatigue
3. Feelings of inadequacy
4. Decreased effectiveness or productivity at school, work, or home
5. Decreased attention, concentration, or ability to think clearly
6. Social withdrawal
7. Loss of interest in or enjoyment of sex
8. Restriction of involvement in pleasurable activities; guilt over past activities
9. Feeling slowed down
10. Less talkative than usual
11. Pessimistic attitude toward the future, or brooding about past events
12. Tearfulness or crying

During hypomanic periods there is an elevated, expansive, or irritable mood and at least three of the following:

1. Decreased need for sleep
2. More energy than usual
3. Inflated self-esteem
4. Increased productivity, often associated with unusual and selfimposed working hours
5. Sharpened and unusually creative thinking
6. Uninhibited people-seeking (extreme gregariousness)
7. Hypersexuality without recognition of possibility of painful consequences
8. Excessive involvement in pleasurable activities with lack of concern for the high potential for painful consequences; e.g., buying sprees, foolish business investments, reckless driving
9. Physical restlessness
10. More talkative than usual
11. Over-optimism or exaggeration of past achievements
12. Inappropriate laughing, joking, punning

D. Absence of psychotic features such as delusions, hallucinations, incoherence, or loosening of associations

E. Not due to any other mental disorder, such as partial remission of Bipolar Disorder. However, Cyclothymic Disorder may precede Bipolar Disorder

reevaluation, 45% received a principal diagnosis of affective disorder: recurrent unipolar depression (7), atypical (bipolar II) (17), dysthymic (14) and cyclothymic (7). As can be seen, the "subaffective" forms composed the majority of cases. The other two major primary diagnoses were anxiety disorder (agoraphobia and obsessive compulsive 18%) and character disorder (sociopathy and somatization 21%). A number of patients met criteria for schizotypal disorder (16%). There was also a group of patients with organic pathology: nonspecific pure organic syndrome (3), temporal lobe epilepsy (3), and residual attention deficit disorder (4).

Follow-up data and family history further supported the close relationship with affective illness in this group of 100 "borderline" patients. Thirty-seven individuals went on to suffer affective episodes; included were twenty-nine major depressions "of melancholic proportions", eleven brief hypomanic episodes, four manic psychoses, and eight mixed bipolar states. By contrast it is noted that there were only seven schizophrenia-like episodes; none meeting DSM III criteria for schizophrenia. Family histories showed 17 patients with first degree relatives with bipolar illness and an additional 17 patients with relatives suffering major depression. Only three subjects had schizophrenia present in first degree relations.

Akiskal's work has demonstrated the severity of impairment that follows from these subaffective syndromes and their similarity to personality disorders. The subaffective dis-

orders begin in young adulthood, are chronic and recurrent, and do not meet the criteria for a major depressive or manic episode. Frequently they have *superimposed on them* a major affective episode. The patients that suffer these unstable and unpredictable shifts in mood often evidence severe problems in social, occupational, and familial achievements, and familial and social relationships. Most important, these patients can respond to pharmacotherapy with dramatic improvement in most areas of their behavior. What is essential for proper treatment, then, is a way to identify those patients with medication-responsive affective disorders from those with personality disorders. Patients with personality disorders may be found to have genetic or acquired receptor abnormalities, neurotransmitter precursor, or enzyme abnormalities and unknown medical illnesses.

While DSM III recognized the problems by shifting depressive neurosis (dysthymic disorder) and cyclothymic personality (e.g., cyclothymic disorder) to the affective disorders, the Manual does not provide guidelines for distinguishing the medication-responsive, chronic affective disorder from personality disorders. Physiologic disturbances and family history data need to be incorporated into future classification.

Within a group of patients presenting with chronic depression, Akiskal et al.[23] compared tricyclic antidepressant responders and nonresponders and noted significant differences along the following dimensions: sex ratio, behavior manifestations, sleep disturbance, family history, substance abuse, rapid eye movement (REM) latency, and TCA-induced hypomania. Like Liebowitz and Klein's[17] work identifying MAOI-responsive patients, this study provides a diagnostic conceptualization with specific treatment implications.

4. Organic Mental Disorders

Another important group of patients that needs to be differentiated within the borderline group is those suffering organic pathology. Temporal lobe and other seizure disorders, residual adult attention deficit disorder, traumatic brain insults, and other nonspecific neurological disturbances with learning disorders and "soft neurological signs", are all potential causes of unstable personality disorders. Andrulonis and co-workers[25] are trying to identify features that will distinguish patterns among these groups. Preliminary data indicate that male sex, early onset of illness, learning disabilities, delinquent behavior at school, and family history positive for alcohol or drug abuse are more common among patients with neurological syndromes. These different behavior syndromes have dramatically different responsiveness to medications; their delineation will suggest more efficacious treatment approaches with specific indications for anticonvulsants, stimulants, antipsychotics, or antidepressants. For example, Klein and colleagues[26] have described a syndrome they call "emotionally unstable character disorder" in which they find an increased number of neurologist soft signs[27] and beneficial response to phenothiazines and lithium.[28]

H. Major Affective Disorder

Major depressive episode, as defined in DSM III, (see Table 6) describes a heterogeneous group of patients and provides little guidance in the choice of treatment approach. Not only are there no indications for a specific class of antidepressants, but there is no measure for deciding if medication should be used at all. Furthermore primary depression cannot be distinguished from secondary depression associated with other medical disturbance on the basis of cross-sectional symptomatology. There are several subtypes noted that do in fact have significant treatment implications: with delusions, with melancholia, and with manic episodes (bipolar). However there was no attempt made to define subtypes by biochemical or neurophysiological measures, by past personal or family history of psychiatric illness, or by medication response. Current symptomatology alone has only a limited association with treatment response and additional measures are necessary for a close fit of diagnosis and indicated medication.

Table 6
DIAGNOSTIC CRITERIA FOR MAJOR DEPRESSIVE EPISODE

A. Dysphoric mood or loss of interest or pleasure in all or almost all usual activities and pastimes. The Dysphoric mood is characterized by symptoms such as the following: depressed, sad, blue, hopeless, low, down in the dumps, irritable. The mood disturbance must be prominent and relatively persistent, but not necessarily the most dominant symptom, and does not include momentary shifts from one dysphoric mood to another dysphoric mood; e.g., anxiety to depression to anger, such as are seen in states of acute psychotic turmoil. (For children under six, dysphoric mood may have to be inferred from a persistently sad facial expression.)

B. At least 4 of the following symptoms have each been present nearly every day for a period of at least 2 weeks (in children under 6, at least 3 of the first 4).
   1. Poor appetite or significant weight loss (when not dieting) or increased appetite or significant weight gain (in children under six, consider failure to make expected weight gains)
   2. Insomnia or hypersomnia
   3. Psychomotor agitation or retardation (but not merely subjective feelings of restlessness or being slowed down) (in children under six, hypoactivity)
   4. Loss of interest or pleasure in usual activities, or decrease in sexual drive not limited to a period when delusional or hallucinating (in children under six, signs of apathy)
   5. Loss of energy; fatigue
   6. Feelings of worthlessness, self-reproach, or excessive or inappropriate guilt (either may be delusional)
   7. Complaints or evidence of diminished ability to think or concentrate, such as slowed thinking, or indecisiveness not associated with marked loosening of associations or incoherence
   8. Recurrent thoughts of death, suicidal ideation, wishes to be dead, or suicide attempt

C. Neither of the following dominate the clinical picture when an effective syndrome (i.e., criteria A and B above) is not present, that is, before it developed or after it has remitted:
   1. Preoccupation with a mood-incongruent delusion or hallucination (see definition below)
   2. Bizarre behavior

D. Not superimposed on either Schizophrenia, Schizophreniform Disorder, or a Paranoid Disorder

E. Not due to any Organic Mental Disorder or Uncomplicated Bereavement

Fifth-digit code numbers and criteria for subclassification of major depressive episode. (When psychotic features and melancholia are present the coding system requires that the clinician record the single most clinically signficant characteristic)

6- In remission. — This fifth-digit category should be used when in the past the individual met the full criteria for a major depressive episode but now is essentially free of depressive symptoms or has some signs of the disorder but does not meet the full criteria

4- With psychotic features. — This fifth-digit category should be used when there apparently is gross impairment in reality testing, as when there are delusions or hallucinations or depressive stupor (the individual is mute and unresponsive). When possible, specify whether the psychotic features are mood-congruent or mood-incongruent. (The non-ICD-9-CM fifth-digit 7 may be used instead to indicate that the psychotic features are Mod-incongruent; otherwise, mood-congruence may be assumed.)

Mood-congruent psychotic features. — Delusions or hallucinations whose content is entirely consistent with the themes of either personal inadequacy, guilt, disease, death, nihilism, or deserved punishment; depressive stupor (the individual is mute and unresponsive)

Mood-incongruent psychotic features. — Delusions or hallucinations whose content does not involve themes of either personal inadequacy, guilt, disease, death, nihilism, or deserved punishment. Included here are such symptoms as persecutory delusions, thought insertion, thought broadcasting, and delusions of control, whose content has no apparent relationship to any of the themes noted above.

3- With melancholia. — This category should be used when there is loss of pleasure in all or almost all activities, lack of reactivity to usually pleasurable stimuli (doesn't feel much better, even temporarily, when something good happens), and at least three of the following:
   1. Distinct quality of depressed mood; i.e., the depressed mood is perceived as distinctly different from the kind of feeling experienced following the death of a loved one
   2. The depression is regularly worse in the morning
   3. Early morning awakening (at least 2 hr before usual time of awakening)
   4. Marked psychomotor retardation or agitation
   5. Significant anorexia or weight loss
   6. Excessive or inappropriate guilt

2- Without melancholia

0- Unspecified

The distinction of unipolar from bipolar depression is one that has major treatment implications and is supported by familial studies.[29] Not only would lithium be a consideration in the treatment of bipolar depression,[30] but tricyclic antidepressants could have negative effects in precipitating manic episodes or rapid cycling. We would suggest the addition of rapid cycling (greater than four episodes per year) as a fifth digit subtype, as it has important treatment implications (lithium is often only partially effective, and these patients may be good candidates for carbamazepine.)[31] In addition we feel that the choice of "terma typical bipolar" for the syndrome of major depressive episodes with hypomanic episodes is inconsistent; throughout the Manual "atypical" is used as a residual category, but this syndrome is thought to be quite common.

The presence of psychotic thinking in depression also has important implications for treatment. Although there is some controversy among clinicians, most believe that antidepressants alone are inadequate treatment for this syndrome. Electroconvulsive therapy (ECT) or combination treatment of antipsychotics plus tricyclic antidepressants is generally recommended.[32]

1. Melancholia

The subtype, "with melancholia", defines a depressive disorder which is most closely associated with a demonstrable neurophysiological abnormality and disturbances in observable physical behaviors. The category derives from historic attempts to describe a subgroup requiring and responsive to pharmacological treatment. Over the years a number of features have been proposed as the distinguishing criteria of this group: one or another cluster of vegetative symptoms, lack of identifiable precipitant, absence of premorbid character disorder, or degree of severity. These patients have been called endogenous or nonneurotic by prior clinicians.

The present conceptualization in DSM III draws in large part from Donald Klein's work.[33] He coined the term "endogenomorphic" and argued that it was a pervasive lack of reactivity of mood that was the hallmark of this group. He contrasts this with "demoralization" the patient stemming from a variety of causes. Demoralization is associated with the loss of the anticipation of enjoying oneself, but retains a positive response to pleasurable activities. (This distinction can be seen in the nonspecific, positive response of certain patients to the process of hospitalization; it is acknowledged in research strategies that incorporate a week of observation before a comparative medication trial, to separate out the environment-responsive patients.) Thus, the essential criterion in DSM III for melancholia is "loss of pleasure in all or almost all activities, lack of reactivity to usually pleasurable stimuli (doesn't feel much better, even temporarily, when something good happens).

There is an additional requirement in DSM III that three of a group of other behavioral disturbances also be present. (See Table 7). The choice of those specific characteristics remains a controversial area. In a thorough review of a variety of methodological approaches, Nelson and Charny[32] conclude there is consistent support for the following symptoms as associated with melancholic depression: distinct quality of depressed mood, diurnal variation with worsening in the morning, psychomotor change, and inappropriate or excessive guilt. A surprising finding was lack of discriminating significance for changes in sleep, appetite, and weight. These latter three features had long been held to be vegetative disturbances in autonomous depression, and are included in the DSM III melancholia criteria. Their more recent review[34] suggests that severity of depression, loss of interest, and decreased concentration should be substituted as features in future categorizations, and sleep and eating disturbances be omitted.

The diagnosis of melancholia is one of the few diagnoses in DSM III with specific treatment implications. What is lacking, however, is the inclusion of neuroendocrine and biochemical measures that add another degree of validity to the syndrome. Furthermore, abnormal results

Table 7
DIAGNOSTIC CRITERIA FOR DYSTHYMIC DISORDER

A. During the past 2 years (or 1 year for children and adolescents) the individual has been bothered most or all of the time by symptoms characteristic of the depressive syndrome but that are not of sufficient severity and duration to meet the criteria for a major depressive episode
B. The manifestations of the depressive syndrome may be relatively persistent or separated by periods of normal mood lasting a few days to a few weeks, but no more than a few months at a time
C. During the depressive periods there is either prominent depressed mood (e.g., sad, blue, down in the dumps, low) or marked loss of interest or pleasure in all, or almost all, usual activities and pastimes
D. During the depressive periods at least three of the following symptoms are present:
   1. Insomnia or hypersomnia
   2. Low energy level or chronic tiredness
   3. Feelings of inadequacy, loss of self-esteem, or self-deprecation
   4. Decreased effectiveness or productivity at school, work, or home
   5. Decreased attention, concentration, or ability to think clearly
   6. Social withdrawal
   7. Loss of interest in or enjoyment of pleasurable activities
   8. Irritability or excessive anger (in children, expressed toward parents or caretakers)
   9. Less active or talkative than usual, or feels slowed down or restless
   10. Inability to respond with apparent pleasure to praise or rewards
   11. Pessimistic attitude toward the future, brooding about past events, or feeling sorry for self
   12. Tearfulness or crying
   13. Recurrent thoughts of death or suicide
E. Absence of psychotic features, such as delusions, hallucinations, or incoherence, or loosening of associations
F. If the disturbance is superimposed on a preexisting mental disorder, such as Obsessive Compulsive Disorder or Alcohol Dependence, the depressed mood, by virtue of its intensity or effect on functioning, can be clearly distinguished from the individual's usual mood

on thyrotropin-releasing hormone (TRH), dexamethasone suppression test (DST), or diurnal cortisol tests could be taken as measures of fundamental lesion and used to define a subcategory of affective disorder. Researchers could then work backwards and try to elucidate associated secondary behavioral symptoms and describe a syndrome. However, there is an exceedingly complex interaction of a neurophysiological disturbance with the intellectual, personality, and developmental factors which shape its ultimate behavioral expression. Therefore, there will be limitations to a descriptive approach to diagnosis. Just as all other disorders in medicine may have a variety of symptom presentations, the defining criteria must ultimately be pathophysiological processes.

II. PERSONAL AND FAMILY HISTORY

A crucial component in the evaluation of psychiatric disorders is a comprehensive review of past personal and family history of medical and psychiatric illness and prior responses to treatment. There is a growing body of evidence demonstrating a genetic inheritance for the major syndromes: affective illness, schizophrenia, and anxiety disorders. Moreover, data regarding the patients premorbid personality and adaptive functioning, responses to medications (including reactions to drugs of abuse), and symptoms of previous episodes of illness can be used to great advantage in planning therapeutic strategies. This information must be actively elicited in interviews with both patient and reliable family members and documented with reports from previous treating physicians. Detailed descriptions of symptoms (not just diagnosis) and dose and duration of medication (for example, an adequate medication trial would be 21 days at therapeutic blood levels) are required to make effective use of this data.

Family history of psychiatric illness has become an increasingly important piece of information in the diagnosis and treatment of mental disorders. Due to the present lack of knowledge regarding pathophysiological mechanisms underlying psychiatric conditions, po-

sitive family history has become an important criterion in the phenomenological approach to the categorization of disease. It is of particular relevance when presenting symptoms are consistent with several different disorders.

The approach to the patient who presents with an acute psychotic disorder most clearly embodies the principles we have delineated. In other sections of this book we carefully examine the treatable physiologic derangements that present with mental disorders. In the case of acute psychosis, a number of organic processes would first have to be ruled out; this would include toxic states (e.g., amphetamine abuse or drug withdrawal), a metabolic abnormality, or some other disease process. If that workup is negative, the clinician is still left with a differential diagnosis including schizophrenia, one of the "other" psychoses (schizophreniform, brief reactive, schizoaffective), paranoid disorder, manic psychosis, and delusional depression. To proceed, one must then make use of family history, prior episodes, and treatment response, and past level of functioning. One of the most important developments in modern psychiatry has been the recognition that there are no cross-sectional pathognomonic symptoms. The following discussion demonstrates how this other information contributes to proper diagnosis and treatment.

A number of studies have demonstrated separate familial inheritance for schizophrenia and the affective disorders.[35,36] In the Iowa 500 Study, Winokur and co-workers[35] found the morbidity risk for schizophrenia to be significantly higher in the families of schizophrenic patients than in the families of patients with affective disorders. Moreover, the morbidity risk for affective disorders was significantly higher in families of patients with affective disorder; incidence of affective disorders in the families of schizophrenic patients was no different from that of the general population. The families of the affectively ill had an incidence of affective disorder nearly three times higher. This separation of these two disorders makes the finding of a positive family history an important contribution to the accurate diagnosis in a particular individual.

It has been well documented that for many years American psychiatrists have overdiagnosed schizophrenia and underdiagnosed manic-depressive psychosis.[7] Many of these patients have been referred to as "good prognosis" or "acute" schizophrenics in earlier studies. As comprehensively reviewed by Pope and Lipinski,[7] when the family pedigrees of these responsive patients with acute psychosis are examined, a much greater incidence of affective disorder is found than schizophrenia. It has been noted that the Schneiderian first rank symptoms or mood incongruent delusions are found in as many as 25% or more of patients with manic psychosis.[9,37] It was the assumption of specificity for schizophrenia of symptoms such as these that was responsible for much of the misdiagnosis. In actuality, their presence does not predict treatment response nor prognosis when found in the presence of the psychomotor and mood disorder of bipolar illness. This situation has been acknowledged in the expansion of the criteria in DSM III for the diagnosis of schizophrenia to include a 6-month duration of illness and lack of mood alteration. (See Table I.) The importance of this approach lies in its directing clinicians towards use of proper medications. Not only will a large group of patients now receive lithium as indicated, but also they will not be exposed to chronic treatment with neuroleptics and the attendant risk of serious side effects (e.g., tardive dyskinesia).

In a recent study of schizophreniform disorder, Pope and colleagues[38] found that these patients with brief psychotic disturbances were similar to those with affective disorder, even when the presenting episode lacked clearly defined affective symptoms. They frequently found a past personal history and family history positive for affective disorder, a positive DST, a positive response to antidepressant or lithium treatment, and a good short-term course. While limited by small sample size, this study demonstrates the crucial importance of personal and family history for diagnosis and the shortcomings of diagnosis by cross-sectional and not longitudinal symptoms. These acute psychoses are now recognized as

distinct from schizophrenia, as is repeatedly demonstrated in family studies and course of illness. While it is premature to conclude that they are always related to affective disorders, it is noteworthy that patients with a past history of affective disorder may present with psychosis without mood disturbances. In addition, the contribution of laboratory tests to diagnosis is impressively demonstrated; in 5 out of 6 cases DST was positive.

This discussion is also relevant for the category of schizo-affective disorder, which has been recognized in DSM III as a residual category without clear validation. Rosenthal, Fieve, et al.[39] found no difference in several important measures between bipolar patients who did and did not also meet RDC criteria for schizo-affective disorder. A number of studies have used family pedigree to further define these patients. Most conclude that a close relationship with affective disorder exists. However, there also seems to be a subgroup related to schizophrenia. At this time, it seems most prudent to approach these schizoaffective patients as a heterogeneous group.[40]

Information regarding past history can also be a crucial indicator of treatment response in patients meeting criteria for schizophrenia. Klein and colleagues[26] have defined a subgroup as "childhood asocial" who share some of the following characteristics: learning disorder and "soft neurological signs", poor peer relationships, and emotional eccentricity. They find that these patients have a poor prognosis and limited response to neuroleptics.

Further, they have a strong potential for further psychotic disorganization when treated with antidepressants. Similarly, a group of schizophrenic patients are found to suffer a toxic confusional state when treated with lithium; additional research is needed to better predict who may be at such risk.[26] Currently, studies are also underway to identify subgroups of schizophrenic patients on measures of anatomic or physiologic abnormality, family history, and as symptom clusters. Some results suggest that there are subgroups of patients with negative symptoms, enlarged ventricles on CAT scan, and negative family history who have a poor prognosis and minimal response to neuroleptics.[41-45] It is believed that the underlying pathophysiology will be discovered to be some neurological insult. The differentiation of these patients from those with positive symptomatology (e.g., paranoid delusions and hallucinations) who do respond to neuroleptics may become the most important distinction in the future subtyping within schizophrenia.[41,43]

Major depression with delusions is another disorder where past history information assumes crucial importance. It is generally accepted that these patients do not respond well to antidepressants alone and require either ECT or combination treatment with TCA and neuroleptics.[32] Moreover, Roose has recently reported that this group of patients represents the most serious risk for suicide.[46] It is often difficult to demonstrate the presence of delusions, and frequently they will be suppressed but present in a patient with severe agitated depression. In this respect, it is noteworthy that some clinicians recommend initiating treatment with neuroleptics for an agitated depression as it provides prompt relief of the most troublesome symptoms.[26]

As Charney and Nelson[32] report, patients with delusional depression have a high prior history of delusional depression and the content of the delusions tends to be similar over repeated episodes. Furthermore, the symptoms that best discriminated delusional from nondelusional patients were increased feelings of guilt, rumination, agitation, and referential thinking. It is recommended that one's suspicion for suppressed delusions be high in the face of this constellation of symptoms, especially if the prior history is positive for a delusional episode. In this way, proper treatment with neuroleptics or ECT will not be needlessly delayed.

In patients with major depression without delusions, family history of illness and response to medications can also be very helpful. Several pedigree studies have been reported[47,48] where there was a preferential response to a specific class of antidepressant among family members. In some families it was MAOI, in others TCA that was consistently effective.

Likewise, a history of family response to lithium would raise suspicion for bipolar illness (with attendant caution in the use of TCA) and recommend its use in other relatives.

A. Neuroendocrinological Confirmation of DSM III Diagnosis

A major goal of research in biological psychiatry has been to identify measurable biological abnormalities that would reliably confirm a psychiatric diagnosis, identify the major psychiatric disorders, and aid in differential diagnosis and choice of treatment. One strategy for augmenting clinical diagnosis is to measure neuroendocrine and other biological correlates that, in addition to helping to elucidate the biological mechanisms of psychiatric disorders, may define more homogeneous groups of psychiatric patients and guide the choice of pharmacotherapy. The development in the past 25 years of effective and specific pharmacotherapies for major depression, manic-depressive illness, and schizophrenia has underlined the importance of diagnosing these disorders accurately. The efficacy of tricyclics and monoamine oxidase inhibitors in depression, lithium in manic-depression, and antipsychotic (neuroleptics) in schizophrenia, as well as the demonstration of a strong genetic component in the etiology of affective disorders and schizophrenia, have given credibility to the working assumption that neurobiological abnormalities underlie many of the major psychiatric disorders. Despite the advances of clinical nosology that DSM III offers,[49] the use of biological markers may define more clearly homogeneous groups of psychiatric patients and guide choice of treatment.

For example, the term "depression" can be applied to a spectrum of clinical presentations that may appear similar but which may respond differently to antidepressant medications.[50] In particular, it is important to identify patients with the full-blown medical syndrome of depression, called endogenous depression in the older literature and called major depressive disorder in DSM III. In this subgroup of depressives with major depression, the clinician would think in terms of genetic and other biological predispositions as of etiological significance. Most importantly, in this subgroup, somatic treatment, usually antidepressant medications, would usually be the initial focus of treatment. Distinguishing major from nonmajor depressions on the basis of symptoms and history alone can be extremely difficult in many cases, making choice of antidepressant medication, psychotherapy, or a combination difficult. Such treatment decisions would be aided by laboratory markers for major depression.

Several avenues of research, including studies of metabolites in the cerebrospinal fluid (CSF), have suggested that such patients with major depression have changes in brain monoaminergic neurotransmission as part of the pathophysiology of their mood disorders.[50] Such changes may be of use as diagnostic markers. Obviously, studies of spinal fluid metabolites and other, more invasive techniques are not clinically practical techniques for identifying depressed patients with neurochemical changes underlying their depression. The approach that has shown most promise for clinical use, and the approach our group has pursued the most actively, has been the "neuroendocrine strategy".

1. The Neuroendocrine Strategy

The neuroendocrine strategy involves measuring changes in peripheral hormone concentrations, sometimes after provocation, as markers of major psychiatric disorders. Because the monoamine neurotransmitters norepinephrine (NE), serotonin (5HT), and dopamine (DA) regulate the hypothalamic factors that control the pituitary and hence other glands,[51] changes in neuroendocrine systems reflect changes in the monoamine systems thought to be involved in mood disorders. For this reason, the neuroendocrine strategy has been called the "window into the brain". It may not be sheer coincidence that the neurotransmitter systems involved in mood regulation and endocrine regulation are similar. The vegetative symptoms of depression, including disturbances in sleep, appetite, weight, and libido — the hypothalamic symptoms of depression — have long suggested neuroendocrine abnormalities in depression.

Table 8
SUMMARY OF NEUROENDOCRINE ABNORMALITIES IN PATIENTS WITH MAJOR DEPRESSIVE DISORDERS

Hormone	Basal	Challenged
GH	—	Insulin, L-dopa
		Amphetamine and clonidine stimulation ↓
		TRH stimulation ↑
PRL	↑	TRH stimulation ↓
LH	↓	LHRH stimulation ↑
TSH	—	TRH stimulation ↓ (unipolar)
ACTH/cortisol	↑	Dexamethasone nonsuppression; amphetamine stimulation ↓

Table 9
CLINICAL USES OF NEUROENDOCRINE TESTS IN DEPRESSION

1. Diagnosis
2. Prediction of treatment response
3. Documentation of biological state change with treatment
4. Prediction of relapse

Patients with major depressive disorder have been reported to have a number of reproducible neuroendocrine abnormalities (Table 8). Patients with major depression have a decreased growth hormone (GH) response to a number of provocative stimuli, including insulin-induced hypoglycemia,[52] L-dopa,[53] clonidine,[54] and amphetamine[55] and an augmented GH response to thyrotropin-releasing hormone (TRH).[56] Other neuroendocrine abnormalities reported in major depression included increased prolactin (PRL) secretion,[57] decreased luteinizing hormone (LH),[58] decreased LH response to gonadotropin releasing hormone (LHRH),[59] increased cortisol secretion,[60] failure to suppress cortisol production on the dexamethasone suppression test (DST),[61] decreased cortisol secretion in response to dextroamphetamine,[62] and decreased thyroid-stimulating hormone (TSH) and PRL response to TRH.[63-66] Neuroendocrine tests may have multiple uses in the diagnosis and treatment of the depressed patient (Table 9).

The focus of this section will be on two neuroendocrine challenge tests — the DST and the TRH test — which have been shown to be useful markers for major depression and with which our group has considerable experience. We will review and summarize the use of these tests, as well as present some of our own data on these two tests in affective disorders.

B. Hypercortisol Secretion and the DST

It has been well documented that a significant proportion of patients with major depressions secrete abnormally high amounts of cortisol from the adrenal gland.[60] This has been reported by measurement of the serum cortisol at multiple time points throughout the 24-hr period, as well as by more integrated measures such as 24-hr urinary-free cortisol secretion. Recent studies have suggested that measurement of serum cortisol over a 3-hr period from 1 to 4 correlates well with 24-hr cortisol secretion and may be useful as an index of integrated cortisol secretion. In addition to hypercortisol secretion, many major depressives show loss of the normal diurnal variation in cortisol secretion. The normal circadian rhythm of cortisol consists of secretory bursts that decrease from 4 p.m. to midnight, and peak around 9 a.m. (see Figure 1).[51,56]

Secretion of cortisol by the adrenal is stimulated by the pituitary hormone adrenocorti-

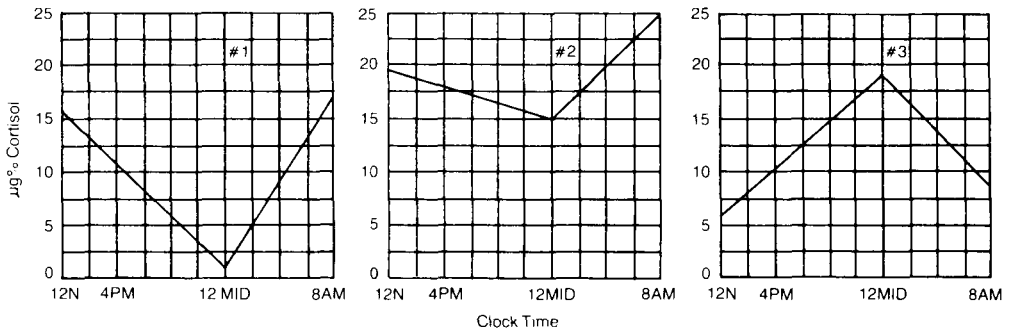

FIGURE 1. Changes in normal diurnal cortisol secretion pattern in major depression.

cotrophic hormone (ACTH). ACTH production is in turn controlled by corticotropin releasing hormone (CRH). This hypothalamic-pituitary-adrenal (HPA) axis shows inhibitory feedback control, which is utilized in the DST, a test of HPA regulation.[51]

In the DST, 1 mg (or 2 mg) of the synthetic corticosteroid dexamethasone is administered orally at about 11 p.m. The normal response is that this excess corticosteroid is "read" by the pituitary and hypothalamus like an excess of cortisol, and cortisol production is suppressed for at least 24 hr. Failure to suppress on this DST was first used as a diagnostic test for Cushings Syndrome. The finding of importance to psychiatry is that approximately 45% of major depressives fail to suppress cortisol production on the standard DST.[61] Failure to suppress is defined as any cortisol value $\geq$ 5.0 μg% at any time in the 24 hr after dexamethasone administration (Figure 2). Thus while most patients with major depression do not have true Cushing's Syndrome, about half of them have a Cushing's-like biochemical profile.

Carroll et al.,[61] who have pioneered the use of the DST as a laboratory test in psychiatry, have reported a rate of nonsuppression as high as 67% in a melancholic subgroup of major depressives and have proposed the DST as a diagnostic test for this disorder. The DST does not seem to differentiate between unipolar and bipolar depression. However, DST nonsuppression seems clearly to differentiate major depression from nonmajor depressions, and primary from secondary depressions. Failure to suppress on the DST has been reported to be rare in psychiatric disorders other than major depression, with a false-positive rate of less than 5% in appropriately pre-screened populations. However, some recent studies suggest higher levels of nonsuppression in certain subtroups of patients with psychiatric disorders other than major depression. An initial study suggested that DST nonsuppression may identify a subgroup of major depressives defined by family history as familial pure depression.[67] However, subsequent studies have not confirmed this finding. Carroll et al.[61] have reported the diagnostic confidence level of an abnormal DST in the diagnosis of major depression in a mixed population of psychiatric patients to be approximately 95%. This means that, in such a population, the failure to suppress on the DST identifies a patient with a major depression 95% of the time. One must keep in mind that the diagnostic confidence (or predictive value) of the DST, like any diagnostic test, will vary depending on the prevalence of the illness in question in the population tested.[68]

The DST begins with administration of 1 mg of dexamethasone orally at about 11 p.m. The patient will experience no subjective effects from this test. Small samples of blood are obtained by venipuncture at a number of time points in the 24 hr after dexamethasone administration for assay of serum cortisol. Competitive protein binding and radioimmu-

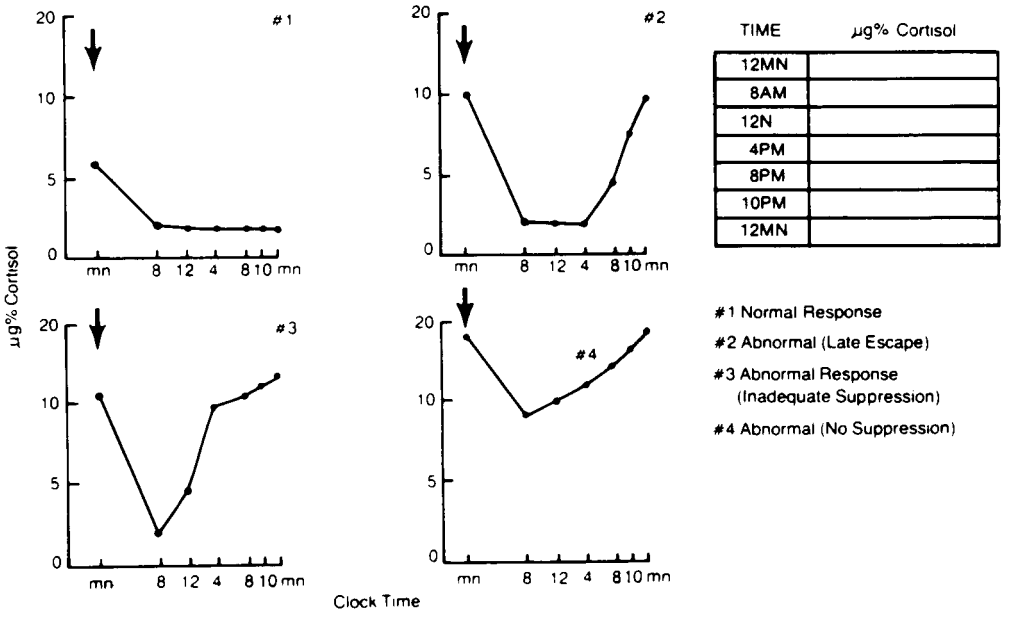

FIGURE 2. Patterns of abnormalities on the dexamethsone suppression test in major depression.

noassay (RIA) are the two most commonly used assays. The clinician utilizing this test must be surethat the laboratory being used has a cortisol assay which is sensitive and reliable in the lower ranges of cortisol from 3 to 8 µg% which are crucial for the DST in psychiatry.[56,61]

Carroll et al.[61] and others have utilized two post-dexamethasone time points for determination of cortisol: 4 p.m. and 11 p.m. We have reported that, by increasing the number of time points in the 24 hr post-dexamethasone to six, the sensitivity of the test for major depression is increased by about 40%, with only a small loss of specificity. Specificity has been reported increased and sensitivity decreased with increase in dosage of dexamethasone from 1 mg to 2 mg. It has been suggested that a cut-off of 4 µg% or lower for nonsuppression may be optimal, depending on the assay. The optimal parameters for the DST in psychiatry need to be studied further.

Certain factors that can affect the validity of the DST must be taken into account in screening psychiatric patients appropriate for the DST.[61] While usual therapeutic doses of benzodiazepines, neuroleptics, tricyclics, and lithium do not affect the DST, other medications can. Barbiturates, phenytoin, carbamazepine, and other medications that induce hepatic enzymes and hence speed the metabolism of dexamethasone can cause false positives. It is noteworthy, however, that a recent study showed that the DST can be useful in alcoholics 3 to 4 weeks after detoxification in identifying patients with major depression.[69]

Failure to suppress on the DST and hypercortisol secretion are dissociated in some patients.[56,70] In other words, some major depressives have elevated diurnal cortisols while showing normal suppression on the DST, and some are felt to suppress on the DST despite normal diurnal cortisols. More research needs to be done to explain this dissociation. However, a practical implication of the finding is that measurement of diurnal cortisol may complement the DST as a measure of HPA axis hyperactivity.

What are the mechanisms of HPA axis activation in major depression? Studies measuring ACTH levels before and during the DST are not in complete agreement, but suggest that DST nonsuppression is associated with increased ACTH levels. At the level of the brain, loss of noradrenergic inhibition and increased serotonergic stimulation of the HPA axis in

some depression may account for DST nonsuppression.[51] The recent identification and synthesis of CRH may lead to a new generation of studies further elucidating the mechanism of HPA axis hyperactivity in major depression.

C. The TRH Test

A large number of independent investigators have confirmed the finding that patients with major depression have blunted response of the pituitary hormone TSH to an infusion of the hypothalamic tripeptide TRH.[63-66] There is some controversy as to whether unipolar and bipolar depressives differ on the TRH test.[71] The TRH test is a standard endocrinological procedure, first used in the diagnosis of thyroid disease.[51] We have suggested that TRH test has utility as a diagnostic test in psychiatry in euthyroid patients with affective disorders.[56,65,71,72]

The TRH test consists of measurement of TSH response to infusion of TRH. An indwelling venous catheter is placed in patients who are at bedrest at 8 a.m. after an overnight fast. At 9 a.m., 500 μg of synthetic TRH are administered over 30 sec through the catheter. The patient experiences only mild, transient autonomic symptoms such as the urge to urinate. Before and 15, 30, 60, and 90 min after TRH administration, small samples of blood are obtained via the catheter for measurement of serum TSH in duplicate by RIA. The maximum TSH response, or Δ TSH, is determined for each patient by subtracting the baseline TSH from the peak TSH level after TRH infusion. GH and PRL also may be measured after TRH infusion, since patients with major depression may have a positive GH response to TRH or blunted PRL response not found in most other psychiatric patients or normal controls.

Several factors can decrease the TSH response to TRH and they must be taken into account in interpreting TRH test results in depression.[51] These include hyperthyroidism, corticosteroids, some drugs of abuse, alcoholism, and age over 60 in males. Factors which can augment the TSH response to TRH include hypothyroidism and lithium. Many commonly used psychotrophics, including benzodiazepines, neuroleptics, and tricyclic antidepressants, do not significantly interfere with the TRH test.[73]

We have found the definition of Δ TSH $\leq$ 7.0 microinternational units per milliliter μIU/mℓ as a blunted TSH response to TRH useful in discriminating subgroups of depression. In one study,[65] we administered the TRH test to 145 consecutive patients who met Research Diagnostic Criteria (RDC)[74] for major depression, primary unipolar subtype, or nonmajor depressions (minor or intermittent depression). The patients with nonmajor depressions all met DSM III criteria for dysthymic disorder, adjustment reaction, or personality disorder. Excluded from this study were patients with alcohol or drug abuse or addiction or use of lithium in the previous 6 months. Patients were free of all medications except acetaminophen and flurazepam for at least 3 days prior to the TRH test. All were euthyroid based in physical exam, clinical assessment, and normal thyroxine (T4), triiodothyronine (T3) — uptake, and baseline TSH. The mean Δ TSH 7.3 ± 0.5 μIU/mℓ in the 105 unipolar patients was significantly lower ($p \geq .01$ by t-test) than that of 10.9 ± 0.7 μIU/mℓ in the 40 patients with nonmajor depressions. (Figure 3). Sixty-five of the unipolar depressed patients, but only four of the nonmajor depressed patients and none of the controls showed a Δ TSH $\leq$ 7.0 μIU/mℓ (see Table 10). These intergroup differences were significant at the $p \geq 0.01$ by chi-square test. If a Δ TSH $\leq$ 7.0 μIU/mℓ is used as a diagnostic test to identify patients with a clinical diagnosis of major unipolar depression in this group of patients and controls, the sensitivity is 56%, the specificity is 93%, and the diagnostic confidence level is 91%.

We have also found that manic patients tend to have blunted TSH response to TRH, whereas patients with schizophrenic psychosis tend to have a normal response.[75] It is important to differentiate these two groups of patients, who can appear similar in their acute phase of illness, because of the better prognosis and response to lithium of the manic patient. We administered the TRH test to 30 consecutive euthyroid, nonalcoholic admissions who met RDC for mania, and 30 who met RDC for schizophrenia, undifferentiated subtype.[65]

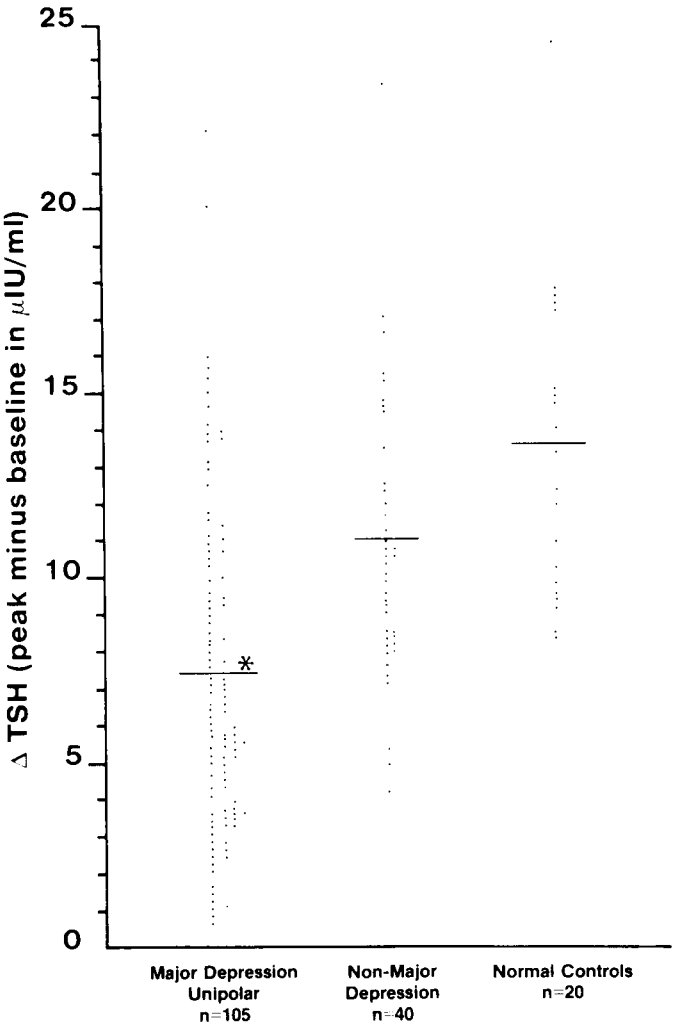

FIGURE 3. The TRH test in major unipolar depression, nonmajor depressions, and controls. * = mean Δ TSH in unipolar depression significantly less than in nonmajor or controls ($p < .01$).

All the schizophrenic patients were actively psychotic. None of the 60 patients had been treated with lithium within the previous 6 months. The mean Δ TSH of 6.4 ± 0.5 μIU/mℓ in the manic patients was lower than that of 10.2 ± 0.8 μIU/mℓ in the schizophrenic patients and that of 13.4 ± 1.0 μIU/mℓ in 20 normal controls ($p > 0.001$) (see Figure 4). Using the criteria of Δ TSH ≤ 7.0 μIU/mℓ as blunted, 18 of the 30 manics, but only 8 of the 30 schizophrenics and 0 of the 20 controls, showed a blunted TSH response to TRH (see Table 11). This difference was significant at the $p > 0.05$ level by chi-square, thus, the TRH test may be a diagnostic tool in distinguishing mania from schizophrenia. Because TRH secretion is regulated in part by NE, DA, and 5HT, changes in TSH response to TRH in depression and mania may reflect the changes in monoamine systems thought to be involved in mood disorders.

D. Combined Use of the DST and TRH Test

We studied 124 consecutive euthyroid, nonalcoholic, or drug abusing inpatients with

Table 10
BLUNTED TSH RESPONSES TO TRH IN SUBGROUPS OF DEPRESSION

		Δ TSH in μIU/mℓ	
	N	>7.0	≤7.0
Normal controls	20	20	0
Nonmajor depressions	40	36	4
Major depressions, primary unipolar subtype	105	45	60[a]

[a] $p < 0.01$.

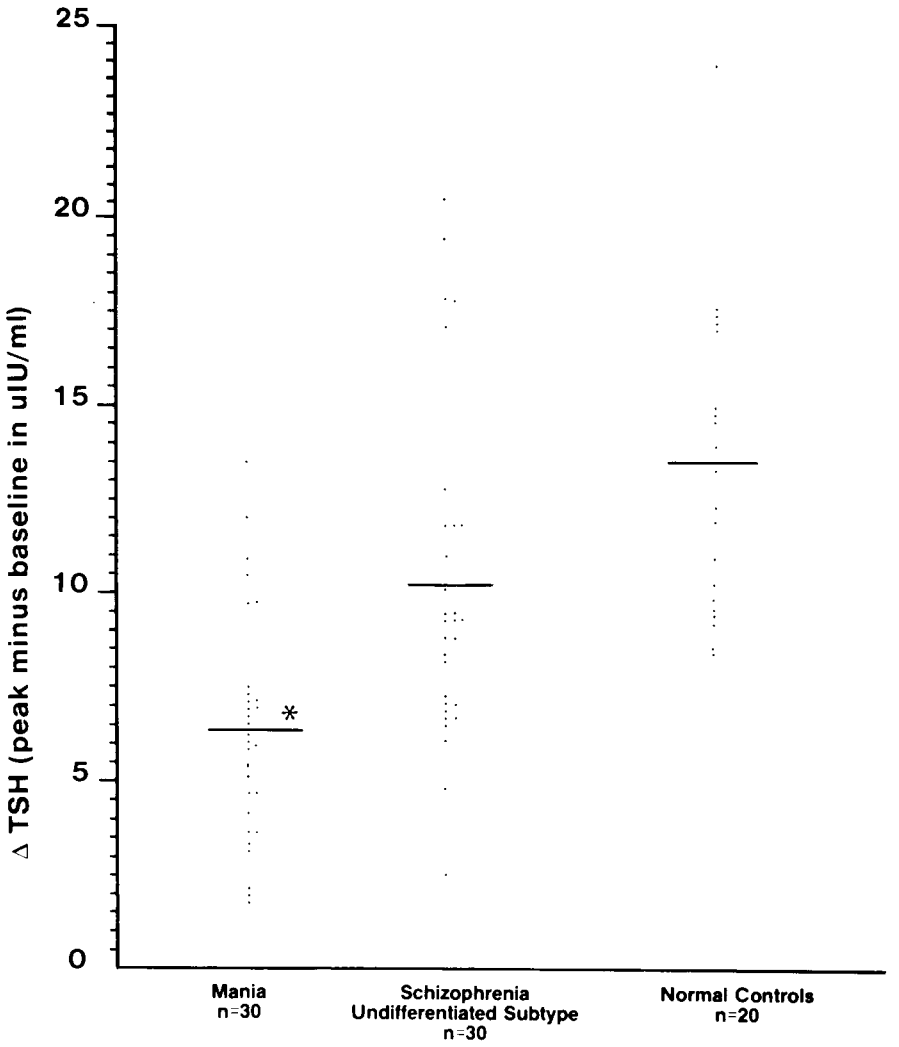

FIGURE 4. The TRH test in mania, schizophrenia, and controls. * = mean Δ TSH in mania significantly less than in schizophrenia or controls ($p < .001$).

Table 11
BLUNTED TSH RESPONSES TO TRH IN PATIENTS WITH MANIA AND SCHIZOPHRENIA

		Δ TSH in μIU/mℓ	
	N	>7.0	≤7.0
Normal controls	20	20	0
Schizophrenia	30	22	8
Mania	30	12	18[a]

[a] $p < 0.05$.

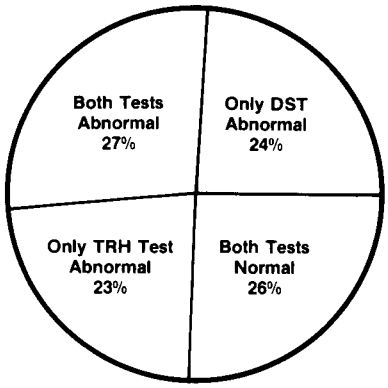

FIGURE 5. Dexamethasone suppression test (DST) and TRH test abnormalities in 124 inpatients with major depressive disorder, primary unipolar subtype.

major depressive disorder, primary unipolar subtype, who had a 1-mg DST following a TRH test.[70] Of these, 51% failed to suppress on the DST and 50% had a blunted TSH response to TRH. There was no relationship between these abnormalities by chi-square test. Twenty-three percent had an abnormality on the TRH test only, 24% on the DST only, 27% on both, and 26% on neither. (See Figure 5.) Thus, each of the two tests seems necessary and complementary in the neuroendocrine evaluation of the depressed patient.[70,76] Using both tests, 74% of the unipolar patients could be identified as having a neuroendocrine abnormality.

Preliminary data from our studies have suggested an association between patients having abnormalities on both the DST and TRH test and need for electroconvulsive therapy (ECT).[77] In an open study of inpatients with unipolar depression treated by physician's choice treatment, seven of eight patients who were given ECT had both neuroendocrine abnormalities, as opposed to only 6 of 19 patients in whom antidepressants only were used. Patients were given ECT because they had been refractory to other treatments or had severe or life-threatening symptoms such as psychosis, suicidality, or refusal to eat. Perhaps patients with abnormalities on both the DST and TRH test represent a subgroup or more severely ill depressives with characteristics treatment responses.

E. Special Diagnostic Uses of Neuroendocrine Tests

There are a number of areas of diagnosis which present particular difficulties to the

Table 12
SPECIAL DIAGNOSTIC USES OF NEUROENDOCRINE MARKERS FOR DEPRESSION

1. Depression in borderline personality disorder
2. Depression in childhood and adolescence
3. Depressive pseudodementia vs. dementia
4. Catatonia
5. Schizoaffective disorders

clinician. In these a series of laboratory tests might be particularly useful (see Table 12).

Depressed mood is almost ubiquitous in the course of patients with borderline personality disorder. It is often difficult to know whether the dysphoria represents a true depressive illness requiring antidepressant medication, or whether it is more accurately seen and treated as part of the character disorder. Several studies, including ours, have shown a high rate of DST and TRH test abnormalities in borderline patients, suggesting many borderline patients have depression similar to major depressions in nonborderlines.[78,79]

The diagnosis of major depression and, hence, choice of antidepressant medication treatment can be more difficult in children and adolescents because of developmental changes which color the diagnostic picture. In a study of inpatient adolescents[80] without drug or alcohol abuse, we found that 8 of 15 adolescents with major depression showed nonsuppression on the DST, whereas only 1 of 12 patient adolescent controls failed to suppress ($p > 0.025$) (see Table 13). Thus, the DST appears to have the same utility in adolescents as in adults as a marker for major depression.

The DST has also been suggested as a test that can help differentiate patients with so-called "depressive pseudodementia" who may respond to antidepressant treatment from patients with true dementia.[61] There have been conflicting reports in this area, however.[81] DST nonsuppression has also been suggested as a marker for the subgroup of patients with catatonia and schizoaffective disorder who have an illness more like an affective illness, and who may respond to medications such as tricyclic antidepressants and lithium.[82]

F. Relationship of DST and TRH Test Abnormalities to Treatment Response

The possibility that neuroendocrine tests may aid the clinician in predicting responses to treatment is an exciting area of current research.[83] Several groups have reported preliminary studies suggesting that nonsuppressors on the DST are more likely to respond to the so-called "serotonergic" tricyclics, such as amitriptyline and chlorimipramine.[84] Other groups have reported simply that depressed patients with neuroendocrine abnormalities are more likely to respond to, and hence are candidates for, somatic treatment, be it antidepressant medications or ECT.[61] One study of patients with which schizophrenic and schizoaffective disorders showed that the DST nonsuppression was a better predictor of response to tricyclics and lithium than clinician's judgment.[82] We have preliminary data suggesting that, although there was no association between TRH and DST abnormalities and response to tricyclics among major depressives, patients with abnormalities on both the DST and TRH test were more likely to need ECT.[77] Obviously, this is an area for further research.

G. Normalization of the DST and TRH Test and Prognosis

Failure to suppress on the DST and blunted TSH responses on the TRH test in major depressions tend to normalize with clinical and neurobiological improvement during the course of treatment.[73,85-87] We have shown this normalization to the DST in patients successfully treated with ECT. On the TRH test, we studied 14 unipolar depressed patients who had a blunted TSH response and who showed marked clinical improvement after

Table 13
DEXAMETHASONE SUPPRESSION TEST ABNORMALITIES IN ADOLESCENTS WITH MAJOR UNIPOLAR DEPRESSION

	Dexamethasone suppression test	
	Suppression	**Nonsuppression**
Major unipolar depression	7	8
Control patients	11	1

Note: $p < .025$, The Fisher Exact Probability Test.

antidepressant medications and/or ECT.[85] These patients had the TRH test repeated after improvement. The mean Δ TSH increased significantly from 4.0 ± 0.6 to 8.1 ± μIU/mℓ ($p > 0.01$ by paired t-test). The number of patients with Δ TSH ≥ 7.0 μIU/mℓ increased significantly from 0 to 9 out of 14 after improvement (see Figure 6).

By repeating the DST and TRH test during the course of treatment, the clinician can obtain initial prognostic information about when the neurobiological abnormalities of depression are in remission. This information may help determine when antidepressant medications or ECT is no longer needed, and when continued or different treatment is needed. This use for the DST and TRH test in confirming successful treatment is particularly important in psychiatry, where efficacy has been questioned.

Several studies have shown that patients who have the persistance of DST or TRH test abnormalities after treatment have a much higher probability of relapse, regardless of clinical appearance or outcome up to that time.[73,86] The prognostic value of the DST and TRH test in depression is a very exciting and practical application of these tests to clinical practice. Patients who have not normalized on the TRH test despite apparent recovery may need closer monitoring, prophylactic antidepressants for a longer time, and other appropriate measures in view of their higher likelihood of relapse.

H. Growth Hormone Response to Insulin Hypoglycemia

The blunted GH response to insulin-induced hypoglycemia[52] is of special interest because of the reported relationship between low GH response and low urinary excretion of MHPG, the major metabolite of NE in the brain.[88] GH response in bipolar manic patients shifted downward in comparison to unipolar depressives.[88] Another group reported that bipolar depressives and unipolar depressives differed significantly in their GH response to L-dopa.[89] These studies which are another example of the "neuroendocrine window into the brain", suggest GH challenge tests may help define differences in NE metabolism in subgroups of patients with affective disorders.

III. CONCLUSIONS

In the 1980s, the DST, TRH test, and other biological tests are becoming part of the nosology for the diagnosis of depression and other psychiatric disorders that includes both clinical descriptive and laboratory information. One of these tests being positive gives strong confirmation to the diagnosis of major depression and need for somatic treatment. However, a negative test result does not rule out this disorder. With appropriate education of patients and their families, the DST and TRH tests are generally well tolerated and valued as adding objective information about the illness in question. Psychiatrists, like their colleagues in

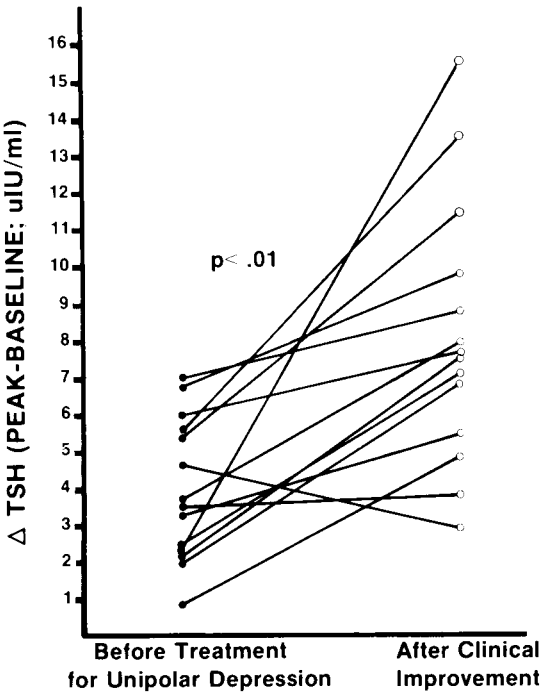

FIGURE 6. The TRH test before and after clinical improvement in 14 patients with major unipolar depression.

other branches of medicine, will be using laboratory tests to augment good clinical judgment in confirming diagnosis and planning treatment.

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Chapter 2

PSYCHIATRIC MISDIAGNOSIS

Todd W. Estroff and Mark S. Gold

TABLE OF CONTENTS

I. INTRODUCTION

One of the more recent discoveries of modern psychiatry is that the majority of psychiatric disorders show a remarkably low response to initial treatment.[1] The rates of relapse of patients who are systematically followed for a period of a year or more is disconcerting.[1,2]

Depressed patients who receive vigorous treatment with antidepressants, monoamine oxidase inhibitors, or electroconvulsive therapy (ECT) show initial response rates that are somewhat better than placebo or cognitive therapy. ECT response rates (showing a marked or moderate improvement) are the highest and yet are rarely above 80%.[2] Even if there is an excellent initial response to any kind of treatment, it is clear that there is an increasing tendency toward relapse following hospitalization.[1,2] The quality of response even among "responders" varies considerably and many patients classified as responders ask for another treatment or switch physicians. Response rates are far worse and relapses are more common and severe in bipolar affective illness and schizophrenia. There are many factors which contribute to psychiatric nonresponse, incomplete response, and relapse.

One of the major reasons for these treatment failures is that many of these patients are being treated for psychiatric disorders when in fact they are suffering from physical illness or drug or alcohol abuse.[3-6] Psychiatric symptomatology can be and frequently is the first manifestation of a reversible physical illness. Contrary to the beliefs of most psychiatric and nonpsychiatric physicians, this occurrence is not rare.[3-6] It has been, in fact, repeatedly documented by many different authors that physical illness needs to be vigorously excluded before a psychiatric diagnosis can be made.[3-6] At a recent meeting, the consensus of a panel of experts was that out of the group of DSM III-diagnosed, unipolar, major depression disorders, 30 to 40% would eventually be found to be primarily secondary to physical illness.

This chapter is devoted to a discussion of physical illnesses which can present with only psychiatric symptoms and are thus indistinguishable from any of the symptom descriptions in the Research Diagnostic Criteria, and the psychiatric section of the DSM III Manual.[7]

It is assumed by the DSM III committee, and it is clear from looking at the differential diagnosis trees (of "psychotic features," "irrational anxiety and avoidance behavior," "mood disturbance," "antisocial, aggressive, defiant or oppositional behavior," "physical complaints and irrational anxiety about physical illness," "academic and learning difficulties," and "organic brain syndromes"), that physical illnesses must be ruled out first and foremost before proceeding through the decision tree. If a physical illness is found, the diagnosis must then move into the section on organic mental disorders. This first assumption and weakest link of DSM III is unfortunate. While these sections partially cover the spectrum of the physical disorders that present with psychiatric symptomatology, this classification becomes inadequate when considered in the context of the recent work. It is vague and imprecise at times. The most glaring example is "organic affective disorder" which does not distinguish between depression and mania or bipolar and unipolar disorders. An alternate way of more precise classification is to diagnose the disorder as it presents psychiatrically and add "secondary to" the physical illness. This alternate orientation will be emphasized throughout this chapter.

II. OUTPATIENT STUDIES

Hall et al.[3] studied 658 consecutive psychiatric outpatients and found that 9.1% of these patients had medical disorders that *produced* the psychiatric symptoms. The additional patients in whom medical disorders were mostly or partially causative were discussed but not quantified; 46% of these patients could have been identified by their initial treating physicians. These physicians either did not know enough or take enough time to take a

careful history, perform a physical exam, or order appropriate testing which could have revealed their patient's illness before referring them on.

In another study of outpatients, Koranyi[5] excluded all patients who were immediately hospitalized as well as those patients who failed to complete a comprehensive assessment. An initial sample of 2670 patients and a final sample of 2090 patients who had been completely evaluated was examined; 43% of these patients were suffering from one or several major physical illnesses, 46% of which were undiagnosed at the time of referral. Of the total population, 7.74% had a physical illness which was causative of their psychiatric symptoms.

III. INPATIENT STUDIES

Herridge[6] studied 209 consecutive admissions to an inpatient unit and found that at least 5% had *major* physical illnesses which were causative and presented as a psychiatric disorder.

Hall et al.[4] conducted a prospective study of 100 admitted state hospital patients. Patients with known physical disorders along with sociopathic personality disorders and persons with significant histories of alcohol or drug abuse were omitted. An intensive search for causative physical illness revealed that 46% of the patients had a previously unrecognized and undiagnosed physical illness that was specifically related to their psychiatric symptoms and either caused these symptoms or substantially exacerbated them. Hall notes that, "28 of 46 patients evidenced dramatic and rapid clearing of their psychiatric symptoms when medical treatment for the underlying physical disorder was instituted. Eighteen patients were substantially improved immediately following medical treatments."[4] These studies clearly show that physical illness is either a precipitant or associated condition which needs to be considered in any diagnostic formulation. While these studies are alarming by themselves, more sophisticated and provocative testing techniques have been used successfully to help diagnose thyroid disease[8] and identify low dose drug and alcohol abuse in our psychiatric patients. These new tests will expand the percentage of medical illnesses found even further.[9]

IV. CLASSIFICATION OF PHYSICAL ILLNESS ASSOCIATED WITH PSYCHIATRIC SYMPTOMS

The previously cited studies refer only to physical illness which presented as psychiatric disorder and is in whole or in part *causative* of the psychiatric symptoms. It is important to be as specific as possible when discussing the interaction of physical illness and psychiatric disorders. Physical illness can cause or worsen psychiatric symptoms to a variable extent. Some disorders, which present exclusively with psychiatric symptoms, are wholly causative of the psychiatric symptomatology. These disorders, if treated properly and if not progressed to an irreversible stage, should result in a total clearing (a cure) of all the psychiatric symptomatology without institution of psychiatric treatment. If the condition has produced an irreversible change, the physical disorder totally explains the symptomatology (Figure 1). Other disorders exacerbate or in part cause the observed psychiatric symptomatology and, when treated, result in a significant but only partial clearing of the psychiatric symptoms (Figure 2). These are major causes of poor response and relapse but they will only be noted where appropriate in this chapter and will not be emphasized. Another group of disorders are those psychiatric symptoms which are in reaction to previously existing illness and will be considered only in passing in this chapter (Figure 3). Still other illnesses are concomitant and are not related to the psychiatric disorders and, when treated, produce no effect on the psychiatric symptoms (Figure 4). Finally, there are illnesses which present like and are mistaken for physical illness and are often treated incorrectly as such by nonpsychiatric practitioners (Figure 5).

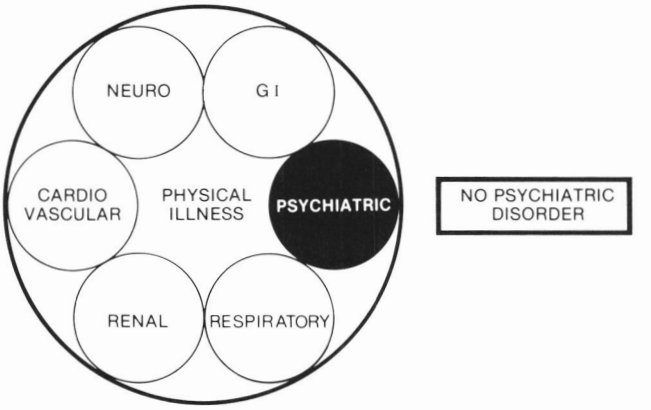

FIGURE 1. This represents physical disorders which are entirely causative of psychiatric symptoms. In this example there is no psychiatric disorder. Treatment of the physical illness results in total cure.

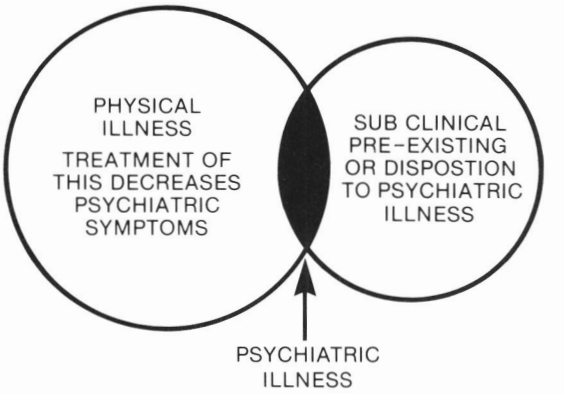

FIGURE 2. This represents the situation in which physical illness exacerbates a nonclinical psychiatric disorder to the point where it becomes clinically evident. Treatment of the physical illness partially clears the psychiatric disorder.

V. BOTH PSYCHIATRISTS AND NONPSYCHIATRISTS FAIL TO DIAGNOSE PHYSICAL ILLNESS

The previously cited studies suggest that psychiatric patients, whether they present to an outpatient department, are seen in a voluntary hospital setting, or are committed, have a very high percentage of medical illness which is previously unrecognized and undiagnosed.[3-5] Koranyi[5] reported that, of all the sources referring patients to his clinic, nonpsychiatrists failed to find 32% of physical illness in patients they referred, while psychiatrists missed 48% of the physical illness in the patients they referred to his outpatient clinic. Most striking of all was that 83.5% of all patients referred by social agencies or who were self-referred had undetected physical illness at the time they were seen in the outpatient department. This documents that doctors and psychiatrists are better than the patients themselves and other mental health workers in diagnosing physical illness, but their performance is poor by any standard. It is also noteworthy that Hall et al., in two studies,[3,4] and Koranyi[5] all found the

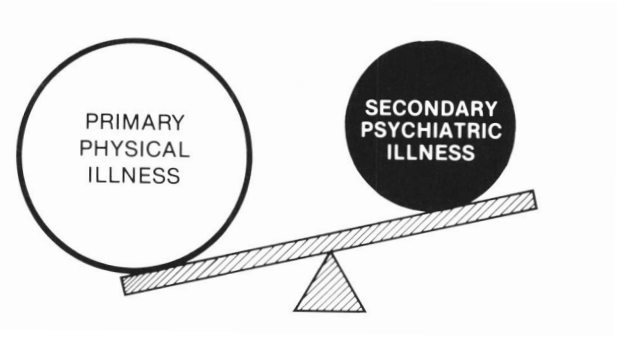

FIGURE 3. This represents the psychiatric disorders which occur in reaction to primary physical illness, usually a chronic disease. Treatment of the physical disorder can relieve the psychiatric disorder.

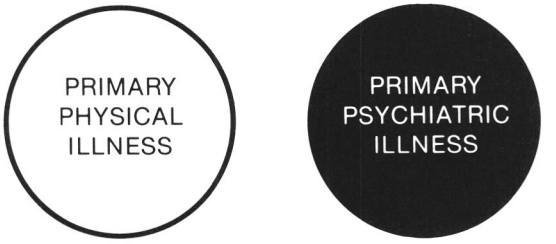

FIGURE 4. In this diagram there is no relationship between physical illness and psychiatric disorder. Treatment of either disorder does not affect the other.

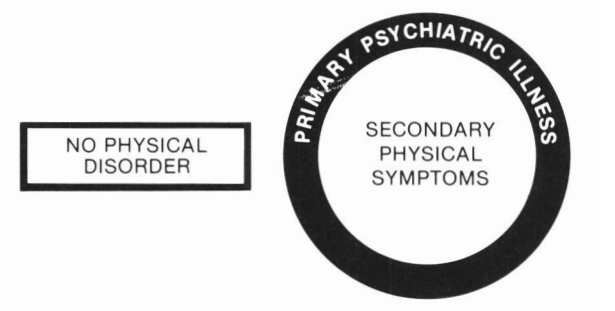

FIGURE 5. This represents a psychiatric disorder with prominent symptoms. There is no physical disorder. Treating the physical symptoms produces no result. Treating the psychiatric disorder results in total clearing of all symptoms.

same 46% rate of physical illness among patients referred to outpatient clinics or among committed inpatients when physical illness was actively sought and pursued with appropriate testing and referral. Similar findings were found by Hoffman,[10] who reported that, of 215 patients referred to a specialized medical psychiatric inpatient unit for further evaluation, the referring diagnosis was inaccurate in 41% of the cases and 24% of cases were changed from physical to psychiatric or from psychiatric to physical illness.

VI. REASONS PSYCHIATRISTS FAIL TO DIAGNOSE PHYSICAL ILLNESS IN PSYCHIATRIC PATIENTS

The factors which lead to these diagnostic errors are important and need to be scrutinized in detail. Klein et al.[11] feel that errors in diagnosis, "cannot be attributed to random sloppiness, bad faith, or lack of desire to help a patient to the utmost." They propose a variety of reasons which include simple lack of knowledge, educational lag in residency training programs, lack of continuing medical education, and resistance to new information. This can lead to a selective rejection of certain facts of the case so that the patient will more easily fit into the physician's speciality or orientation, and permits the psychiatrist to maintain his allegiance to certain schools of psychiatric and/or medical thought. This often results in a distortion and misperception of the patient and his sometimes obvious physical illnesses.

Many psychiatrists are particularly unequipped to deal with physical illness in their patients despite being physicians. One of the most unfortunate chapters in the history of psychiatry was the elimination of the internship requirement to enter psychiatric training. Happily this has been reversed since 1978. However, the actual and symbolic significance of this event will continue to reverberate throughout psychiatry since many new psychiatrists with internships will be taught psychiatry by psychiatrists who never had or minimized these important medical diagnostic skills. In addition, large numbers of those psychiatrists who had internships have actively avoided or forgotten the clinical skills they were supposed to have acquired during medical school and internship. McIntyre and Romano[12] found that less than 35% of practicing psychiatrists give their patients a physical examination; 32% of psychiatrists admitted that they felt *incompetent* to perform even a rudimentary physical. We suspect these numbers are much greater. As a result, when psychiatric patients are examined by psychiatrists, the exam is at best perfunctory and not directed towards searching out those medical disorders which could present with psychiatric symptoms. Most psychiatrists use the same means of sidestepping these issues as nurses, social workers, psychologists, and other nonmedical psychotherapists. They all consult either the patient's family doctor, internist, pediatrician, or gynecologist for a medical clearance to rule out physical disorders. Unfortunately, this is a grave mistake. Reliance on the other medical specialties has been suggested by Hall et al.[3,4] and Koranyi[5] to provide "a false sense of security for the treating psychiatrist."[4] Koranyi[5] used this procedure in the past and rejected it because, "My early practice consisting of a referral for routine medical consultation proved to be insufficient and unsatisfactory." He prefers to have the psychiatrist perform the examination himself because, "a thorough and unprejudiced physical examination with the appropriate biochemical screening is a singularly important act to be performed with the greatest thoroughness on all patients." He goes on to state that, "the examiner must continually entertain the question that 'other than obvious' might be the cause or contributing factor to the presenting symptom?". Sadly, few psychiatrists either act or think in this manner.

There are very few experts in the field of medical disorders which present as psychiatric illness. Although there has been a recent increase in the number of articles which address the subject[3-6,10,13,14] and four recent books devoted to the subject,[15-18] this knowledge has not spread widely and is unappreciated by many psychiatric and nonpsychiatric physicians. Some psychiatrists denounce what they call over-examination and testing of psychiatric patients. This is quite surprising considering that making an accurate diagnosis before starting treatment is emphasized and stressed so much in all other branches of medicine. It is also disturbing that so little attention and systematic research is focused on these issues. Ongoing research in the field, other than those articles cited previously, is so sparse that the spectrum of presentation for various physical disorders and the psychiatric disorders for which they may be confused has not been fully delineated in a prospective fashion.

We cannot continue to rely on pharmaceutical detail men to help psychiatrists to educate

themselves to these issues and switch over from the mode of practice of the 1960s to the 1980s and 1990s. Most psychiatrists and researchers will acknowledge that folate deficiency with a normal complete blood count (CBC) can produce depression or anxiety, but that knowledge has not changed their mode of practice even though high rates of physical illness presenting psychiatrically have been documented since the 1930s. Malpractice judgments against psychiatrists who fail to diagnose physical illnesses such as folate deficiencies may be the ultimate issue which brings these issues clearly into psychiatric consciousness. Hopefully more psychiatrists will set their practices up on the much more medically based model of the 1980s and 1990s in contradistinction to the 1950s and 1960s model of an attractive office with chairs and talking therapy for all patients no matter what their diagnosis. Future psychiatrists will have offices equipped with stethoscopes, opthalmoscopes, blood pressure cuffs, exam tables and blood drawing and analyzing equipment.

VII. DIAGNOSTIC ERRORS OF NONPSYCHIATRISTS

Factors which contribute to diagnostic errors by nonpsychiatric specialists, i.e., internists, surgeons, pediatricians, are their lack of knowledge about physical disorders which may present psychiatrically; lack of time to carefully examine the patient from a biopsychosocial perspective; and a tendency to refer patients with psychiatric symptoms to a psychiatrist rather than taking the time to consider other possible causes for the psychiatric disturbance.

In addition, nonpsychiatrists confronted with medical patients who also have psychiatric symptomatology tend to label those patients as the least likable of the patients they see and often call them "crocks" or other such perjorative names. Goodwin et al.[19] studied 22 patients in a systemic lupus clinic and asked the treating physicians to rank the patients in order of like and dislike. "The group of most disliked patients contained all the patients with signs of organic brain damage and all suicidal patients." Dislike of a patient by a physician was a bold clue to neuropsychiatric impairment. Unfortunately, dislike of a patient also leads to many diagnostic errors both in medicine and psychiatry. We feel that our dislike for a certain patient is a key sign to ourselves that a diligent search for a possible physical and psychiatric disorder must be made with compulsive attention to diagnostic precision and detail.

Teitelbaum,[20] in a recent editorial in the *JAMA*, described the lack of integration of medical and psychiatric care and states that expecting all psychiatrists or internists to be both expert in psychiatry and medicine is "unrealistic". "Both internists and psychiatrists should be able to recognize both physical and psychological disturbances in their patients and make appropriate referrals to their opposite colleague." He also feels that another major problem preventing collaboration between psychiatrists and other physicians is that they both try to oversimplify an extraordinarily complex situation. We could not agree more.

With rare exceptions, neither internist nor psychiatrist, without diagnostic testing, possess enough clinical skills to pick up the majority of the physical illnesses which present psychiatrically or contribute to a psychiatric presentation. Even when the correct differential diagnosis is constantly on their minds, a psychiatrist may be unable to adequately work a patient up because of the nonmedical nature of his office practice.

There also exists a group of diseases which we call the "Great Mimickers in Psychiatry" (these diseases will be dealt with in a further section of this chapter). These disorders are truly on the borderline of psychiatry and internal medicine and neurology. Most of them are not detectable by physical examination or by "routine" laboratory screening. The diagnosis may not be made unless the attending physician is aware of the existence of these diseases and the diagnosis is actively pursued through aggressive specialized chemical testing; 50, 100, or 150 similarly appearing patients may have to be tested to find one of these patients. We feel that this search is always worth it. Many times such an intensive search

is dismissed by our informed colleagues as a search for "zebras" and not justified on a cost effective basis. However, it is interesting to note the behavior of these same colleagues when they or members of their family start to have psychiatric symptoms. They insist that no stone be left unturned in the search for a more treatable cause of these symptoms.

We feel that if these disorders are looked for they will be found in greater frequencies than expected. It is worth it if we save or cure one patient in 100 from the stigma of being labeled mentally ill, properly treat the unresponsive misdiagnosed medical patient and avoid a prolonged psychiatric hospitalization.

VIII. WAYS TO AVOID MISDIAGNOSIS

By setting up and adhering to a standardized evaluation procedure for all inpatients *and* outpatients, many mistakes can be avoided. This evaluation includes careful history taking, extensive physical examinations by psychiatrists who also know internal medicine, and use appropriate laboratory testing to separate physical illness from primary psychiatric illness.

A. The Use of Psychiatric Laboratory Tests

Laboratory tests can be used to confirm the psychiatric diagnosis in many cases. Reliable and specific neuroendocrine tests such as Diurnal Cortisol, Dexamethasone Suppression Tests (DST), and the TRH (Thyrotropin Releasing Hormone)-TSH (Thyrotropin Stimulating Hormone) Release Test may be used to provide more diagnostic certainty. For example — a positive DST and/or a positive TRH test in a suspected case of a major depressive disorder is highly suggestive that it is a *primary* psychiatric disorder. These tests can also be positive in a characteristic manner in certain thyroid diseases, and hyper- or hypoadrenal disorders.[8] In addition, they may also be successfully used as screening tests for certain physical illness.

The patients who present with affective symptoms in whom all neuroendocrine tests are negative are at much greater risk for having a physical disorder presenting psychiatrically, and should be scrutinized much more carefully than those patients with positive neuroendocrine tests.

B. New Technologies in Psychiatry and Medicine

New tests are being devised which are increasingly sensitive in helping to diagnose medical illnesses presenting with psychiatric symptoms. This is well exemplified in the case of subclinical hypothyroidism (please see Chapter 3 in this book). This syndrome is a good example of what may be considered by some nonpsychiatric colleagues as a symptomless nondisease. Other examples include subclinical vitamin deficiencies and neurotransmitter precursor abnormalities which may be etiologically related to psychiatric illness. New technologies will aid us in the detection of more and more subtle forms of disease which present psychiatrically. Eventually, there will be a new class of experts in physical illness which present psychiatrically. By picking up these physical disorders and treating them specifically, these psychiatrists will be able to increase the treatment success rate by increasing diagnostic accuracy. There is need for more study in this area with prospective studies using DMS III or RDC criteria to examine the spectrum and frequency with which various physical illnesses present psychiatrically.

C. Specificity of Presenting Psychiatric Symptoms

From the previously cited studies and many others, it becomes clear that no matter how closely the first presentation of a psychiatric patient may conform to classical DSM III descriptive criteria, it does not guarantee that the patient is suffering from a psychiatric disorder. One of the best examples of this is the presenting symptom of catatonia. For many years, it has been clear that catatonia is not specific for schizophrenia and can be caused

by a wide variety of neurologic, metabolic, psychiatric, and other disorders. Unfortunately, this information is not widely known by psychiatrists or internists.[21-23] The differential diagnoses include: arteriosclerotic Parkinsonism and lesions of the basal ganglia, viral encephalitis, akinetic mutism, vascular lesions of the temporal lobes, tumors of the septum pellucidum infringing on the fornix, tumors and traumatic hemmorhage in the region of the third ventricle, focal lesions of the thalamus, frontal lobe tumors and lesions, anterior cerebral arterial aneurysms, AV malformations of the posterior cerebral circulation, diffuse brain trauma, diffuse encephalomalacia following closed head injuries, petit-mal epilepsy, status epilepticus, the postictal phase of epilepsy, Wernicke's encephalopathy, tuberous sclerosis, general paresis of syphilis, narcolepsy, acute phase of encephalitis lethargica, and cerebral-macular degeneration. Many metabolic conditions are associated with catatonia: diabetic ketoacidosis, hypercalcemia from parathyroid adenomas, pellagra, acute intermittent porphyria, homocystinuria, membranous glomerulonephritis, and hepatic encephalopathy. It has also been associated with poisoning with organic fluorides, illuminating gas, mescaline, large quantities of ethyl alcohol, chronic intoxication with amphetamines, and acute PCP (phencyclidine) intoxication. It has also been associated with medications such as aspirin overdoses, ACTH, and antipsychotic medications. The list of conditions and drugs which produce catatonia is indeed impressive.[24] Even if all of the previously mentioned disorders have been ruled out, and the diagnosis of a psychiatric disorder is fairly certain, there is still no guarantee that the catatonia is due to schizophrenia. Abrams and Taylor[23] found that, out of 55 patients who displayed one or more catatonic signs, only 4 met research criteria for diagnosis of schizophrenia, while 39 had affective disorders, 3 had a reactive psychosis, and 9 had organic brain disease.

This nonspecificity of medical disease causing specific behavioral syndromes applies to other disorders as well. The differential diagnosis of depression is long and involved. Giannini et al.[16] list 91 possible disorders which can present as depression. Hall[17] lists 24 medical illnesses that frequently induce depression and 77 medical conditions which *can* present as depression. Giannini lists 28 causes of auditory hallucinations, 26 causes of euphoria, 8 causes for mania, 56 causes of delusions, 21 causes of depersonalization, and 12 causes of hyperventilation. Hall et al.[3] found that visual hallucinations were present almost exclusively in medically induced psychiatric disorders. Thus there are a variety of physical disorders which can cause the same symptomatology.

To summarize, many patients who present with psychiatric symptomatology actually have medical illnesses. The psychiatric symptoms are merely the first and most obvious symptom of the physical illness. It is also apparent that no psychiatric sign or symptom is pathognomonic of psychiatric disorder and cannot be caused by a physical disorder. Many psychiatrists and most nonpsychiatric physicians are either unaware of these facts or actively ignore them. Most patients who present psychiatrically are not given a thorough physical examination and medical workup looking for possible medical causes of the psychiatric symptoms which would be reversed by treating the primary disease. The presence of catatonia or visual hallucinations changes the differential diagnosis so dramatically that the patient must be considered to have an underlying causative medical illness until proven otherwise by a diligent search for any possible underlying disorder. In addition, psychiatric neuroendocrine tests either can help confirm a primary psychiatric diagnosis or point the way to consideration of physical illness causing psychiatric illness.

The following section will review various medical disorders which can present psychiatrically. We will make an attempt to delineate the psychiatric spectrum with which these physical disorders may present to either the psychiatrist or the nonpsychiatric physician. We call these illnesses the "Great Mimickers in Psychiatry".

IX. THE GREAT MIMICKERS IN PSYCHIATRY

The great mimickers of psychiatry are disorders which we want to emphasize. These are diseases which are not easily picked up either by history, physical examination, or routine blood examination. Because they are uncommon diseases, neither psychiatrists nor nonpsychiatric physicians see them with much frequency in their practices. Many of them require very specific testing in order to confirm their existence. However there is a much higher chance of their being detected by an alert physician who is aware of this group of diseases. The most important point we can make about the great mimickers is that many of them are treatable and reversible if the diagnosis is made early enough in the course of the disease and specific treatment is instituted rapidly. We feel that this is one area of medicine in which the psychiatric physician must be a better clinician than any other internists, pediatricians, neurologists, and other medical and surgical subspecialists.

The Carcinoid Syndrome

Carcinoid tumor may present with severe depression, hypomania, periodic confusion, or anxiety. It may be accompanied by spontaneous flushing of the upper body which may be precipitated by consuming certain foods or alcohol, epinephrine administration, excitement, or exertion. An attack may be accompanied by abdominal pain and diarrhea. The syndrome accompanies a variety of tumors which occur in the GI tract and lungs. These tumors secrete various biologically active substances including dopamine, histamine, ACTH, and serotonin. Serotonin-secreting tumors are most common.

If this disorder is suspected, the diagnosis may be confirmed by an increase urinary excretion of 5 hydroxyindoleacetic acid (5-HIAA) which does not normally exceed 9 mg daily.[15]

Cancer

Many malignant tumors may present with psychiatric symptomatology sometimes months to years earlier than physical symptoms or signs. This subject has been recently reviewed in detail.[14]

Central nervous system (CNS) tumors present with psychiatric symptomatology, especially if they occur in the temporal and frontal regions. The most common symptom is a change in personality. Left-sided tumors present more frequently as irritability or depression, while tumors of the parietal and occipital lobes tend to be relatively silent. Limbic system tumors can present as depression, delusions, assaultive behavior, and confusional states. Spinal cord tumors are most likely to present and be misdiagnosed as conversion symptoms.[25]

Endocrine and other hormone-secreting tumors most frequently present psychiatrically. Peterson and Perl[14] claim that carcinoid, pheochromocytoma, and ACTH-secreting tumors, especially Oat Cell carcinoma of the lung, present psychiatrically most frequently. (Please see the sections in this chapter on hyperadrenalism caused by ACTH-secreting carcinoma.) Pituitary, thyroid, parathyroid, renal, ovarian, and stomach cancers can also secrete hormones and present psychiatrically. (Pancreatic carcinoma is discussed later in this chapter.) Peterson and Perl[14] feel that a high index of suspicion is indicated when the patient presents in an atypical fashion with a personality change, depression with a weight loss greater than 20 lb, or is unresponsive to a first trial of standard psychiatric treatment.

Dehydration

Patients may have dehydration on the basis of either the loss of water or water and sodium. The diagnosis is made by electrolyte measurement and postural changes in blood pressure.

The psychiatric symptomatology is usually that of an organic brain syndrome and often includes weakness, lethargy, confusion, and coma.

Diabetes Mellitus

In a study by Hall et al.,[4] patients with diabetes millitus presented psychiatrically and met the RDC diagnosis of schizophrenia, major depression, and personality disorders. Koranyi[5] noted that it may also present as impotence with normal libido and marital problems. The diagnosis is made by demonstrating an elevated fasting blood sugar or an abnormal response to a glucose load at 1 and 2 hr. The presence of glucose in the urine is less precise as individuals have different thresholds for spilling glucose into their urine. The presence of ketones in urine should also raise the possibility of diabetes.

Drugs

Psychiatric symptoms can often be the result of adverse reactions to any kind of drug. These reactions can be either iatrogenic or self-induced in the case of illicit drugs and alcohol or result from misuse or abuse of over-the-counter medication or some combination of these. Drug reactions can resemble all known psychiatric symptomatology. Many other drugs can precipitate a psychiatric disorder by bringing out a latent psychiatric vulnerability.[26]

Illicit drugs — Conservative sources such as the AMA book *Drug Abuse: A Guide for the Primary Physician*[27] estimates that the age group 18-25 years has the highest percent of illicit use in all drug categories. The 1979 data show that marijuana was used in one month in 35.4% of 18- to 25-year-olds, while 9.3% used cocaine, 4.4% used hallucinogens, 2.6% amphetamines, 2.1% nonbarbiturate-nonbenzodiazepine sedatives, 2.0% benzodiazepines, and 1.2% used inhalents. Yago et al.[28] documented 43.4% of Los Angeles County Psychiatric Hospital Emergency Room patients were positive for PCP and the clinical picture mimicked mania, depression, and schizophrenia. Drug and alcohol abuse can complicate the psychiatric diagnostic process and make it difficult to find the primary diagnosis.[26] We recently saw a 32-year-old, white male present with an acute psychosis which we originally thought was a bipolar affective disorder, manic phase, but this was proved inaccurate by the presence of cocaine in both blood and urine. Another patient who presented as depressed and suicidal had barbiturates, benzodiazepines, and marijuana in his urine. Hospitalized psychiatric patients sometimes abuse drugs in the hospital resulting in severe exacerbations of their illnesses. The only way to make the diagnosis is to be constantly aware of the magnitude of the problem, take a careful history, and finally to do sensitive and accurate testing of blood and urine. Adverse reactions to any abusable drug can resemble any known psychiatric symptoms from psychosis to mild anxiety states and must be considered in all psychiatric disorders no matter how classical the presentation (Figure 6).

Prescribed drugs — Psychiatric symptoms occur in at least 2.7% of patients taking prescribed medication on a regular basis according to the Boston Collaborative Drug Surveillance Study of 9000 patients.[29] The spectrum of adverse psychiatric reaction is well known and extensive lists have been compiled and published.[30,31] An extensive review of this literature is beyond the scope of this book. During a diagnostic evaluation, it is preferable to discontinue as many medications for as long as possible or substitute medications less likely to cause psychiatric side effects in patients.

Adverse drug reactions have a wide spectrum of psychiatric presentations. They will not be diagnosed unless a high index of suspicion is in the mind of the treating psychiatrist and sensitive testing is performed to confirm the diagnosis.

Hyperadrenalism (Cushing's Syndrome)

Cushing's syndrome may present as psychosis, depression, euphoria, or anxiety. Depression is the most commonly mentioned symptom. In one study using structured interviews

	Schizophrenia	Acute Psychosis	Major Depression	Manic Depression	Personality Changes	Organic Brain Syndrome	Panic Anxiety Disorder	Other
PCP	+	+	+	+	+	+	+	+
Toluene			+		+	+		+
Marijuana	+	+	+	+	+		+	
Amphetamine	+	+	+	+	+	+	+	
Cocaine		+	+	+	+	+	+	
Sedative Hypnotic		+	+		+	+	+	+
Heroin			+		+	+	+	
Methadone			+		+		+	

FIGURE 6. This shows the spectrum of possible psychiatric presentations each drug of abuse may cause. (Data for this figure come from references 26-28 and Fair Oaks' experience.)

and RDC criteria, depression was present in 83% of patients with Cushing's disease.[32] This same study found that many of the 30 patients with endogenous Cushing's syndrome met RDC criteria for either mania or hypomania prior to the depression. This may account for other reports of mania or euphoria associated with exogenous administration of either corticosteroids or ACTH.[33-40]

The diagnosis of hyperadrenalism (Cushing's syndrome) is made by elevated measurements of plasma and 24-hr urine cortisol levels, which are resistant to dexamethasone suppression at 2- or 8-mg dosages. This syndrome can be separated into at least three separate diseases: adrenal hyperplasia, pituitary or hypothalamic stimulation of adrenal secretion, and ectopic secretion of ACTH by tumors. Various manipulations with high-dose dexamethasone suppression, metapyrone, and vasopressin are necessary to differentiate between the hypothalamic/pituitary and ectopic ACTH hyperadrenal states and are beyond the scope of this text. For an excellent review see Gold's article.[41]

Hypoadrenalism (Addison's Disease)

Hypoadrenalism commonly presents psychiatrically as depression psychosis or organic brain syndrome.[37] The diagnosis is usually made on the basis of low diurnal serum cortisol, low 24-hr urine cortisol excretion, and is easily treated with steroid replacement therapy.

Hypoglycemia

Many patients diagnose themselves as hypoglycemic in order to explain their psychiatric symptomatology. There is little if any proof that all such patients have symptomatic hypoglycemia. In fact, Ford et al.[42] studied 30 volunteer patients who considered themselves hypoglycemic. Eighteen were found to have reactive hypoglycemia with a glucose 65 mg% or below. However, of these, only 15 had a glucose below 60, 4 below 50, and only 1 below 40. Seven of the 30 had normal glucose tolerance tests and 5 had a diabetic profile during a 5-hr glucose tolerance test. However, there are several conditions which can cause symptomatic hypoglycemia — the most prominent of which are insulinoma and the exogenous administration of insulin.

Insulinoma is probably the most frequent cause of symptomatic hypoglycemia. Glucose levels between 30 and 40 mg/mℓ produce mild delirium and progressive impairment of cerebral function to deep coma at below 10 mg/100 mℓ and may produce bizarre behavior which can be indistinguishable from schizophrenia, depression, dementia, or anxiety attacks.[37] The diagnosis depends on simultaneous documentation of increased plasma insulin and hypoglycemia[38] using a 5-hr glucose tolerance test. If this is not positive, then a 72-hr fast may be diagnostic. If this is not positive but insulinoma is still suspected, an intravenous tolbutamide test may be helpful. If the glucose is 50, the insulin level should be greater

than 6 μIU/mℓ. If the glucose is 40, the insulin should be greater than 100. Gordon et al.[43] noted that there are a wide variety of other tumors that can secrete an insulin-like growth factor which can lower blood glucose to symptomatic levels. These tumors include: adrenocortical cancer, lymphoma, hepatoma, hemangopericytoma, fibrosarcoma, neurilemoma, mesothelioma, malignant pheochromocytoma, and leiomyosarcoma.

Also overlooked in many emergency room situations is hypoglycemia in insulin-dependent diabetics, who either intentionally overdose or have a hypoglycemic reaction. Diabetics taking oral hypoglycemic agents may also be susceptible. Examples in emergency settings observed by this author include a 45-year-old man who was labeled as drunk and "crazy" and ignored. When his blood glucose was checked it was 16! He promptly returned to normal mentation and behavior after administration of glucose. Also seen was a 55-year-old woman with adult-onset diabetes, who was taking oral hypoglycemic agents, who came to the emergency room. She was acting very bizarrely and strangely and was taking her clothes off inappropriately in public. She was labeled as a "psych" case by the nurses and a psychiatrist was summoned. Her blood glucose was 45 and she also responded to intravenous glucose administration.

If the question of factitious hypoglycemia caused by surreptitious insulin administration arises, C peptide determination is helpful as endogenously produced insulin has a high C peptide level, whereas exogenously injected insulin does not.[44]

Hyperparathyroidism

The psychiatric disturbances seen in hyperparathyroidism are directly related to the serum calcium levels. The higher the serum calcium, the more severe the resultant psychiatric disturbance is. Serum calcium levels of 12 to 16 mg/100 mℓ are associated with personality changes. Acute psychosis can accompany values above 16 mg/100 mℓ. There are alterations of consciousness at levels between 16 and 19 mg/mℓ. Somnulence and coma occurs above 19 mg/100 mℓ.[45,37] Elevated plasma calcium may also be seen in vitamin-D intoxication, in later stages of bone cancer, and with secretion of a parathyroid hormone-like substance.[37]

All of the psychiatric symptomatologies attributable to serum calcium are reversible when the serum calcium is restored to normal.

Hypoparathyroidism

Hypoparathyroidism with resultant low serum calcium levels is much less common than hyperparathyroidism. This most commonly presents as an organic brain syndrome, and may appear to be delirium tremens or other psychosis. It is reversible by restoration of the low serum calcium level to normal.

Diagnosis of both hyperparathyroidism and hypoparathyroidism is first suspected upon seeing an abnormal serum calcium level on routine blood screening or from a history of parathyroid disorders in the family and/or previous parathyroid surgery.

Hyperthyroidism

Hyperthyroidism may present in a variety of manners resembling panic disorder, depression, anxiety, neurosis, and mania. As noted previously, there was a very high incidence of hyperthyroidism in Hall's prospective study of 100 committed inpatients. Of these hyperthyroid patients, three met the RDC diagnosis for schizophrenia and three fit the diagnosis for manic depressive illness. One of these three was in a thyroid storm during admission. Little-known and appreciated is the fact that hyperthyroidism may present as depression. Kronfol et al.[46] described the case of an elderly woman with a severe delusional depression secondary to thyrotoxicosis. Treating the thyrotoxicosis resulted in complete resolution of her depression. Carney et al.[47] obtained routine thyroid screening on 191 psychiatric inpatient admissions and found 7 clinically hyperthyroid who had symptoms — 5 of whom appeared

to have an affective psychosis, 1 had a neurotic depression, and 1 with symptoms indistinguishable from schizophrenia. Nine hypothyroid patients were found, five with affective psychosis, two resembling schizophrenia, one with epilepsy, and one with alcoholism. They also found that the psychiatric symptoms preceded the clinical evidence of the thyroid disease. Despite the 8.4% occurrence rate of abnormal functioning, they surprisingly concluded that thyroid dysfunction was not a major determinant of psychiatric disturbance. Since they did not routinely check TSH levels or employ a TRH test their figures are probably an underestimate.

The diagnosis of hyperthyroidism is made by the classical signs and symptoms of hyperthyroidism along with elevated T3, T4, a depressed level of TSH, and a low TSH response to TRH administration.

Hypothyroidism

Hypothyroidism has been classically associated with psychosis in the form of "myxedema madness." It is also associated with depression and organic brain syndromes. Gold and coworkers[8] have demonstrated that there is a subtle form of hypothyroidism, "subclinical hypothyroidism", in which all the thyroid function tests including T3, T4, T3 uptake, and TSH are normal in the presence of exaggerated TSH response to administration of intravenous TRH. These depressions have successfully been treated with thyroid hormone alone or in combination with tricyclic antidepressants. Please see the following chapter in this volume.

Hyper- and Hyposecretion of Sexual Hormones

Little is known about this area of endocrinology and its possible psychiatric presentations.

It is well known that sexual drive in men decreases as the serum testosterone level decreases and that chronic marijuana use lowers testosterone in males.[48] The effects of testosterone on mood states is not well known. It is interesting to note that Klaiber et al.[49] administered large doses of oral estrogens in 23 severely depressed women who had been refractory to conventional treatment, and found that this caused a significant decline in Hamilton ratings for depression. In contrast, some women appear to get opposite effects on mood state from taking estrogens. This interesting area deserves closer scrutiny under well-controlled conditions.

Grades of gonadal failure exist and are being operationally defined by the use of the LH-RH test in psychiatric and drug abusing patients.

Heavy Metal Poisonings

Heavy metal poisoning can occur with environmental exposure, pica, or poisoning, with a wide variety of metals including: magnesium, copper, zinc, manganese, lead, mercury, thalium, bismuth, aluminum, arsenic, and bromides.[4,15,50-52] Most consistently they produce an organic brain syndrome. Occasionally heavy metal poisoning can mimic major depression and somewhat less frequently acute psychosis.[4,15,50-52] In children, lead poisoning, however, can be indistinguishable from attention deficit disorder with hyperactivity[53] (Figure 7).

The most important thing to keep in mind about these conditions is that unless they are actively looked for with heavy metal screens of urine and blood, they will rarely be found or properly treated. If these conditions are detected and treated early enough, the psychiatric symptoms are for the most part reversible.

Huntington's Chorea

Huntington's chorea is a familial disorder with an autosomal dominant inheritance pattern. It usually appears between ages 35 and 50 with the triad of choreiform movements, dementia in adult life, and a history of similar symptoms in other family members.

There is a high incidence of symptoms resembling both mania and depression in patients with Huntington's chorea. This was noted even in Huntington's original article of 1872,[54]

	Schizophrenia	Acute Psychosis	Major Depression	Manic Depression	Personality Changes	Organic Brain Syndrome	Panic Anxiety Disorder	Other
Magnesium		+	+			+	+	
Hypocalcemia		+	+			+	+	
Hypercalcemia		+	+		+	+		
Zinc			+					
Manganese	+		+			+		
Lead		+	+			+		*
Mercury		+	+	+		+		**
Thalium		+				+		
Bismuth			+			+		
Aluminum						+		
Lithium						+		
Arsenic	+		+		+	+		
Bromides		+	+			+		+
Organophosphate	+		+			+		

* Learning Disabilities Retardation A.D.D. with Hyperactivity
** Irritability

FIGURE 7. This shows the spectrum of possible psychiatric presentations each heavy metal or toxin may cause. (Data for this figure are from references 4, 15, 50 and Fairs Oaks' experience.)

"The tendency to insanity and sometimes that form of insanity which leads to suicide is marked."

It is possible for the psychiatric manifestations of this disease to occur before any of the choreiform movements or any of the signs of dementia. A positive history of Huntington's disease in other family members may be helpful in establishing this diagnosis.

Infectious Mononucleosis

Infectious mononucleosis may be followed by a syndrome which is identical to a major depressive episode. Significant symptoms of anxiety, especially in women, may persist for up to a year after the resolution of the infection.[55-57] The diagnosis of infectious mononucleosis is made by a positive heterophile or mono spot test.

Infectious Hepatitis

Psychiatric symptomatology before, during, or after infectious hepatitis of any type, either A, B, or non-A non-B, can range from mild lethargy to psychosis.[58] The most common complication is anxiety and/or depression. These may occur at any time from the acute phase into the convalescent phase even when no signs of active liver damage can be demonstrated. There are even some reports of suicide and acute delusional mania following hepatitis.[58]

The diagnosis of hepatitis is made by measuring liver function tests, (in particular elevated SGPT), Hepatitis B antigenemia, or a change of antibody production profiles against either Hepatitis A or Hepatitis B virus. Patients with non-A non-B hepatitis may exhibit the same psychiatric symptoms as those which develop after Hepatitis A or Hepatitis B infection.

Insulinoma

Please see the section on hypoglycemia.

Multiple Sclerosis

Multiple sclerosis is a demyelineating neurologic disease characterized by "lesions which are widely separated in space and in time in the central nervous system." It has been associated with a wide variety of psychiatric symptomatology including mania and depres-

sion.[59] These symptoms may also be misdiagnosed as hysterical, malingering, or anxiety disorders because of their puzzling array of neurologic and psychiatric symptoms which wax and wane over time. This is particularly true since these patients developing lesions in the frontal and temporal lobes may appear and act quite bizarrely.[13]

Narcolepsy

Narcolepsy is a disorder of sleep characterized by a pentad of symptoms including narcoleptic sleep attacks, cataplexy, sleep paralysis, hypnogogic hallucinations, and disturbed nocturnal sleep. It is not necessary for the entire spectrum of these symptoms to be present to make the diagnosis of narcolepsy. In addition to these symptoms, one pathognomonic finding is rapid-eye-movement (REM) sleep at the onset of sleep. This, however, is not invariable. These patients may also go into normal non-REM sleep during the day as well as at night. Therefore, a negative EEG finding does not rule out the diagnosis of narcolepsy. It may be necessary for a number of recordings to be made during daytime sleep attacks or during normal sleep to find REM sleep patterns at the beginning of sleep.[60,15]

Patients with narcolepsy have often been misdiagnosed as schizophrenic, thyroid cases, or malingerers.[61] Roth also noted that there was a high incidence of endogenous depression in narcoleptics. The diagnosis of narcolepsy is made by a high index of suspicion and finding sleep attacks in the presence of any of the symptoms of the pentad, singularly or in combination. The diagnosis is confirmed by finding a REM sleep pattern on EEG at the onset of sleep. There may be multiple negative findings before this is actually documented.[60,62-65]

Normal Pressure Hydrocephalus

Normal pressure hydrocephalus is characterized by a triad of dementia, ataxia, and incontinence, although the symptoms vary rather widely.[66] Patients with this disorder may present with behavior problems, persucatory delusions,[67] or psychotic depression.[68] Normal pressure hydrochephalus may be reversible by a ventricular shunting procedure.[66]

Pancreatic Carcinoma

Of all the malignant tumors that present psychiatrically, pancreatic carcinoma is the most notorious.[14,15,69-74] The first signs of the tumor are often severe depression with crying spells, insomnia unresponsive to sleeping medication, and anxiety associated with the fear that the patient has a very serious illness.[14,15,69-74]

Other common symptoms of pancreatic carcinoma, such as pain, weight loss, and jaundice, occur late in the course, possibly due to the retroperitoneal location of the tumor.

Psychiatric symptoms may precede others by a substantial period of time.[74] Pancreatic carcinoma rarely occurs before age 40. The index of suspicion of the treating psychiatrist must be very high when presented with a male patient 50 years old or older who has a severe depression with weight loss or with patients who have a history of preexisting or new onset diabetes and/or a history of heavy alcohol intake.[14]

The diagnosis may be confirmed by pancreatic ultrasound examination or with an abdominal CAT scan and with a needle or open biopsy of the pancreas.

One of the reasons for the rapid mortality is that the illness may remain silent except for the psychiatric symptomatology until very late in the course of the illness. When detected via other symptoms, it is often so far advanced that death usually occurs within 1 year. An alert psychiatrist who detects this illness may provide the margin necessary to substantially prolong the patient's life after the diagnosis is made.[15]

Panhypopituitarism

Panhypopituitarism encompasses some of the features seen with other endocrine deficits

such as: hypothyroidism, hypoadrenalism, and hypogonadism. Psychiatric presentations are common in pituitary failure and usually present with depression and lack of libido. Occasionally, severe metabolic crises with coma and delirium occur.[33]

In acute or long-standing hypopituitarism, frank psychosis may be found.[36] The causes of hypopituitarism may be idiopathic, as a post partum pituitary necrosis or pituitary tumors.[36]

Porphyria, Acute Intermittent

The porphyrias are rare, inborn errors of metabolism which are transmitted in an autosomonal dominant pattern.[15,75-84] They represent a group of diseases in which there is an excess excretion of porphyrin precursors. There are two types of porphyrias; the first type results from excess accumulation of porphyrin precursors in bone marrow and blood forming cells. The second kind are the hepatic porphyrias, which include acute intermittent porphyria, hereditary coproporphyria, and porphyria veraigata, which produces skin lesions. All of the hepatic porphyrias can present with psychiatric symptoms, but acute intermittent porphyria is the most common.[15,75-84]

These diseases are extremely rare and have extremely variable presentations[77] and may not have accompanying physical signs or symptoms. Routine lab work is often normal. There are four common presentations which may occur singly or in combination in acute intermittent porphyria. First is abdominal pain with nausea and vomiting, the second is constipation, the third is psychiatric symptoms, and the fourth is neuromuscular, with motor and sensory neurologic problems which may involve motor weakness, loss of vision, paresis — especially in the legs, and weakness which may progress to bulbar paralysis and death.[15]

Acute attacks of acute intermittent porphyria may be precipitated by alcohol intake, barbiturates, sulfonomides, decreased intake of carbohydrates, pregnancy, menstruation, infection, oral contraceptives, chloroquine, aldomet (alpha-methyldopa) grieseofulvin, and sodium valproate.[76] The psychiatric symptomatology and presentation of this disorder run the whole gamut of psychiatric symptomatology from organic brain syndrome to neuroses to hysterical personality, psychosis, conversion disorder, catatonia, and depression, which is especially pronounced between attacks.[15,75-84] Kaelbling et al.[85] screened 2500 psychiatric patients and found 35 with positive urines for porphobilinogen. This represents a 1.5% rate of occurrence in his psychiatric population.

The diagnosis is based on the demonstration of excess porphobilinogen and delta amniolevulinic acid in the urine, which are elevated in almost all acute attacks and often in the latent state as well. However, these may be negative and it may be necessary to demonstrate a decreased level of uroporphobilinogen 1 synthethase in RBC.

The treatment of this disorder is a high-glucose diet which can inhibit the enzymes responsible for the increased porphobilinogen production. Phenothiazines may be effective for the psychotic symptoms and reducing the abdominal pain.

Acute attacks can be prevented by avoiding the offending agents, and they can be treated once they occur if the proper diagnosis is made. This is an example of a medical illness in which treatment with phenothiazines will result in the clearing of the psychiatric symptomatology. However, this does not mean that, just because it responds to phenothiazine medication, it is a psychiatric disorder.

Post Concussion Syndrome

The post concussion syndrome occurs as the aftereffects of brain damage from severe head injury. It may present psychiatrically as anxiety, depression, excess anger, loss of emotional control, mood swings from euphoria to depression, and social disinhibition.[86,87] It can mimic schizophrenia and other functional psychoses.[86] These patients could be mistakenly discharged from the hospital with a combination of psychiatric disorder, intellectual impairment, and physical residua with which they are ill equipped to cope.

Surprisingly, blunt, closed-head trauma produces more immediate change of consciousness and of later mental disability than focal, penetrating head wounds and results in a much longer-lasting residua of psychiatric disability and physical disability.[86]

If death does not occur within the first 48 hr the duration of stupor and coma have been found to be the most important predictors of long-term outcome. Numerous small hemorrhages, gliosis, and ruptured axons are often observed at post-mortem examination of the victim's brain.[86]

Lesions of the left hemisphere, especially the left temporal lobe, tend to produce more psychiatric symptoms as well as intellectual deficits. Affective and behavioral symptoms are more frequently observed in right hemisphere damage. A syndrome consisting of euphoria, lack of judgment, and childish, disinhibited behavior may be seen in frontal lobe damage.[86]

Brown et al.[87] studied head injuries in children and found a high rate of new psychiatric disorders in children following severe head injuries. New psychiatric disorder was related to the severity of injury as measured by post traumatic coma which lasted at least 7 days. These disorders were distributed evenly across the psychiatric spectrum with the exception of a syndrome of "social disinhibition", which is quite similar to the previously mentioned frontal lobe syndrome in adults.

While mild head injury in children has not been associated with increased rates of psychopathology, some evidence of new psychiatric distress exists in adults including increased fatigue, nervousness, anxiety, depression, restlessness, irritability, and prolonged elation as much as several months after the head injury.[86] There is a tendency for these symptoms to be worse if the patient is involved in a law suit concerning the head injury.[86]

The treatment of these disorders is generally to minimize the damage at initial presentation to the hospital. The psychiatric disorder may occur after the patient has been released from the hospital, and treatment is symptomatic.

There are no diagnostic tests for post concussion syndrome, but a history of severe head injury, especially one resulting in coma of more than 2 days, is highly suggestive of this.

Pheochromocytoma

Pheochromocytomas have been noted to produce psychiatric symptoms. Most frequently they mimic panic attacks. They have also been noted to produce severe chronic depression and depressive psychoses.[15] During acute attacks, the anxiety may be so intense that it produces acute transient psychosis.[88] The tumors arise in chromophobe tissue and are most commonly located in the adrenal medulla, although they have been found outside the adrenal. The tumors can secrete dopamine, norepinephrine, epinephrine in varying ratios.[89] These hormones may be secreted continuously or episodically and may result in continuous or acute attacks of hypertension. The acute episodes are most commonly associated with headache, perspiration, and palpitations, although this is not an absolute necessity. Many of the other symptoms are completely compatible with the diagnosis of panic disorders, including nausea, weakness, nervousness, chest pain, dyspnea, paresthesias, tightness in the throat, and dizziness or faintness.[90] Acute attacks may be precipitated by such unusual factors as: emotional stress, laughing, sleeping, sexual intercourse, shaving, gargling, straining at stool, sneezing, hyperventilation, or pregnancy in young women.[15,91]

Pheochromocytoma is a disease of the young and is most often present between the ages of 5 and 25.[88,91] The diagnosis is based on the demonstration of elevated levels or urinary free catecholamines, vanillylmandelic acid (VMA), and metanephrine. All of these assays must be performed by 24-hr urine collection. The most commonly accepted chemical test is the finding of VMA excretion greater than 6.5 mg/24 hr. Provocative tests are also useful in the diagnosis of pheochromocytoma. The injection of histamine causes the release of the

catecholamines and, if blood pressure rises more than 40 points, a pheochromocytoma is probably present.

The cold pressor test should result in a rise in blood pressure of at least 20 points. Blocking tests are also used including the administration of alpha blockers, such as Regitine® (phentolamine) and, more recently, of clonidine. However, provocative tests are dangerous because they may produce hypertensive crises and blocking tests are dangerous because they may produce profound hypotension and shock.

It is important for psychiatrists to consider the possibility of a pheochromocytoma in a young patient presenting with panic attacks or severe anxiety. It is especially important to check their blood pressure at the time they are seen and, ideally, during an acute attack.

Since there is a well-established provocative test for panic attacks (sodium lactate infusion), it is suggested that those individuals that have a negative sodium lactate infusion test with a clinical picture of panic disorder should then have their urinary catacholomines and VMA checked.

Pheochromocytoma is a *90% curable* disease with definitive surgical excision of the tumor.[15,91]

Partial Complex Seizures (Temporal Lobe, Epilepsy, Psychomotor Epilepsy)

Psychomotor epilepsy and temporal lobe epilepsy are two diagnostic labels which have been superceded and included in international classification of seizure disorders under the term "partial seizures with complex symptomatology" or "partial complex seizures". This change was made in order to acknowledge that occipital, frontal, and parietal lobe seizures may cause many of the same psychiatric symptoms which have been associated with epilepsy in general and with temporal lobe foci in particular.

Many authors have concluded that this class of epilepsy is much more likely to have psychiatric manifestations.[92-99] Most make a distinction between those symptoms which occur between seizures and those which occur during seizure. Between seizures, personality changes include hyposexuality, hyperreligiosity, hyperethicality, extensive and compulsive writing and drawing,[94,100] as well as mood changes alternating between opposite extremes of good and bad, creating a Jekyl and Hyde personality.[101] Other psychiatric symptoms which have been reportedly associated with partial complex seizures include depression, anxiety, hysteria, hypochondriasis, "schizophrenia", confusional psychoses, antisocial personality, and epileptic personality.[92] Most authors also feel that partial complex seizures predispose patients to psychotic manifestations and in particular paranoid hallucinatory psychoses.[93,96,100-103] There is also a raging debate among various neurologists relating violence and aggression to this particular form of epilepsy. Strong advocates can be found on both sides of the debate.[104,105]

The diagnosis is made by having a strong index of suspicion and the realization that this disorder may present with hallucinations of any type — olfactory, gustatory, or visual. It may also be confused with panic disorders, severe depression and anxiety, mania, aggression, episodic violence, and special subjective experiences such as *deja vu* or *jamais vu*.

The diagnosis is confirmed by finding an epileptiform focus which is most clearly brought out by a sleep-deprived EEG with nasopharyngeal leads. It is rare for an abnormality to appear only in a nasopharyngeal lead,[106] but using this lead can increase the diagnostic precision. The stress of sleep deprivation uncovers significantly more epileptic foci than in non sleep-deprived EEGs. Figures on this range from a 56% increase[106] to two to three times that of non sleep-deprived EEGs.[107] It is also helpful to obtain EEGs during the specific pheonomenon under investigation. This can occasionally be done with continuous 24-hr ambulatory EEG and/or video tape monitoring.

We feel that all psychiatric patients should have a sleep-deprived EEG with nasopharyngeal leads. In addition, there may be certain patients who have histories which are highly sugges-

tive of partial complex seizures and, yet, in whom no demonstrable focus may be documented. Under these circumstances, a therapeutic trial with Tegretol® (carbamazepine) may be indicated.

Treatment of the seizure disorder itself may produce remarkable changes in the patient's psychiatric symptomatology. It is interesting to note that there is a group of patients who are refractory to treatment with medication — the group with severe personality disorders and sociopathic traits including those individuals who abuse alcohol and other drugs.[108] Taylor[96] has shown that this group of patients, which he labeled "psychopathic", had remarkable improvements along with a noticeable decrease in aggressiveness after being treated with a temporal lobectomy. This was also noted and reconfirmed by Siegel[109] who found that those patients with schizophrenia and schizophrenic-form psychoses are not responsive to surgery.[110]

Partial complex seizures can mimic any of the entire spectrum of psychiatric disorders: "the number of patients with schizophrenia diagnosed and treated by neurologists is equaled only by the number of patients with psychomotor epilepsy diagnosed and treated as schizophrenia by psychiatrists."[111]

Syphilis (General Paresis)

Syphilis is a chronic, systemic, infectious disease caused by *Treponema pallidum* and it is usually transmitted by sexual contact. It can invade the central nervous system as a primary infection; however, only 10 to 15% of those infected develop late effects of invasion of the cerebrum.

At one time syphilis accounted for 10 to 20% of all admissions to state hospitals for the insane.[112] Since the institution of effective treatments of this disease, there has been a remarkable decrease in the first admission rate to New York State psychiatric hospitals from 8 per 100,000 population in 1910 to less than 2 per 100,000 in 1950. This makes syphilis (general paresis) a disappearing psychiatric disorder which most psychiatrists have never seen.[112]

This disorder is one of the all-time great mimickers of *any* medical or psychiatric disorder, and in the past has earned its title along with tuberculosis as one of the original great mimickers in medicine. Hall et al.,[4] in their prospective study of 100 committed state hospital patients, in whom obvious physical disorders had been eliminated, found two cases of syphilis, one of which presented as indistinguishable from RDC schizophrenia and the other as indistinguishable from RDC manic-depressive illness.[113]

Again, it should be noted that this is a disease which is preventable, easily treatable, and in some cases totally reversible. Any delay in the diagnosis and institution of treatment may result in both neurologic and psychiatric tragedies for the afflicted individual.

Systemic Lupus Erythematosis

Systemic lupus erythematosis is a relatively uncommon disease which occurs in 2 to 3 per 100,000 population with a 9:1 ratio favoring females. It presents between ages 10 and 70 and may be accompanied with a wide variety of psychiatric symptoms, including mania, depression, schizophreniform or schizophrenic psychosis, organic brain syndrome, and may often be labeled as a conversion disorder. It is ignored or overlooked in young females presenting with psychiatric symptoms and complaining of arthralgias, despite the fact that arthralgias are the most common first presentation of this disorder. Systemic lupus erythematosis is an autoimmune disorder, and there is evidence for both a vascular and autoimmune mechanism contributing to the psychiatric symptoms.[114] The vascular lesions are due to a vasculitis wich affects medium-sized arterioles and often affects cerebral arteries. This may result in the leakage of serum containing autoantibodies to the coroid plexus into cerebral tissue.[114-117] The association of systemic lupus erythematosis and schizophreniform psychosis

is so strong that psychosis is listed as one of the 14 criteria of the American Rheumatism Association for the diagnosis of lupus. Only four of these are required in order to make such a diagnosis. Interestingly, other autoimmune diseases such as rheumatoid arthritis,[118] scleroderma (PSS, progressive systemic sclerosis) polymyositis, and dermatomyositis, all have negative associations with any psychiatric disorder except that patients with rheumatoid arthritis may have secondary psychiatric symptoms related to the severity of the disease and its interference with daily activities.[119] Impotence may occur in scleroderma.[120,121] There are some reports of ankylosing spondylitis linked to schizoaffective disorders and atypical psychosis.[118] There is also a preliminary report of psychosis and paranoid delusions occurring along with an aseptic, meningitis-like syndrome which was responsive to corticosteroids in patients with mixed connective tissue disease.[122]

It appears that the psychiatric disorders associated with systemic lupus erythematosis are largely primary manifestations of the disease and, indeed, may be the first presentations of the disease before any other signs appear. This is well documented in Feinglass et al.[123] Of their 140 patients with SLE, 3% had a psychiatric presentation as the first and only manifestation of the disease, and 23.5% of the 140 had psychiatric symptoms which either preceded the diagnosis or occurred within the first year following diagnosis. There are multiple reports of systemic lupus erythematosis linked to psychotic diseases[4,114,116,117,123-129] and nonorganic, nonpyschotic psychopathology.[129]

Systemic lupus erythematosis can mimic any kind of psychiatric disorder ranging from mild anxiety to severe psychosis simulating schizophrenia, although none of the previously mentioned studies have used RDC diagnostic criteria and structured interviews.

Most of the criticisms and suggestions for improved study of the psychiatric phenomenon caused by systemic lupus erythematosis have yet to be implemented despite the discussion by Gurland et al. in 1972.[124] The diagnosis of systemic lupus erythematosis is made by the finding of 4 of the 14 criteria set forth by the American Rheumatism Association. The best, most useful, and inexpensive screening test for collagen vascular disease and systemic lupus erythematosis in particular is an antinuclear antibody (ANA). The ANA will be positive in 99% of all lupus cases, and it will only pick up a small number of false positive cases. There is one report of anti-nuclear antibody being positive in 80% of hospitalized depressed patients,[130] but the significance of this is unclear.

The area of immunologic causes of psychiatric illness is an area which is little explored, one which and many authors feel may lead to new advances in psychiatry.[116,117,131,132]

Temporal Lobe Epilepsy

Please see the section on Partial Complex Seizures.

Wilson's Disease (Hepatolenticular Degeneration)

Wilson's disease is a rare, inborn error of copper metabolism which is transmitted by an autosomal recessive pattern. It occurs in approximately 1 out of 200,000 people. It is a disease which occurs early in life between 6 and 20 years of age and is caused by the deposition of excess copper into body tissues.[133] Wilson's disease is a reversible and treatable disease if it is detected early enough.[133] "More patients are referred initially to psychiatrists than to neurologists, internists or pediatricians. The psychiatric manifestations may be prominent."[133] The increased copper deposition is produced by two simultaneous defects in copper metabolism — one is a decreased production of ceruloplasmin, the copper transport protein; the second is decreased copper excretion into the bile.

The first signs of Wilson's disease are either psychiatric or neurologic including poor coordination, tremor, difficulty pronouncing, an unusual laugh on inspiration, or decreased school performance. It is not necessary for any of the classical triad of Wilson's disease,

Kayser-Fleischer corneal rings, liver disease, or neurologic dysfunction, to be present when this disease presents psychiatrically.[134]

The psychiatric diseases or symptoms reportedly mimicked by this illness include mania, depression, schizophrenia, schizo-affective disorder, hysteria, conversion disorders, anxiety, toxic psychosis, hyperactivity, confusional state,[15] psychoneurosis, personality change, or school phobia.[50]

The diagnosis is made by having a high index of suspicion and performing the proper tests. Routine laboratory testing can often be normal. The disease will only be detected in the laboratory by *decreased* serum levels of copper and ceruloplasmin and increased 24-hr urinary copper excretion and increased liver copper on liver biopsy. The diagnosis is then confirmed by the presence of Kayser-Fleischer rings. If the diagnosis is made in one individual, all family members, especially siblings, must be screened for early asymptomatic Wilson's disease.[135] Again, we emphasize that this is a treatable and reversible disease if it is caught early enough in its course. This disease is treated with D-penicillamine, a copper chelating agent. If this disease is not treated, the result is almost invariably death. Strickland et al.[149] found on follow-up that 35 out of 36 patients with Wilson's disease who had not been treated with penicillamine were dead. Of 35 patients who were treated, 31 were found to be alive, and 18 of these 35 were found to be asymptomatic.

In Hall's prospective study of 100 admitted state hospital patients, in whom physical illness had been excluded, one case of Wilson's disease appeared.[4] It presented indistinguishablyfrom RDC schizophrenia. Cartwright goes so far as to say, "Psychiatric inpatient services might be well advised to screen routinely all admissions of patients under thirty years of age with a ceruloplasmin determination."[133]

Vitamin Deficiencies

There are certain vitamin-deficient states which have clearly documented psychiatric symptomatologies. If these vitamin-deficient states are diagnosed and treated, it can result in complete clearing of the psychiatric symptoms. It is not known exactly what percentage of these cases are overlooked by modern-day psychiatrists, but we feel that this area is unexplored and needs a great deal of further research. Subclinical vitamin and precursor deficiencies or relative deficiencies also appear to exist. The brain and brain neurotransmitter systems, when compared to the bone marrow or red blood cells, appear to be the least forgiving and most readily influenced "end organ" expressing signs and symptoms first.

Among the better-known vitamin deficiencies associated with psychiatric symptoms are folate[4,15,76,136-139] and vitamin B_{12} deficiency,[15] as well as niacin (nicotinic acid) deficiency. Folic acid deficiency presents with fatigue and lassitude. Marked deficiency can present with burning feet, restless leg syndrome, and/or a depression which is unresponsive to antidepressant therapy. Carney and Sheffield[140] found, in a retrospective study of 102 psychiatric inpatients with folic acid deficiency, that exogenous folic acid administration decreased hospital stays of patients with endogenous depression, schizophrenia, or organic psychosis. Thornton and Thornton[139] found that 169 hospitalized psychiatric patients had significantly lower folate levels (below 5.9 ng/mℓ) than those found in 80 normal, nonhospitalized control subjects. Coppen and Abou-Saleh[138] found a higher rate of affective morbidity in those patients with low folate levels as compared to those patients with normal folate levels in patients treated in a lithium clinic. Hall et al.,[4] in their prospective study of hospitalized state psychiatric patients found three cases of folate deficiency, two of which presented as RDC schizophrenia and one as RDC schizoaffective disorder. Normal CBC folate deficiency occurs frequently and is often misdiagnosed and mistreated.

Vitamin B_{12} deficiency may also present psychiatrically. This frequently occurs in the absence of any signs of anemia or bone marrow changes, and may present neurologically as a peripheral neuropathy or myelopathy (subacute combined degeneration). It has been

known to present with a wide spectrum of psychiatric disorders including apathy, irritability, dementia, confusional states, paranoid states, and schizophreniform psychosis.[15] Depression with suicide attempts have also been reported.[141]

Unfortunately, normal serum vitamin B_{12} levels are deceptive and cannot be relied on. Kolhouse et al.[142] and Whitehead and Cooper[143] both found that the newer radioisotope dilution techniques for measuring vitamin B_{12} are not accurate and provide a false sense of confidence. They advocate greater reliance on clinical picture and B_{12} bioactivity assays using the bacteria *Euglena gracils* or *Lactobacillus leichmannii*. If the medical suspicion of vitamin B_{12} deficiency exists in psychiatric patients, it should be treated despite "normal" levels of B_{12} in serum.

Niacin (nicotinic acid) deficiency was in the past a great cause of psychiatric symptomatology and state hospitalizations in psychiatric hospitals in the past. Overt niacin deficiency (pellagra) is currently nonexistent due to changes in dietary habits. It used to be rampant in the form of pellagra which occurred in epidemic proportions between 1900 and World War II. At its maximum there were 7000 deaths per year and over 200,000 people were afflicted with pellagra in the U.S.[15] Subacute and subclinical deficiencies exist and may be important. Severe niacin deficiency causes pellagra which has the classical presentation consisting of the four Ds: dermatitis, diarrhea, dementia, and death.[144] This disorder has presented in the past as almost any type of major psychiatric symdrome including acute confusional psychosis, acute mania, melancholia, dementia, catatonia, and dementia precox.[15] Spivak and Jackson[145] recently reported a patient who presented with mania and no evidence of organicity with primary niacin deficiency. At the present time, this deficiency is most frequently seen in addicts, alcoholics, and patients with liver disease and may present with agitation and anxiety.

Zinc deficiency has been a cause of dwarfism with anemia and hypogonadism in Iran and Egypt.[146] It is also implicated in a decrease in the sense of taste and smell and acrodermatitis enteropathica.[147] Henkin et al.[148] found that three out of six patients who developed a zinc deficiency became "frankly depressed" and one developed "acute organic mental syndrome with paranoid ideation".

Vitamin B_6 deficiency has been mentioned as causative in organic brain syndromes, depressions, and toxic psychoses.[15]

Thiamine deficiency has been implicated in the Wernike-Korsakoff syndrome (cerebral beriberi). The syndrome, once it develops, generally presents psychiatrically with an organic brain syndrome, fatigue, and apathy which could be mistaken for depression. In more severe cases, it can present as an agitated delusional and a halucinatory state which is very similar to delirium tremens. This is called Korsakoff's psychosis.[15]

These vitamin deficiency disorders are important because they may present psychiatrically and, if treated, should result in reversal of psychiatric and neurologic symptomatology. Failure to pick up these deficiencies and treat them may result in permanent damage and/or permanent psychiatric or neurologic disability.

X. FREQUENCY OF OCCURRENCE OF PHYSICAL ILLNESS PRESENTING AS PSYCHIATRIC SYMPTOMS

We will now present the disorders in the declining order with which they were found in Hall's prospective study of 100 committed state hospital patients.[4]

As a general category of diseases, endocrine disorders present most frequently associated with psychiatric symptoms. This fact is also made evident by the wide number of articles that review this subject matter in extensive detail[33-40] (Figure 8).

Of the endocrine disorders causing psychiatric symptoms, hypothyroidism is responsible for the largest percentage. In Hall's study,[4] there are 8% cases of hypothyroidism and

	Schizophrenia	Acute Psychosis	Major Depression	Manic Depression	Personality Changes	Organic Brain Syndrome	Panic Anxiety Disorder	Other
Hypothyroid	+	+	+	+	+	+		
Hyperthyroid	+		+	+			+	
Diabetes Mellitis	+		+		+			+
Hypoglycemia	+		+		+	+	+	+
Cushing's Disease		+	+	+			+	
Addison's Disease	+		+			+		
Hyper-Parathyroidism		+	+			+		
Hypo-Parathyroidism		+				+		
Pheochromo Cytoma		+	+				+	
Carcinoid			+	+		+	+	
Ovarian Failure			+					
Testicular Failure			+					+
Pan Hypopituitarism		+	+	+	+	+	+	

FIGURE 8. This represents the spectrum of possible psychiatric presentations which many endocrine disorders may cause. (Data for this figure are from references 3-5, 13, 15, 23, 88 and Fair Oaks' experience.)

Hashimoto's thyroidism and 6% cases of hyperthyroidism. This subject is dealt with more extensively in the chapter on thyroid disorders in this volume. The next most frequent are disorders of glucose regulation, with the most common being diabetes mellitus. Hall found diabetes in 5% of his cases and hypoglycemia in 4% of his cases. Koranyi[5] also noted previously undetected diabetes in his outpatient population. In addition to the thyroid disorders and disorders of glucose regulation, 1% of the cases had either Addison's disease or hyperparathyroidism. The grand total of endocrine disease was 29%.

The next most commnly involved organ system is the central nervous system, accounting for 10% of all cases. Epilepsy was responsible in 3%, temporal lobe epilepsy in 3%, psychomotor epilepsy in 1%, CVA in 1%, Pick's disease in 1%, and a post concussive syndrome in 1% of cases (Figure 9).

Toxic and withdrawal disorders were found third most commonly with one case each of toxic encephalopathy, impending DTs, lead poisoning, arsenic poisoning, digitalis poisoning, acute central cholinergic syndrome, and chemical hepatitis (Figure 7).

Nutritional disorders and infectious diseases are tied as the next most common with six cases each. Nutritional disorders were composed of three folic acid deficiencies, two cases of malnutrition and one case of dehydration, while infectious diseases had two cases of syphilis, two cases of viral hepatitis, one case of unknown viremia, and one case of Brucellosis (Figure 10).

Unusual metabolic disorders were found in three cases (3%). There was one case of Wilson's disease, one case of acute intermittent porphyria, and one case of G6 PDase deficiency, and there were five cases of "other" syndromes, two cases of severe anemia, two cases of hypertension and one case of polycystic ovaries. More than one diagnosis was made on some patients, accounting for a total of 65 disorders which were causative of the psychiatric symptoms in 46 patients. It should be noted that the disorders mentioned previously are only those disorders which were felt by the researchers to be causative of the psychiatric symptoms. Illnesses which either exacerbated or were unrelated to psychiatric disorder have been totally excluded from our discussion.

From this, it is easy to see that, at least among committed hospitalized psychiatric patients, uncommon disorders present much more commonly than in the general population or those seen by nonpsychiatric physicians. It would not be surprising if many of these disorders are unrecognized and therefore missed by psychiatrists seeing outpatient populations. Of course,

	Schizophrenia	Acute Psychosis	Major Depression	Manic Depression	Personality Changes	Organic Brain Syndrome	Panic Anxiety Disorder	Other	Hysteria
Narcolepsy	+		+						
Epilepsy	+	+	+		+	+		+	
Partial Complex Seizures	+	+	+	+	+			+	+
Normal Pressure Hydrocephalus		+	+			+			
Huntington's Chorea			+	+	+	+			
Multiple Sclerosis			+	+			+		+
Parkinson's Disease			+			+			
Post Concussion Syndrome	+		+	+	+		+	+	+
Picks Disease	+					+			
Tumors	+		+	+	+	+		+	+

FIGURE 9. This represents the spectrum of possible psychiatric disorders mimicked by various primary central nervous system disorders. (Data for this figure are from references 4, 13, 15, 54, 60, 62, 66-68, 86-88, 92, 98, 100, 101 and Fair Oaks experience.)

	Schizophrenia	Acute Psychosis	Major Depression	Manic Depression	Personality Changes	Organic Brain Syndrome	Panic Anxiety Disorder	Other
Syphilis	+			+		+		
Viral Hepatitis	+	+	+	+			+	
Infectious Mononucleosis			+				+	
Malaria					+			
Pneumonia Bacterial	+					+		
Pneumonia Viral			+					
Brucella			+			+	+	
Tuberculosis			+	+				
Viremia		+			+	+		

FIGURE 10. This represents the various possible psychiatric disorders caused by various infectious diseases. (Data for this figure are from references 4, 5, 10, 57, 58, 75 and Fair Oaks' experience.)

there may be wide variations in the rate and clinical spectrum of these physical illnesses according to geographical location, the level of medical care (primary, secondary, or tertiary), and the type of practice and speciality of the treating physician. Rare disorders will tend to occur more commonly in academic centers and tertiary referral centers. It is important for each physician, clinic, and hospital to be familiar with his particular spectrum of physical illnesses which presents psychiatrically (Figure 11).

XI. THE PSYCHIATRY OF THE 1980s AND 1990s

With all the previously documented diagnostic errors that are occurring and the relatively low rates of successful treatment, the inescapable conclusion is that the two are related. It stands to reason that folate deficiency, hypothyroidism, or diabetes presenting as depression will not respond except on a temporary placebo basis to traditional psychiatric treatments. Successful identification will lead to more effective medical and psychiatric treatment. The question now arises "What is the best way to maximize the diagnostic and thus therapeutic precision of both psychiatric and medical illnesses which present psychiatrically?"

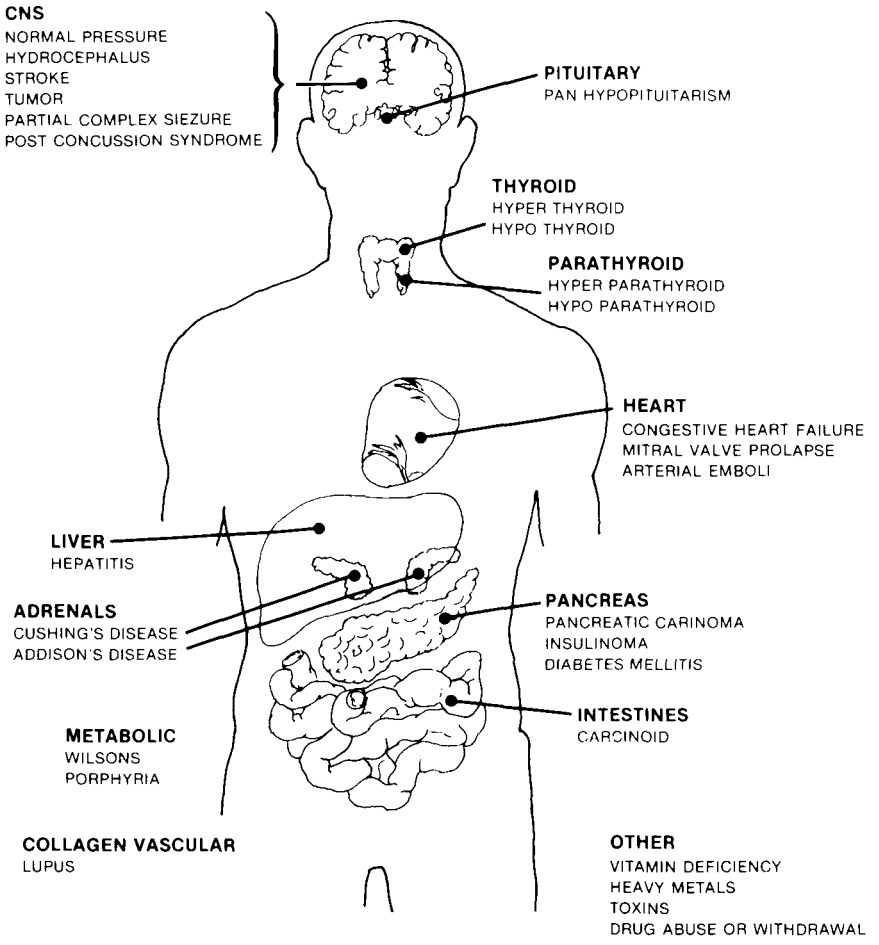

FIGURE 11. This represents the various organ systems and specific diseases most likely to produce psychiatric symptoms.

We propose the following for both psychiatric inpatients and outpatients (Figure 12):

1. A detailed history of all present and past psychiatric and medical illnesses. At Fair Oaks we use highly trained, Master's level nurse clinicians to repeat each physician's history. They look for significant details that might have been missed. Detailed questionnaires and structured rating instruments are also used.

2. A complete physical, neurological, and endocrinological examination is performed by a physician who is fluent in both psychiatry and internal medicine. This is not the perfunctory examination mentioned earlier in this chapter, but one directed toward finding those physical illnesses that can cause psychiatric symptoms. We have a well-lit specialized examination room with a good examination table and a complete array of specialized examination instruments which our physicians know how to use.

We especially examine for thyroid abnormalities, carotid bruits, arterioschleretic changes in the retinal vessels, cardiac murmurs, abdominal bruits, and skin and nail fold changes which may indicate collagen vascular disease. In addition, a thorough neurological examination is completed.

3. Lab tests are ordered to correspond to the major issues in the differential. The bias is to actually rule out a possible diagnosis by testing rather than relying solely on clinical

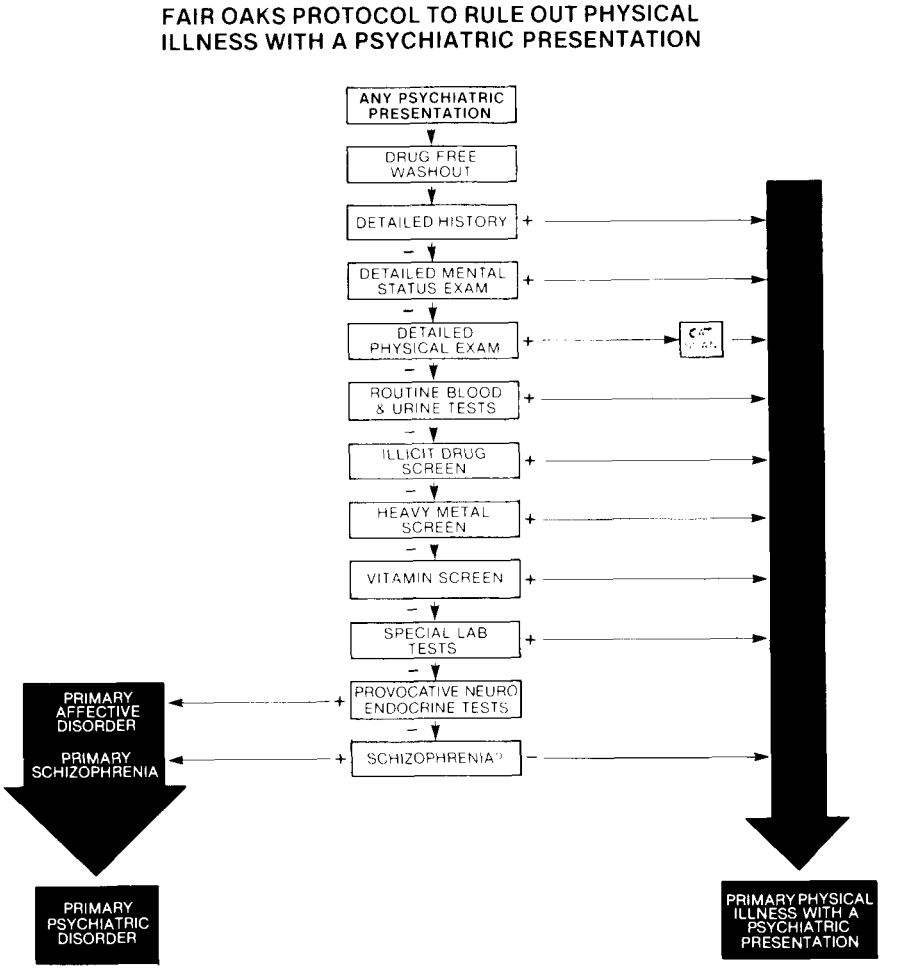

FIGURE 12. This represents schematically the systematic process we use at Fair Oaks Hospital to insure that we do not miss any psychiatric disorder which might present as psychiatric symptoms.

impression which we find inaccurate in about 25% of cases. The possible tests include:

CBC with differential
Sedimentation Rate
SMA 22

Total Protein	Direct Billirubin
Albumin	Alkaline Phosphatase
Globulin	LDH
A/G Ratio	SGOT
Calcium	Glucose
Inorganic Phosphate	SGPT
Triglycerides	Sodium
BUN	Potassium
Uric Acid	Chloride
Creatinine	Iron
Total Billirubin	

RPR
Urinalysis
EKG
Chest X-Ray
EEG Sleep Deprived with Nasopharyngeal Leads
Comprehensive Urine for Drug Abuse

Opiates	Phencyclidine (PCP)
Methadone	THC (Marijuana)
Amphetamine	Alcohol
Barbiturates	Propoxyphene
Cocaine	Methaqualone
Benzodiazepines	

Blood Levels of all Psychiatric and Anti Seizure Medications
Blood Levels of Cocaine, Heroin, Methadone, Amphetamine, Barbiturate, Δ9 THC, Benzodiazepines, Alcohol and Methaqualone
Vitamin Deficiency Evaluation

Niacin (B_3)	Pyridoxine (B_6)
Riboflavin (B_2)	Thiamine (B_1)
Ascorbic Acid (Vitamin C)	Folate
Vitamin A	B_{12}

Diurnal Cortisols at Midnight, 8 a.m., Noon, 4 p.m.
TRH:Thyroid Test
Dexamethasone Suppression Test
ANA
Serum Copper — in patients under 30 years old
Ceruloplasmin — in patients under 30 years old
Porphobilinogen
Platelet Serotonin Transporter
Platelet Monoamine Oxidase
Urine for Heavy Metals

Antimony	Lead
Arsenic	Mercury
Bismuth	Selenium
Boron	Teleurium
Cadmium	Thalium
Cobalt	Zinc
Copper	

We feel that individual clinicians and hospitals should set up a protocol to evaluate complaints such as depression, psychosis, and anxiety and evaluate the yield of the various tests after a consecutive series of 100 to 500 patients. These standardized measures are necessary to avoid diagnostic error and to force psychiatrists (including ourselves) into different modes of thinking and different differential diagnoses than they would ordinarily pursue.

The practice of psychiatry is going to change radically in the future. We hope that the information contained in this chapter will help present and future psychiatrists to more easily make this change.

XII. SUMMARY

In summary, the current poor rates of good outcomes in some psychiatric patients may

be due to undetected medical illnesses presenting with psychiatric symptoms as their first manifestation. This applies to outpatients as well as inpatients. Medical doctors and psychiatrists detect more of these physical illnesses than social agencies or the patients themselves, but they are often inaccurate. Reasons for this include lack of knowledge, resistance to learning new facts, lack of an internship prior to psychiatric residency training, and forgetting previously learned medical skills. Psychiatrists avoid facing these issues and obtain a false sense of security by having other physicians certify that there is no medical illness causing psychiatric symptoms. This area of medicine is complicated and both psychiatrists and other physicians oversimplify it.

The Great Mimickers of Psychiatry is a particularly difficult group of diseases to differentiate from Primary Psychiatric Disorders. Psychiatrists must look out for and aggressively test for these disorders in order to make the correct diagnosis. Psychiatric laboratory tests such as diurnal cortisol, DST, and TRH, are helpful in differentiating primary from secondary psychiatric symptoms since psychiatric symptoms are nonspecific.

Psychiatry in the 1980s and 1990s must change so that it is much more medically oriented. Awareness of these problems at Fair Oaks Hospital has led to the development of standardized evaluations for inpatients in specialized Neuropsychiatric Evaluation Units as well as for outpatients. All psychiatric patients should have detailed medical and psychiatric histories taken and detailed physical examinations should be performed. Specialized laboratory testing in these patients can be a helpful adjunct in confirming a medical diagnosis.

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Chapter 3

THYROID FAILURE AND CLINICAL MISDIAGNOSIS

Mark S. Gold and John S. Carman

TABLE OF CONTENTS

I. INTRODUCTION

Descriptive diagnostic systems, such as the DSM III,[1] have put added emphasis on the need to accurately diagnose major depression and to actively rule out medical illnesses. Since there is a psychiatric diagnosis only after a vigorous exclusion process of viable competing diagnoses, it is difficult to imagine a diagnosis of depression in the absence of a 5- to 14-day comprehensive medication and drug-free evaluation. This neuropsychiatric evaluation unit (NPEU) program is designed to provide, within 7 to 10 days, a comprehensive neuropsychiatric assessment that results in specific and individualized treatment recommendations for the patient. Neurochemical, neuroendocrine, physical, psychodiagnostic, and neurological testing is combined with family and psychosocial assessment as well as rating scales and extensive clinical diagnostic interviewing. The interdisciplinary team of the unit typically consists of psychiatrists who have chosen to specialize in this area, psychopharmacologists, psychologists, neuropsychologists, psychometricians, nurse clinicians, nurses, occupational therapists, mental health workers, substance abuse experts, and family social workers, as well as part-time internists and neurologists. The evaluation includes physical, endocrinological, and neurological examination and ratings, electroencephalogram (usually sleep-deprived), evaluation of cognitive function, assessment of family dynamics and life skills, drug use, and abuse profiles and laboratory studies. After the evaluation, the patient is either discharged or transferred to a nonpsychiatric medical hospital or to a treatment unit within a psychiatric hospital. In the absence of a NPEU program, the physician must rule out known and likely illnesses which may manifest symptoms similar to or indistinguishable from major depressive disorders, anxiety disorders, thought disorders, and others. One of the most common illnesses imitating naturally occurring psychiatric illness is thyroid dysfunction. Excess thyroid activity (e.g., over the person's own normal) can produce anxiety, panic, and even delusions and hallucinations. Reductions in thyroid function can induce dementia, depression, and problems in living and thinking. In this chapter we will focus on the failing thyroid gland and its relevance to psychiatric diagnosis and maximizing treatment response. The importance of this syndrome becomes clearer when we recognize that even the mildest forms of subclinical hypothyroidism presents with and includes major depressive symptomatology.[2,3]

In general, hypothyroidism is routinely considered in the differential diagnosis of decreased attention, arousal, and memory or depressive and anergic states. Thyroid failure is screened for by history (e.g., recent physical) or by medically oriented psychiatrist with Thyroid (Function) Tests such as Serum Thyroxine (T4), Triiodothyronine (T3), and occasionally basal Thyroid Stimulating Hormone (TSH).[4] These approaches are neither systematic nor rigorous enough to identify the majority of patients who have thyroid disease as the primary diagnosis or who have thyroid failure as a major precipitant to their depression. The family physician as the doctor who listens carefully or the psychiatrist as the neurobehavioral specialist are the most likely clinicians to see early thyroid failure. Until recently, the relevance of "chemical hypothyroidism", especially to psychiatrists, was poorly appreciated. During the past 5 years, our understanding of clinical hypothyroidism has broadened and, with the aid of improved laboratory tests, the diagnosis can now be made at a much earlier time in the natural history of the illness.[5,6] This means that many hypothyroid patients can be identified long before they develop classic myxedematous symptoms. Early thyroid failure, with its predilection for behavioral presentation, is much more likely to present as depression, anergia, or problems concentrating and thus present to a generalist or psychiatrist. Even when overt or classical hypothyroidism is present, it is usually diagnosed well before the patient is referred to a psychiatrist. With advances in thyroid testing and our clinical data suggesting early thyroid failure may preferentially present as a behavioral syndrome, testing depressed patients for evidence of covert, mild, or overt hypothyroidism has become

more routine. This notion is supported by evidence that small decreases in thyroid hormone production may change adrenergic receptor sensitivities in the brain and thus modify behavior.

There are now numerous studies demonstrating strong correlations between mood disorders and provocative neuroendocrine testing abnormalities, such as the Dexamethasone Suppression Test (DST) and TSH response to Thyrotropin Releasing Hormone (TRH).[7-17] These data have been reviewed elsewhere in this book. In addition, there are basic data showing that TRH itself can alter mood[7,18] and reverse central depressant syndromes; there are also data that TRH is widely distributed throughout the brain and, by implication, may be of critical importance outside of the hypothalamic pituitary axis.[19-21] Thyroid hormone and TRH also have "arousal" effects on the organism, which may reflect the neuromodulatory influences of this peptide on catecholamine and indoleamine pathways in the brain.[3,19,22] Clinical studies, which in many cases preceded basic science understanding of thyroid-biogenic amine interactions, have demonstrated antidepressant effects of thyroid hormone and imipramine given together in the treatment of depression.[22] There is a report of improved mood in response to TSH given alone to depressed women.[23] Thus, it has been evident for some time that thyroid gland function influenced mood and vice versa. The relevance of these data to the practice of medicine was the missing link.

A large body of basic and clinical data[13,14,24-26] plus the newly improved understanding of diagnostic techniques for early hypothyroidism have prompted our recent studies of the coexistence and relationship between the continuum of hypothyroidism from overt to subclinical present in depressed patients. As we will show, these studies demonstrated that DSM III or RDC psychiatric diagnosis did not rule out thyroid failure as the primary diagnosis. In other words, clinicians without the benefit of comprehensive thyroid testing cannot differentiate primary thyroid from primary affective disorder. In addition, TRH testing identified two new patient groups who were previously included in the descriptive diagnosis of major depression — thyroid hormone responders and thyroid plus antidepressant responders.[27,28] In our studies, the incidence of hypothyroidism in patients with a chief complaint of depression or anergia who meet the criteria for major depressive disorder, unipolar subtype, appeared to be greater than previously believed, and has been recently supported by additional studies in both inpatients and outpatients. In view of the importance of the thyroid dysregulation in evaluating affective disorders, this chapter will review some important points regarding the regulation of thyroid hormones, laboratory assessment of thyroid function, our recent data on the "hypothyroidism or depression" dilemma, and recommendations for the evaluation of hypothyroidism.

II. THYROID REGULATION AND MEASUREMENT

The thyroid is an endocrine gland and part of a neuroendocrine system called the Hypothalamic-Pituitary-Thyroid (HPT) Axis (Figure 1). This axis serves to translate input from the central nervous system into influences on hypothalamic-pituitary hormonal output which in turn controls thyroid hormone secretion. The HPT axis and the subsequent impact of the thyroid hormone on some peripheral tissues have been delineated, but the nature and extent of circulating thyroid hormonal effects on catecholamine receptors and cell bodies has not yet been elucidated.

The hypothalamus secretes a tripeptide hormone called Thyrotropin Releasing Hormone (TRH) into the portal hypopheseal circulation which transports TRH to the pituitary gland.[24] Release of TRH is influenced by input from the limbic system, other areas in the central nervous system (CNS), and probably from circulating levels of TRH and thyroid hormones formed in the brain and thyroid.[25,26] While TRH probably has a number of extra-HPT functions, its HPT effects are better understood. TRH acts at specific receptors on the pituitary gland to cause release of Thyroid Stimulating Hormone (TSH) into the circulation. The TSH

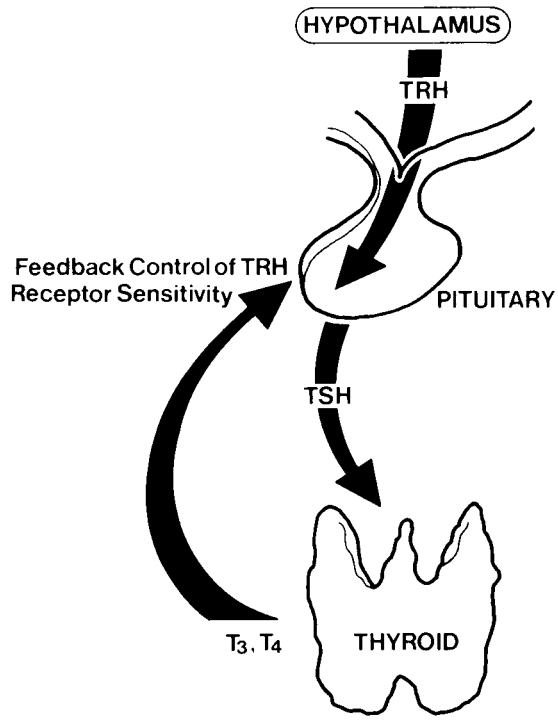

FIGURE 1. Schematic representation of the hypothalmic pituitary thyroid (HPT) axis.

in turn acts on the thyroid gland itself to promote release of thyroid hormone into the peripheral circulation. Serum thyroid hormone levels serve as a long feedback mechanism to modulate the pituitary gland release of TSH. This may occur through thyroid hormone-related changes in TRH receptor sensitivity. In the presence of decreased thyroid hormone levels, as in the subclinically hypothyroid patient, a given amount of TRH stimulates supersensitive TSH receptors, causing a proportionately larger release of TSH. These changes are homeostatic attempts to compensate and promote increased release of thyroid hormones from the gland and generally result in normal thyroid indices and TRH test evidence for reduced thyroid gland activity. Thyroid function can be "normal" when compared to the wide range of laboratory normals but could be abnormal for the individual. Reduction in a particular individual's normal level of thyroid hormone can produce increased TRH receptor sensitivity and more TSH released per molecule of available TRH. This relationship may explain why neurobehaviorally relevant decreases in thyroid hormone are critical to the behavioral specialist but not very relevant to the classical endocrinologist who is looking for myxedema or bodily evidence of inadequate thyroid hormone availability.

There are two active forms of circulating thyroid hormone, L-Thyroxine (T4) and Triiodothyronine (T3). The thyroid gland secretes primarily, but not exclusively, T4, and about one third of this T4 undergoes conversion to T3 by deiodination in peripheral tissues, such as the liver and kidney. T3 is now felt to provide most of the actual thyroid hormone activity in peripheral tissues. Although T4 is secreted at eight to ten times the rate of T3, T3 is three to four times more potent.[25] Both T3 and T4 are bound to serum proteins such as Thyroid Binding Globulin (TBG) and Thyroid Binding Prealbumin (TBPA). Only a relatively small fraction of the total pool of T3/T4 is actually free in the circulation and available to bind receptor sites. It is of interest to note that approximately 40% of the T4 is converted by

deiodination of the inner ring into reverse T3, an apparently inactive form of the T3 hormone which is only now being studied in psychiatric and thyroid illnesses. Whether excessive conversion to reverse T3 can produce a functionally hypothyroid state in the presence of a blunted TRH test is unknown.

III. LABORATORY ASSESSMENT OF THYROID FUNCTION

Laboratory assessment of thyroid function has improved considerably in recent years, both in terms of what can be measured and in the accuracy of the measurement. While not adequate for psychiatric differential diagnosis, the most common screening test is to measure the levels of thyroid circulating hormones themselves.

A. Thyroid Indices

It is important to know what type of test to order and the method of analysis reported by the laboratory in order to properly interpret the test results and correlate them with the clinical state of the patient. Thyroxine (T4) is largely bound to serum proteins, with only a small fraction actually circulating free in the plasma. Total bound T4 in the serum can be measured by either competitive protein binding assay or radioimmunoassay (RIA) techniques. Both the hormone levels and the binding capacity influence total T4. The T4 level measured by these methods is increased by conditions resulting in increases in TBG binding capacity, such as during pregnancy, while taking oral contraceptives, during infectious hepatitis, or by certain antipsychotic medications (e.g., perphenazine). T4 is decreased when TBG is decreased as in patients with nephrotic syndrome. The actual amount of circulating free T4 can be measured directly using dialysis techniques. Free T4 measurement by RIA is gradually replacing total T4 in basal screening tests.

Another useful measurement is an indirect assessment of the number of available binding sites for the hormones on serum proteins such as TBG. This allows for some estimation and correction of the TBG effects mentioned above when measuring total bound T4 and T3. Resin uptake T3 (T3RU) is a determination not of T3 concentration directly but of the available binding sites on the TBG proteins. To determine T3RU, a fixed amount of patient serum is mixed with T3 which has been labeled with radioactive iodine (T3*) and with a resin which absorbs any excess T3* not bound to serum TBG. The test measures the relative amount of excess T3* absorbed onto the resin. In abnormal states in which there is an excess of thyroid hormone (e.g., hyperthyroidism) or a deficiency of TBG, most of the TBG binding sites are already filled with T4 and there is a relative excess of T3* which is absorbed by the resin. The opposite is true in hypothyroidism or conditions in which TBG is increased, when there are relatively more available binding sites on the TBG. More T3* is bound in these conditions and less is available to be absorbed by the resin. The calculated Free Thyroxin Index (FTI) is the product of the total thyroxin and T3RU and the result tends to correct for TBG variation and correlates well with the actual concentration of free thyroxin as determined by dialysis techniques.

B. TSH

Measurement of basal TSH levels allows assessment of both pituitary function and responsiveness to feedback inhibition. Normally, as thyroid hormone levels fall, TSH slowly increases in an attempt to boost thyroid gland output and maintain the individual's "normal" euthyroid state. Repeated compensatory pituitary changes in the face of frank thyroid failure eventually leads to the typical pattern of overt hypothyroidism — decreased T4 and markedly elevated TSH levels. Overt hypothyroidism may occur for a variety of reasons: decreased dietary iodine, radioactive exposure, excessive ablation of thyroid tissue to treat hyperthyroidism, autoimmune thyroiditis with destruction of thyroid tissue and functions, lithium

carbonate treatment, or idiopathic hypothyroidism. In each case, the thyroid gland fails to produce enough thyroxine and the pituitary compensation cannot retain "normal" circulating levels of thyroid hormone. Progressive thyroid failure is immediately compensated for by increasing TRH receptor sensitivity resulting in increased TSH release. When the pituitary can no longer maintain normal basal thyroid hormone levels through super-stimulation of the remaining functional gland by augmenting TSH release, the patient becomes overtly hypothyroid. However, a grey area exists which deserves attention. Patients with "normal" thyroid function and TSH levels in the range of 3 to 20 but who have neurobehavioral and affective complaints fall into this grey area.

C. TRH — Thyroid Test

A provocative test of thyroid function at the pituitary level (and indirectly of thyroid gland function itself) is the TRH thyroid test.[29-34] This test involves administering 500 μg of the hypothalamic tripeptide hormone TRH and measuring the basal TSH and TSH response before (time 0) and a +15, +30, +60, +90 min after TRH. In normal control subjects, the level of TSH increases within 60 min by 7 to 15 μIU/mℓ (micro international units per milliliter) over the baseline values. This peak, minus the baseline TSH, is called the Δ TSH. In hypothyroid patients, the Δ TSH is markedly increased and values of greater than 30 are common. Delta TSH values in excess of 30 can be observed in patients with normal thyroid indices (T3, T4, TSH) through the continuum of hypothyroidism to those patients with decreased T3, T4, and definitely increased TSH. Even when indices are normal, the pituitary is already producing extra TSH to enable the individual to compensate for the subtle decrease in thyroid hormones. Although resting TSH levels may be normal, the pituitary gland has become exceptionally responsive to TRH stimulation at any time of reduced circulating thyroid hormone.[35-40]

D. Thyroid Antibodies

Although it is not a direct measure of thyroid function, screening for thyroid auto antibodies can be useful in assessing the status of the thyroid gland. The immune system is capable of making antibodies to and destroying the thyroid gland. Serum can be tested for the presence of such antibodies to two common antigens — thyroid microsomes and thyroglobulin. The presence of antibodies to either of these antigens is abnormal, and can be directly assessed by analyzing the patients serum for anti-M or anti-T antibodies with available immunologic techniques.[41,42] In symptomatic patients, high antibody titers are considered evidence of an autoimmune disease process involving the thyroid gland. If a patient has high titers of antithyroid antibodies, it is prudent to ascertain whether they have an unrecognized systemic autoimmune disease.

IV. HYPOTHYROIDISM AND DEPRESSION

As mentioned earlier, it has long been recognized that depressive symptoms such as depressed mood, weakness, loss of memory, anergia, loss of concentration, constipation, appetite, sleep, and weight change are often present in patients with overt hypothyroidism.[2,3,5] The clinical signs and symptoms of thyroid failure and the DSM III criteria for major depression share so many common items[1,5] that patients are distinguished only by comprehensive thyroid testing. Psychiatric investigators have studied hypothyroidism in psychiatric patients and have advocated routine testing for many years to rule out thyroid dysfunction. This was largely ignored. Psychiatrists will generally ask if the patient had a recent physical exam and accept the patient's word that it was normal or the psychiatrist will be working in a setting where the examination of the patient is so de-valued that the lowest ranking physician is forced to examine the patient (e.g., an intern or resident). No one will ask what

Table 1
GRADES OF HYPOTHYROIDISM

Grade 1 Overt	Classic clinical sx: anergia weight gain, cold intolerance, constipation, hoarseness, etc.	$\downarrow T_4$, $\uparrow$ TSH, $\uparrow \Delta$ TSH
Grade 2 Mild	Mild or few sx (fatigue, dry skin, constipation)	T_4 Normal, borderline or $\uparrow$ TSH, $\uparrow \Delta$ TSH
Grade 3 Subclinical	No specific thyroid sx, some sx of anergia or depression	T_4, TSH Normal, $\uparrow \Delta$ TSH

was found and normally most of the examination is deferred. Testing, when ordered, is usually restricted to RT3U and T4. This testing is appropriate only for ruling out overt hypothyroidism or myxedema — diagnosis which is primarily clinical. Patients with clinical and chemical evidence of myxedema are readily diagnosed by internists and family practitioners and *rarely* present to psychiatrists. Early and mild forms of thyroid failure present with regularity to the psychiatrist.

Over the past decade it has been increasingly recognized that there is a spectrum of thyroid dysfunction. Recognition of this continuum has led to development of systems for grading degrees of hypothyroidism.[5,6] Development of this system has been aided by the more widespread availability of TRH testing which allows laboratory detection of hypothyroidism at a much earlier stage. Overt hypothyroidism (Grade 1) consists of patients with classic clinical signs and symptoms of hypothyroidism along with the typical pattern of laboratory abnormalities T4, TSH, TRH. Mild hypothyroidism (Grade 2) includes patients with only a few minor or early clinical symptoms, perhaps accompanied by additional nonspecific complaints and signs, plus normal T4 or T3 and borderline basal TSH and $\uparrow$ Δ TSH on TRH testing. Subclinical hypothyroidism (Grade 3) has few if any clinical signs and normal T4, T3 and TSH, however the Δ TSH is increased on TRH testing (Table 1).

Identification of depressed patients with early thyroid dysfunction who were poor antidepressant responders stimulated our interest in the actual incidence of this disorder in psychiatric patients who had symptoms of depression. With the advent of reliable testing, the disease could be separated and the treatment response rate could be improved. Initial efforts focused on assessing the incidence of hypothyroidism in patients depressed enough to require inpatient admission.[27] In a study of 250 consecutive inpatients, admitted for evaluation of depression or anergia, we found that 20 patients (8%) showed some degree of hypothyroidism on comprehensive clinical evaluation and thyroid testing including the TRH test. Of the 20 patients, only 2 patients (<1%) had Grade 1, overt hypothyroidism with positive clinical findings and the typical laboratory pattern. Eight patients (3%) had evidence of mild hypothyroidism with only a few clinical symptoms; such as dry skin, weight gain, fatigue; normal thyroid hormone levels, mildly elevated TSH, and increased Δ TSH. Ten patients (4%) had no clinical symptoms of hypothyroidism other than complaints of anergia or depressed mood with normal T4 and TSH but Δ TSH values of greater than 30. These findings suggested hypothyroidism can be detected at a much higher rate among depressed patients than had previously been appreciated. It may be questioned whether such a finding is a reflection of the increased sensitivity of the TRH test in diagnosing early hypothyroidism in depressed patients or does the inpatient population reflect a skewed and selected sample of atypical or especially ill tertiary referral hospital patients.

To answer this question, similar data have been collected on consecutive outpatients referred for evaluation of depression. We have recently studied 44 psychiatric outpatients, with a DSM III diagnosis of major depression unipolar.[43] Of this group of patients, three

(7%) had a Δ TSH greater than 30 and an additional three had Δ TSH between 20 and 30. None of these patients had Grade 1 hypothyroidism. These data suggest that the incidence of hypothyroidism presenting as a psychiatric syndrome is high, regardless of the sample. Furthermore it suggests a formal RDC or DSM III diagnosis does not in any way rule out a primary thyroid disorder.

Recently developed descriptive diagnostic criteria (DSM III or RDC) are much improved over past diagnostic criteria, but meeting descriptive criteria does not rule out underlying thyroid disease. Actively ruling out the disorder is an essential prerequisite to assigning any psychiatric diagnosis. It is useful to note that, if only "routine" thyroid testing had been done in either the inpatient or outpatient populations, only 10% of the hypothyroid patients would have been detected and the total incidence would be less than 1%.

Given the apparent incidence of thyroid failure in "psychiatric patients", we were interested to know something about the cause. While there are numerous potential etiologies for hypothyroidism, autoimmune mechanisms are frequently implicated and can be screened for with relative ease.[44,45] To investigate the mechanism of hypothyroidism in our patients, we have studied a series of 100 patients admitted for inpatient evaluation and treatment of depression or anergia.[46] Of this group, 15 patients (15%) showed evidence of hypothyroidism (0 patients Grade 1, 5 patients Grade 2, and 10 patients Grade 3). Additional testing for the presence of antibodies to either thyroglobulin or thyroid microsomes showed that 9 of the 15 hypothyroid patients (60%) had positive titers of antimicrosomal antibodies. The presence of antibodies suggests an autoimmune etiology for 60% of the patients with thyroid dysfunction.

In patients without other evidence of thyroid disease, the name Symptomless Autoimmune Thyroiditis (SAT) has been proposed for patients with augmented TSH response to TRH and circulating thyroid antibodies.[46-53] We have found that SAT is an illness characterized by normal thyroid indices (T4, T3), elevated Δ TSH, clinical symptoms of anergia or depression, and the presence of antithyroid antibodies. Finally, screening for thyroid antibodies in the above-mentioned outpatient population showed positive antimicrosomal titer in five of the six patients with Δ TSH $\geq$20 and in addition, two of these patients also showed positive antithyroglobulin titer as well. It should be emphasized that these patients looked like and talked like patients with naturally occurring psychiatric disorders but were not primary psychiatrically ill. The patients who met DSM III or didn't make DMS III for major depressive disorder responded to thyroid hormone as Grade 2 and many Grade 3 patients responded. Patients with a grade of thyroid failure had suffered for years and many had gone from internist to psychiatrist to psychiatrist being tried on psychotherapy, multiple psychopharmacological therapies, and even ECT for lack of response to traditional psychopharmacological treatments.

Among almost 1000 inpatients and outpatients we have studied thus far with symptoms of depression or anergia, nearly 10% have chemical evidence of some grade of hypothyroidism (see Table 2). The majority of these patients were nonresponders to multiple psychopharmacological treatments prior to comprehensive thyroid testing.

Having found this, are there implications for treatment? At present direct, double blind data are limited to answer this question. Grade 1, overt hypothyroidism must be treated with thyroid hormone replacement regardless of what other psychiatric treatment is used. These patients do not respond to traditional treatments for depression though many have received antidepressant and electroconvulsive treatment trials. Patients with mild hypothyroidism, Grade 2, are also poor antidepressant responders and good candidates for thyroid hormone replacement even though serum thyroid hormone levels are normal. Thyroid replacement for Grade 3 patients is an open question of present; however, Wenzel et al.[6] advocate medium dose L-Thyroxine treatment. The available data suggest these Grade 3 patients are at increased risk to eventually develop overt hypothyroidism and myocardial infarctions. Grade 3 patients appear to be presenting to psychiatrists with disturbances of mood and energy in dispro-

Table 2
SUMMARY OF IMPATIENT AND OUTPATIENT DATA ON HYPOTHYROIDISM

	Grade 1	Grade 2	Grade 3
Total 400	3 (<1%)	16 (4%)	24 (6%)

portionate numbers.[27,46] Certainly they are candidates for a trial of thyroid hormone if other treatment approaches are unsuccessful and they must be closely watched for development of more overt hypothyroidism over time. If these patients have a partial response, we added an antidepressant, preferably nortriptyline or imipramine, in doses to produce therapeutic levels for ≥21 consecutive days.

V. THYROID WORKUP

Evaluation of the thyroid gland of the depressed or anergic patient in clinical practice requires that the psychiatrist be aware of and focus attention on three aspects of evaluation — clinical history, physical examination, and laboratory testing. All of these components are mandatory. Overreliance on or neglect of any major area increases the risk of missing hypothyroidism in patients.

The clinical history from a hypothyroid patient may be filled with classic symptoms of decreased thyroid dysfunction or may consist of nothing more than vague complaints of decreased energy or depressed mood. The nature of the clinical symptoms depends in part on the severity or grade of the hypothyroidism. It is helpful to use a standardized method to review with patients possible symptoms of thyroid disease. A thyroid dysfunction checklist allows the clinician to screen for typical symptoms and signs of thyroid disease including both hypo- and hyperthyroidism (see Table 3). Presence of more than four or five positive findings or a family history of thyroid disorder alone on the checklist suggests thyroid dysfunction and a need for vigorous laboratory testing.

In addition to symptoms, the checklist includes several signs of thyroid dysfunction which should be screened for in a brief physical examination. Some signs may be screened for grossly by simple observation, e.g., fine tremor, exophthalmos, sweating, nervousness, hair loss, hoarseness. The patient's clothing may suggest recent weight loss or gain and possible heat or cold intolerance. A few simple physical examination procedures may reveal additional useful information. Blood pressure and pulse, including both the pulse rate and whether there is any irregularity of the rhythm, gives information about hypertension, arrhythmia, and tachycardia. The feel of the skin while taking the pulse allows assessment of whether it is excessively dry or moist. With palpatation of the thyroid gland itself, one can assess whether the gland is enlarged, if so in what ways, and whether the gland is tender. Auscultation of the thyroid for evidence of bruits is easily done at the time blood pressure is checked and is most often positive in the presence of a thyroid goiter. Finally there should be a brief neurological examination to look for evidence of lid lag, fine tremor (hyperthyroidism), and delayed reflexes (hypothyroidism). This screening is very efficient, requiring only a few minutes to review the checklist symptoms with the patient and a few minutes with a blood pressure cuff, stethoscope, and reflex hammer to screen for checklist signs. Presence of positive findings in the history or physical exam suggests a need for extensive laboratory testing.

The most useful laboratory tests for hypothyroidism are total T4, T3, T3RIA, T3RU, TSH, and TRH stimulation test. Table 4 outlines the TRH test protocol. In patients with evidence of overt, Grade 1, hypothyroidism, T4 and TSH will both be abnormal and will

Table 3
THYROID DYSFUNCTION CHECKLIST

	Present	Absent
Positive Family History		
Weight Loss		
Increased Appetite		
Weight Gain		
Cold Intolerance		
Heat Intolerance		
Depressed Mood		
Lethargy/Anergy		
Nervousness		
Sweating		
Constipation		
Hoarseness		
Hair Loss		
Exophthalmos		
Coronary Artery Disease		
Recent M.I.		
Arrythmias		
Pulse 90/minute		
Hypertension		
Dry Skin		
Thyroid Bruit		
Goiter		
Fine Tremor		
Lid Lag		

confirm the clinical diagnosis. Patients with possible Grade 2 or 3 hypothyroidism should have the TRH stimulation test to establish the diagnosis. All patients with a Δ TSH of $\geqslant 20$ should be tested for thyroid antibodies.

Our data suggest that roughly half of the identified hypothyroid patients have positive thyroid antibodies[46] and that the primary etiology for our findings is autoimmune in nature.[53] The etiology of the other 50% who are nonautoimmune needs to be clarified. Environmental factors, dietary iodide deficiency, and over correction of previous hypothyroidism, either through surgery or radioactive iodine treatment, may explain only a small number of cases.

Table 4
TRH TEST PROTOCOL

1. Patients take nothing by mouth after midnight and are at rest in bed by 8:30 a.m.
2. Indwelling venous catheter is placed and a normal saline drip started to keep the line open.
3. At 8:59 a.m. blood is taken through a 3-way stopcock for determination of T_3 RU, free T_4, reverse T_3, T_4, and TSH levels.
4. At 9:00 a.m., 500 μg of TRH is given slowly intravenously over a 30-sec period. Side effects from the infusion may include a transient sensation of warmth, desire to urinate, nausea, metallic taste, headache, dry mouth, chest tightness, or pleasant genital sensation. These effects are generally short-lived and mild.
5. Blood samples are taken through the stopcock before TRH is administered at 15, 30, 60, and 90 min after the TRH infusion to measure changes in TSH.
6. GH and/or PRL can also be measured at 0, 15, 30, 60, 90.

Studies are needed to investigate influences of genetics, age, and geography on early hypothyroidism. The mean age of our patients was 35 years and there was some increase in Δ TSH with age.

VI. LITHIUM

Our data has direct implications for patients treated with lithium carbonate. Lithium-like radioactive iodine acts to produce a decrease in circulating thyroid hormone and at times this can lead to clinical hypothyroidism.[54-61] This effect seems to occur through several mechanisms,[62-65] including inhibition of T4, T3 release from the thyroid, and the decrease in thyroid hormone is initially compensated for by increased TRH receptor sensitivity followed by increased TSH output from the pituitary as in other forms of hypothyroidism. It appears that lithium produces overt thyroid failure in a step-wise fashion over time. Patients first have Grade 3, then Grade 2, then Grade 1. Thus, patients with early hypothyroidism secondary to lithium therapy might be expected to show a gradation of symptoms and perhaps these patients should be considered for thyroid replacement hormones when evidence of Grade 2 or 3 changes occurs. TRH testing with antithyroid antibodies should be part of the pre-lithium workup and repeat testing during therapy should be encouraged, especially when the clinician is thinking about adding an antidepressant for anergia or depression.

It is also interesting to speculate about whether the interaction between (1) lithium and thyroid hormone and (2) thyroid hormone and adrenergic receptors might have implications for understanding affective disorders and for explaining part of the therapeutic effect of lithium in mania. It has been observed that thyroid hormones share the precursor tyrosine with the catecholamines. (Figure 2). This shared precursor structure may manifest itself by interaction between thyroid and catecholamine receptors.[66] Thyroid hormones increase B-adrenergic receptor activity and this facilitates the action of catecholamines like norepinephrine (NE) at central nervous system receptor sites. Subclinical or relative (or chemical) hypothyroid states may act to reduce the sensitivity of these catecholamine receptors and therefore decrease effective availability of neurotransmitters and produce or contribute to a depressed mood.

At the other catecholamine function extreme, it is hypothesized that manic states reflect an excess of NE or dopamine (DA) neurotransmitter activity.[67,68] Recent work on TRH testing in mania is consistant with this and shows that manic patients have a decrease of blunted TSH on TRH testing as do patients given (or taking) amphetamine or cocaine.[69-71] It is theorized that TRH release is facilitated by NE and DA and inhibited by serotonin.[72,73] Assuming that there is increased NE activity in mania, one might expect facilitated TRH release and subsequent reduced sensitivity of TRH receptors on the pituitary gland. When challenged with TRH, one would then expect the TSH response to be diminished, which is

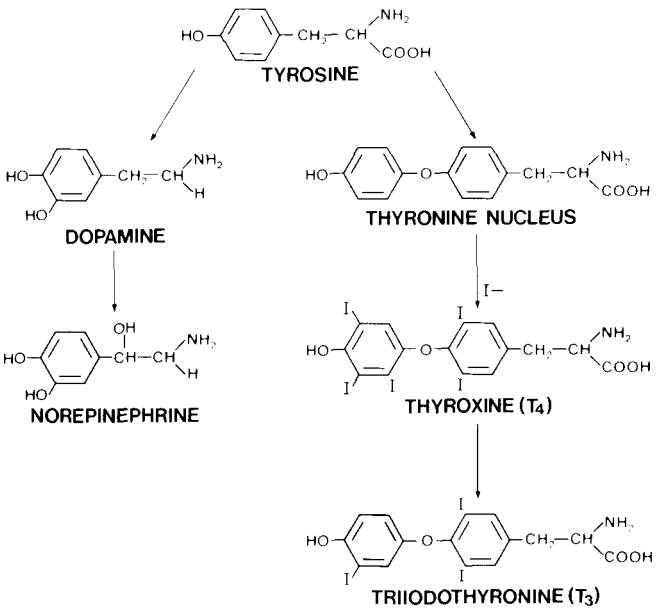

FIGURE 2. The thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) share a common precursor (tyrosine) with the catecholamines.

what is observed. As mentioned, lithium has effects which tend to reduce thyroid hormone levels and it can be hypothesized that this decrease in available hormone is manifested in the central nervous system by a decrease in B-adrenergic receptor activity which would help correct the hypothesized noradrenergic overactivity of the manic state. Such an effect might explain part of the efficacy of lithium in treating manic states and also treating hyperthyroidism.

How many discrete disease entities are included in major depression, or schizophrenia, or anxiety disorders is not precisely known. What is known is that, upon identification of a medical illness and separation of the patient with a primary psychiatric from a secondary psychiatric illness, appropriate treatment planning can begin. Improving efficacy demands precise diagnosis and then well-organized treatment trials while we are following these patients with failing and autoimmune thyroids for definitive answers. We know that giving them antidepressants is a mistake. What we have done is to give all patients with an augmented ΔTSH, Grade 1, and Grade 2 a full thyroid hormone trial. All patients with Grade 3 and antibodies are treated with thyroid hormone. Patients with Grade 3 without antibodies are treated with thyroid hormone, and an antidepressant trial is added when response is partial.

VII. SUMMARY

Clearly a fuller understanding of the role of thyroid hormone in affective states and an expansion of our basic knowledge of hypothyroidism and depression is needed. Screening for hypothyroidism can be done relatively easily and, for the psychiatrist who deals with depressed and anergic patients every day, the yield will be significant. Establishing appropriate medical as well as psychiatric treatment will lead to more consistent therapeutic results and better patient care. One step in improving antidepressant efficacy is in reducing heterogeneity of depressed patients and treating more depressed patients and fewer hypothyroid patients with antidepressants.

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Chapter 4

ANTIDEPRESSANTS: PREDICTING RESPONSE/MAXIMIZING EFFICACY

Irl Extein, A. L. C. Pottash, Mark S. Gold, Richard Goggans, and R. Bruce Lydiard

TABLE OF CONTENTS

I. INTRODUCTION

The pharmacological treatment of the depressed patient can be one of the most rewarding aspects of psychiatric practice. When used properly in the depressed patient[1-3] likely to respond — even the severely depressed patient — improvement can be striking, and patients can be returned to their previous level of functioning within a matter of weeks with a minimum of side effects. However, it has been well documented that many depressed patients, including those with major depressive disorders, receive far from optimal treatment with antidepressant medications.[4] This chapter will focus on the decisions the physician must make in medicating the depressed patient.

We will emphasize the tricyclic and newer "second generation" antidepressants, (Figure 1) and will also discuss the monoamine oxidase inhibitors (MAOI), lithium, and electroconvulsive therapy (ECT) where pertinent. We will present a decision tree for medicating the depressed patient based on review of the scientific literature and personal experience as researchers and clinicians. There are other approaches that might differ to some degree, but the one presented here is a practical one which we have found useful. We will focus on some newer diagnostic and therapeutic approaches that can enhance antidepressant treatment. For example, there are clinical descriptive[5] and biological[6] predictors which can help predict likelihood of antidepressant response to medications. Treatment can be enhanced by attention to appropriate target symptoms, and knowledge of the spectrum of side effects. The physician can be guided in efforts to insure adequate trials of antidepressant medication by monitoring of blood levels,[7,8] and can potentiate unsuccessful antidepressant trials by several new and safe pharmacological methods.[9-12] Neuroendocrine markers can help in proving response or lack of response and in assessing prognosis after a course of treatment.[13-14]

II. THE CLINICAL SPECTRUM OF DEPRESSION AND CHOICE OF TREATMENT

The word "depression" is used to describe a spectrum of conditions from an ordinary human emotion to a medical syndrome with fixed, depressed mood and physiological symptoms.[15] These conditions differ phenomenologically and have different causes and treatment. In general, psychosocial variables such as character structure and environmental stresses would be emphasized as causal at the end of the spectrum that refers to the ordinary human emotion of depression. Biological predisposition receives more causal emphasis at the end that refers to the medical syndrome of depression.

Depressions at the "syndrome" end of the spectrum are often called "endogenous", while depressions toward the other end are called "reactive" or "neurotic". These terms are somewhat misleading. The distinction between "reactive" or "neurotic", and "endogenous" depression rests on the relative presence or absence of the medical syndrome (with its characteristic symptoms and functional impairment), not on the presence or absence of reactive features or neurotic traits. There are some patients who have episodes of affective illness as a medical syndrome which is purely endogenous in that no immediate environmental preciptant can be demonstrated. However, in considering causative factors in many depressions, it is important to remember that there is no single cutoff point between psychosocial input and biological predisposition, but a tremendous area of overlap. Even in depressions with the symptoms of the medical syndrome there can be precipitating events and neurotic traits. In people predisposed to this type of depressive illness, there is a higher incidence with increased psychosocial stress.

Just as a spectrum model is most appropriate for clinical phenomenology and causation, it also can be applied to treatment. Thus, for patients with no syndrome or endogenous elements and for whom depressive feelings seem entirely explicable in terms of neurotic

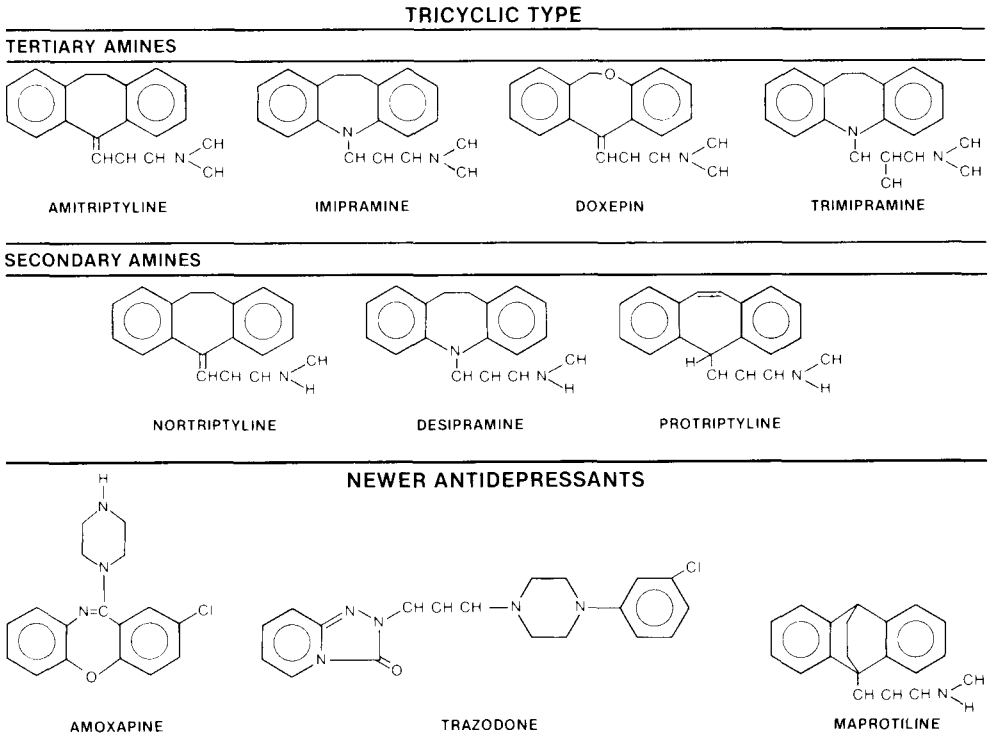

FIGURE 1. Tricyclic and new antidepressants available in the U.S.

character and/or life situation, psychotherapy alone may seem to be the treatment of choice. For patients at the other end of the spectrum who have the medical syndrome of depression seemingly unrelated to psychological conflicts or life events, pharmacotherapy alone would be indicated. For the many patients who fall between these extremes, there is a place for psychotherapy as well as pharmacological treatment. Generally, antidepressant medications are indicated to the extent that syndromal elements are present, independent of the degree to which reactive features or neurotic traits may also be evident. Psychotherapy is usually indicated in depressed patients when reactive or neurotic features are present without severe symptoms of the medical syndrome, or when these features persist after improvement in the medical syndrome.

Thus, the question of psychotherapy vs. drugs is often a false one. Rather, the questions which should be asked are: for what symptoms or incapacities is this patient being treated? At what stage of the illness are different treatments most effectively used? The answers may result in a treatment plan that includes an initial attempt to deal with environmental stress, then antidepressant medication to relieve the neurovegetative symptoms and depressed mood, followed by psychotherapy when the patient has improved enough to be able to explore the issues which may have precipitated the depression. The continued use of medications as prophylaxis against recurrent episodes of depression or mania must be considered in a separate category.

III. CLINICAL PREDICTORS OF RESPONSE

The DSM III definition of major depressive disorder[5] is an effort to reliably define the depressive syndrome most likely to require and respond to pharmacotherapy. This depression

Table 1
CLINICAL PREDICTORS OF RESPONSE TO ANTIDEPRESSANT TREATMENT

Good outcome	Poor outcome
Insidious onset	Delusions[a]
Anorexia	Hypochondriacal or hysteroid traits
Middle and late insomnia	Anxiety
Psychomotor change	
Emotional withdrawal	
Inability to experience pleasure	

[a] Delusions do not necessarily predict poor outcome for ECT.

represents a clearly altered mental state compared to the patient's usual self, has a definite onset, causes a clear impairment of functioning, and has a definite duration. The important point is that patients manifest not only a relatively fixed, autonomous depressed mood but also a cluster of symptoms that involve multiple body systems, such as those regulating sleep, appetite, sexual drives, and gastrointestinal and other visceral functions.

Various investigators have studied depressed patients in hope of finding whether specific symptoms are predictors of response to antidepressant treatment.[16-18] Table 1 contains a summary of the symptoms found to be associated with good and poor response to antidepressant treatment. Changes in sleep, appetite, and psychomotor status are probably the most helpful clinical predictors of good outcome. Insidious onset (e.g., evolving over days or weeks vs. minutes or hours) of such symptoms is more characteristic of the vital, endogenomorphous type of depression which is often responsive to antidepressant treatment. Psychotic depression often responds poorly to antidepressant medication alone. Combination antipsychotic-antidepressant treatment or ECT may be required (see section below on Psychotic Depression). Hypochondriacal, hysteroid, or anxious symptoms were shown to be associated with a poor outcome in one study.[18] The presence of these symptoms, however, should not preclude a trial of antidepressant medication if there are clinical and laboratory data to support the diagnosis of major depressive disorder. As was noted above, it may be that depressed patients with these symptoms may be treated optimally with a combination of pharmacotherapy and psychotherapy.

IV. BIOLOGICAL PREDICTORS OF RESPONSE

As outlined in other chapters of this volume, there are a number of neuroendocrine and other biological markers which are associated with major depressive disorders. These diagnostic tests, such as the dexamethasone suppression test (DST)[19] and thyrotropin releasing hormone (TRH) test,[20,21] have confirmatory utility in identifying *primary* psychiatric major depression and help identify candidates for psychopharmacological treatment or ECT. Some biological predictors have been identified for antidepressants which preferentially inhibit the uptake of norepinephrine (NE). These include the observation of an individual's mood response to a single dose of amphetamine and the level of daily excretion of biogenic amine metabolites such as MHPG (3-methoxy-4-hydroxy phenylglycol).

In 1971 Fawcett and Siomopoulos first reported that the antidepressant response to a 1- or 2-day administration of *d*-amphetamine provided an indication of the fourth-week response to a tricyclic antidepressant.[22] In 1978 Van Kammen and Murphy replicated this earlier study.[23] They found a moderate association between the presence of acute activation and euphoria following oral administration of 30 mg of *d*-amphetamine and the subsequent response to imipramine by the end of a 4-week trial. In another study, low pretreatment

Table 2
EFFECTS OF VARIOUS ANTIDEPRESSANTS ON BLOCKADE OF UPTAKE OF SEROTONIN AND NOREPINEPHRINE

Drug	Serotonin (5-HT)	Norepinephrine (NE)	Predominant effect
Imipramine[a] (Janimine®, SK-Pramine®, Tofranil®)	+ + +	+ + + +	NE
Amitriptyline[a] (Elavil®, Endep®)	+ + + +	+ +	5-HT
Nortriptyline (Aventyl®, Pamelor®)	+ +	+ + +	NE
Protriptyline (Vivactil®)	+ + +	+ + +	NE
Trazodone (Desyrel®)	+ + +	0	5-HT
Desipramine (Norpramin®, Pertofrane®)	+ +	+ + + +	NE
Amoxapine (Asendin®)	+ +	+ + +	NE
Doxepin (Adapin®, Sinequan®)	+ +	+	5-HT
Trimipramine (Surmontil®)	+	+	Equal
Maprotiline (Ludiomil®)	+	+ +	NE

[a] Depends on ratio of tertiary parent to secondary amine metabolite.

levels of MHPG (the major metabolite of norepinephrine and a biological marker of its functional activity in the CNS) correlated with an acute antidepressant response to *d*-amphetamine[24] as well as subsequent response to imipramine. (See Table 2.)

These studies and subsequent efforts by other investigators led Maas to hypothesize that there were at least two broad types of biological depressions — termed Type A and Type B. Type A depressions were felt to be associated with relatively low 24-hr excretion of MHPG, an acute euphoria or behavioral activation in response to 30 mg oral *d*-amphetamine, and a positive clinical response to a trial of imipramine, desipramine, or other norepinephrine-augmenting antidepressants. Type B depressions, on the other hand, were felt to be associated with a lack of response to impiramine, a relatively moderate or high MHPG excretion, and a positive response to amitriptyline or agents which were more likely to affect serotonin-containing neurons.[25]

Patients with bipolar depression were noted to have the lowest MHPG excretion of any clinical subgroup.[26,27] Such patients have been shown to be particularly likely to respond to imipramine and other noradrenergic antidepressants.[28] Also, in bipolar patients, noradrenergic antidepressants seem more likely to induce a switch into hypomania or mania than serotonergic drugs.[29]

Recently the National Collaborative Study on the psychobiology of depression examined the relationship between pretreatment neurotransmitter metabolites and the response to imipramine or amitriptyline treatment. Eighty-seven patients who met research diagnostic criteria for major depression of either the unipolar or bipolar type were included in the study. There were no significant differences in the therapeutic effectiveness of the two anti-depressant drugs in the group of patients as a whole. Low pretreatment MHPG was not associated with either response or lack of response to impramine. No significant relationships were found, however, between urinary MHPG levels and the subsequent response or lack of response to amitriptyline.[30] Low levels of CSF 5HIAA, a metabolite or serotonin, were not related to outcome of amitriptyline therapy, but low pretreatment CSF 5HIAA was correlated with response to imipramine.

Table 3
LOW MONOAMINE DIET FOR MHPG COLLECTION

DO NOT eat the following:

Beverages	Fruits	Dairy
Wine	Banana	Aged cheese
Beer	Pineapple	Sour cream
Alcohol	Plum	
Orange juice	Prune	
Tea	Orange	
Coffee[a]	Raisins	
Colas	Figs	
	Coconuts	
	Walnuts	

Vegetables	Fish	Meat
Avocado	Smoked herring	Brain
Tomatoes		
Broad beans		
Eggplant		

Poultry	Other
Chicken liver	Peanut butter
	Vanilla
	Cocoa

[a] Decaffinated coffee is allowed.

While the National Collaborative Study suggests revision of some of the earlier theories of Maas, the validity of the notion that low MHPG predicts imipramine responsiveness was confirmed by this study. More recent data have accrued on the usefulness of MHPG as a guide to and predictor of response to antidepressant medication [31-33] and can be summarized as follows:

Group I: (MHPG<1900 μg/24 hr) These patients respond preferentially to noradrenergic antidepressants (nortriptyline, maprotiline, desipramine, imipramine) and, in addition, MHPG excretion increases with successful treatment response.
Group II: Intermediate MHPG (1950 to 2500 μg/24 hr) respond to serotonergic-type antidepressants (amitriptyline, perhaps trazodone or tryptophan).
Group III: High MHPG (>2500 μg/24 hr) respond to a broad spectrum of antidepressant treatments but require lengthy treatment at therapeutic levels.

Thus, while controversy continues as to diagnostic usefulness of this measure, MHPG measurement seems to have current empirical usefulness in guiding the choice of antidepressant treatment and as a prediction of response. Tables 3 and 4 outline the protocol for MHPG collection.

V. OTHER BIOLOGICAL PREDICTORS — REM SLEEP AND SLEEP DEPRIVATION

Since REM sleep deprivation is the only effect of antidepressant drugs that has been found

Table 4
PROTOCOL FOR MHPG COLLECTION

1. Patient is to be on low monoamine diet for at least 3 days prior to MHPG urine collection
2. Patient should have 2 or 3 consecutive 24-hr collections
3. Mean value of the 2 or 3 specimens should be calculated and used as the formal MHPG measure
4. Creatinine concentration should be determined and compared to standard 24 excretion values to determine the adequacy of the urine collection
5. Urine should be refrigerated without preservative until MHPG assay

to improve endogenous depression, Vogel et al. attempted to study the mechanism of this phenomenon directly.[34] They concluded that REM sleep deprivation improved depression to the extent that REM inhibitory mechanisms were subsequently invoked. Since a shortened REM sleep latency has been shown to be a sensitive and relatively specific marker for major depression,[35] investigators have hypothesized that a circadian rhythm disturbance may be a fundamental component of the pathophysiology of depression. Antidepressants may be effective to the extent that they normalize this abnormality and delay and reduce REM sleep activity.

Both the acute response in mood and behavior and the prolongation of REM sleep latency on the first few nights after antidepressant administration have been shown to predict subsequent response to medication. Studies using amitriptyline imply that early prolongation of REM latency was a superior predictor of ultimate outcome when compared to clinical assessment based on the symptom profile of the patient.[36] Thus, the observation of early changes in the sleep profile of a patient may be a "biological probe" identifying a medication-responsive individual. Similar sleep EEG changes have been noted in the early phases of treatment with nortriptyline, but these changes have not yet been compared to ultimate outcome measures.[37] Thus, while numerous studies suggest that the effect of antidepressant medications on normalizing REM sleep may be not only a fundamental aspect of their general effectiveness but an early predictor of their efficacy in a given individual, such data do not yet guide the clinician towards the selection of any specific agent. Nevertheless, when altered REM activity can be demonstrated, the chance of response to a biological therapy should be great.

VI. DRUG-FREE OBSERVATION

Given the clinical and biological heterogeneity of DSM III-diagnosed patients along the depressive spectrum, it is not surprising that there is much variation in response rates of different subgroups of depressives to antidepressants. There is a high rate of spontaneous remission as well as placebo response in depressive illness. Up to 50% of a mixed group of depressives will improve over several months without specific treatment.[3] Thus, there is much "noise" in any systematic evaluation of antidepressant efficacy. In populations well defined by DSM III diagnoses and neuroendocrine tests, there is no doubt less. One clinically useful approach to the problem of variability in response is to apply, when practical, a drug-free "washout" or evaluation period when initially assessing the depressed patient. Not only does this allow for a careful psychiatric and medical assessment and relief from the ill effects of medication, but it also insures that patients with spontaneous remissions or response to psychosocial support will be spared unnecessary labeling and medication. This process also maximizes the probability that patients treated with antidepressants will be true pharmacological responders.

It is best to do single medication trials at a time in order to be sure which intervention is having a therapeutic effect. As will be emphasized later, it is important that medication

trials be well defined so that they are adequate in dosage and duration in order to assess the efficacy of a medication for a given patient. Equally important, a medication which has not been helpful after an adequate trial should be discontinued. Though there are some patients who do better on combinations, such as tricyclics plus neuroleptics or antidepressants plus lithium, it is best to add the second medication in a step-wise fashion. There is little place for medications combining a fixed ratio of two medications (e.g., Trilafon® and Elavil® are more effectively prescribed individually than as Triavil®). If two medications are needed, the dosages are best adjusted independently.

VII. TARGET SYMPTOMS

In order to prescribe antidepressants properly, it is important to define target symptoms for the treatment.[1-3] In many clear-cut cases of major depressive episodes with good premorbid functioning, one can aim for virtually an absolute and complete remission of the depressive syndrome. In cases that are less clean cut, especially where there have been characterological and other long-standing problems that may be difficult to sort out from the depression in question, one may aim for improvement and symptoms reduction without expecting remission from all the depressive symptomatology. The physician, as a general rule, can expect antidepressants at best to return the patient to his or her baseline level of functioning before the depression, but seldom affect baseline character structure or functioning. Well-designed studies of female outpatients with major depression have shown that antidepressant medications and psychotherapy have additive benefits, but on different target symptoms.[38] The antidepressants were necessary to alleviate depression symptoms, whereas psychotherapy was necessary to improve social functioning.

The neurovegetative symptoms of depression are useful target symptoms to use in adjusting dosage and monitoring response. Full benefits for antidepressants are not seen until patients have achieved therapeutic levels for 3 to 4 weeks. However, improvement in sleep can often be seen much earlier. If sleeplessness or severe anxiety or agitation are problems, the temporary addition of sedative-hypnotic or low dose of a neuroleptic, particularly at bedtime, can be helpful during the first few weeks of treatment. There is almost no place for use of a barbiturate or barbiturate-like hypnotic in the treatment of depression, considering availability of alternative medications and risk of addiction and lethal overdosage. Improvement in appetite, weight gain, and improvement in energy, concentration, and libido are important targets in monitoring response to antidepressants, as well as changes in the mood itself. Note that depressive cognition, marked by hopelessness, helplessness, worthlessness, and suicidality can accompany the depressed mood and need to be assessed. It is important to interview the patient's family also to monitor progress. Depressed patients are notoriously negative in reporting and are often the last to notice their improvement.

It is the severity of symptoms such as poor nutritional status, psychosis, suicidality, and presence of family supports and cooperativeness of the patient that go into the decision whether to treat the patient as an outpatient or inpatient. In view of the generally favorable response to treatment of depression, it is best in uncertain cases to err on the side hospitalization.

In considering target symptoms, one must distinguish between treatment of the depressive episode and prophylactic use of antidepressants to prevent recurrence. In the prophylactic or maintenance phase, the target is avoidance of relapse. As in all phases of treatment, dosage adjustments must be titrated not only against clinical effects, but taking into account blood levels and side effects, as will be discussed below.

VIII. THERAPEUTIC PLASMA LEVELS AND OTHER CONSIDERATIONS

Absorption of tricyclic antidepressants is quite good. However, plasma levels in patients

given the same dose can vary up to 30-fold. Variation is probably related to first-pass metabolism through the intestine and liver. Genetic factors control the activity of liver microsomal enzymes, which metabolize tricyclics, and may account for the large intersubject variability in plasma levels produced by standard dosages. There is up to ten-fold individual variation in the rate of metabolism of the antidepressants.[7] Because many studies suggest a relationship between therapeutic efficacy of tricyclics and plasma levels,[39] it is important to monitor plasma levels of tricyclics, and not just dosage and clinical effects, in a therapeutic trial of a tricyclic. This is especially important in patients with idiosyncratic or poor response and patients with altered liver metabolism. A number of factors can affect liver metabolism in addition to liver disease. Many elderly patients metabolize antidepressants more slowly, and hence achieve therapeutic plasma levels at markedly lower doses, as low as 25 to 50-mg daily. Pharmacological factors such as cigarette smoking and use of concomitant medications can alter antidepressant levels in clinically significant ways. For example, neuroleptics slow the rate of metabolism such that when combined with a neuroleptic, the antidepressant does need to be reduced as much as 50% to achieve the same plasma level.[40]

There have been many studies of the relationship between steady-state plasma levels of antidepressants (especially tricyclics) and antidepressant effects.[7] As in the case for psychiatry and psychiatric research, not all of the studies in the literature are in agreement. However, the literature suggests that there are clinically important relationships, and therapeutic thresholds or windows have been defined for many of the antidepressants.

The concept of a "therapeutic window" means that there is a plasma-level range within which a patient receives maximum antidepressant benefit, but above which or below which the antidepressant efficacy falls off. This is not simply the same as the observation that efficacy falls off at high levels as toxic effects are seen. The therapeutic window has been best defined for nortriptyline,[39] approximately 50 to 140 ng/mℓ at steady-state (see Figure 2). Steady state is measured 8 to 12 hr after the last dose of antidepressant in a patient who has been on the same dosage for 5 to 7 days. This is usually most practically done in the morning when the patient has had his or her most recent dosage of medication at bedtime the night before.

For other tricyclics, other antidepressants, and most anticonvulsants, therapeutic levels are best described as thresholds required for therapeutic efficacy.[7,8] For antidepressants that are metabolized to substances that are themselves antidepressant, these "active metabolites" must be taken into account also. Thus, amitriptyline is metabolized to nortriptyline, and imipramine is metabolized to desipramine. For patients taking either of the parent medications, plasma levels of both parent and active metabolite must be measured. Therapeutic, steady-state plasma levels for patients on amitriptyline are amitriptyline plus nortriptyline greater than 120 ng/mℓ; for patients on imipramine are impramine plus desipramine greater than 180 ng/mℓ; and for desipramine a therapeutic window may exist but this remains unclear at present. There are preliminary data on therapeutic levels of other antidepressants as well. Table 5 summarizes the usual dosage ranges and therapeutic concentrations which we currently suggest as guidelines for treatment. Measurement of platelet MAO activity can guide proper dosage of MAOI. There are a number of reports that optimal phenelzine response requires at least 80% inhibition of platelet MAO from pretreatment baselines.[41]

The tricyclic "dose prediction test" has been employed to try to ascertain in advance whether a patient is a rapid or slow metabolizer and, hence, the approximate dosage that will be needed to achieve therapeutic levels.[42] This test consists of measurement of plasma level 24 hr after administration orally of a test dose of 50 or 100 ng of a tricyclic. Nomograms have been worked out relating level at 24 hr to anticipated daily dosage needed.

One other practical application of pharmacokinetics is that the long half-lives (about 24 hr) of tricyclic and similar antidepressants to support the practice of giving medication in one dose at bedtime.[7] This practice tends to minimize the impact of side effects, which

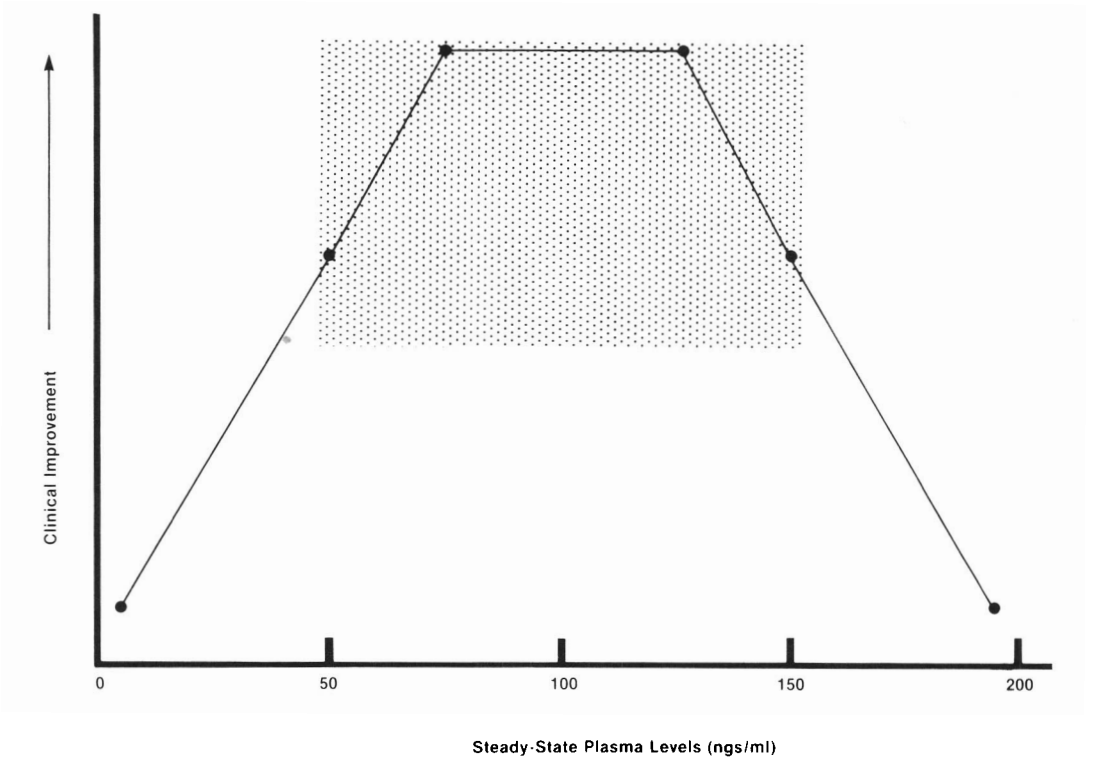

FIGURE 2. Schematic representation of therapeutic window for nortriptyline in depression.

peak, along with plasma levels, 1 to 3 hr after oral administration. Since most all tricyclics and related antidepressants are sedating to some degree, single HS (hour-of-sleep) dosages concentrate the sedative effects when they are needed — at bedtime. MAOI tend to be stimulating and hence should be given in divided doses in the morning and early afternoon.

This may explain why patients with a family history of excessive sedation or other side effects from tricyclic antidepressants frequently have these problems themselves. Genetic factors may also produce variable conversion of tertiary tricyclics (e.g., nortriptyline, desipramine) and also to other active metabolites (10-hydroxynortriptyline from amitriptyline and nortriptyline). Monitoring of a test dose of antidepressant is useful to assess metabolism of this type of drug. For example, 50 mg of nortriptyline (Pamelor®) can be given and plasma level measured 12 and/or 24 hr later (see Table 5).

For dose prediction antidepressant plasma levels to be clinically useful, turnaround time must be 12 to 24 hr after the laboratory receipt of the sample and the chemical techniques must be sensitive enough to differentiate 0.5 ng.

IX. ANTIDEPRESSANT THERAPY

The physician may begin treatment with any tricyclic, since no clinical differences in response to various tricyclics have been demonstrated conclusively. In general, in the absence of a positive personal or family history of clear response, we prefer to begin therapy with nortriptyline or imipramine and to monitor the plasma level closely to insure trial at a therapeutic level for 21 days or longer. It is usually advisable to begin therapy with nortriptyline dose prediction test. If this is not possible, therapy begins at a fairly low dosage and the dosage is increased gradually over a number of days to a therapeutically effective

Table 5
COMPARISON OF TRICYCLIC ANTIDEPRESSANTS FOR CLINICAL USE[a]

Drug	Initial dose (mg)	Therapeutic plasma level (ng/mℓ)	Average daily maintenance dose (mg)
Imipramine (Tofranil®, Janimine®, SK-Pramine®)	100—300	With desipramine[b] 180	75—150
Amitriptyline (Elavil®, Endep®)	150—300	With nortriptyline[b] 120	75—150
Desipramine (Norpramine®, Pertofrane®)	100—300	>125	75—100
Nortriptyline (Pamelor®)	50—150	50—140	50—100
Doxepin (Adapin®, Sinequan®)	200—400	With desmethyldoxepin[b] 110	150—250
Protriptyline (Vivactil®)	30—60	90—170	20—40
Maprotiline (Ludiomil®)	75—150	180—300	75—125
Amoxapine (Asendin®)	200—1400	30—120 (150—450)[c]	200—300
Trazodone (Desyrel®)	50—600	>750	100—300

[a] In average adults, (middle-aged, 150 to 200 lb, taking no other medication).
[b] Major active metabolite must be measured along with original tricyclic.
[c] 8-Hydroxyamoxapine.

level as defined in Table 5. Plasma levels of antidepressant should also be used as a check of compliance, since many patients do not take medication reliably. Medication given in an amount sufficient to maintain therapeutic plasma levels should, if effective, produce within 10 days some improvement in sleep, appetite, and even mood. However, the full effect does not appear until the end of the third week or occasionally even later. If response to 21 days at a consistent therapeutic plasma antidepressant level is negligible or minimal, a change to another antidepressant is recommended. Only after two well-controlled trials, each with a different tricyclic antidepressant, should using a monoamine oxidase inhibitor be considered.

Normally, once a clinical response is documented, antidepressant medication is continued for at least 6 months. During this time, the dosage may be altered as necessary to keep the plasma level in the therapeutic range. Plasma levels are usually monitored on an at least monthly basis or at any time that depressive signs and symptoms reemerge. The tricyclic may be given prophylactically thereafter if episodes of depression recur.

X. NORTRIPTYLINE PLASMA LEVELS AND CLINICAL RESPONSE

We studied the efficacy of nortriptyline when given in doses which produce tricyclic antidepressant (TCA) levels within the proposed therapeutic window in a select patient group to assess the window hypothesis in a group of patients which was biologically homogenous with respect to the TRH test and clinically homogenous with respect to RDC and DSM III and Winokur criteria and excluded psychotic depressive patients. (See Table 6.) Patient compliance issues were controlled by performing this study on inpatients with regular TCA levels. Pharmacokinetic and dose differences were controlled for by administering a nortriptyline dose prediction test, giving the indicated dose, allowing levels to reach steady-state, and changing the dose, if necessary, to maintain nortriptyline levels within the range of 90 to 130 ng/mℓ. With this degree of homogeneity and control, failure to demonstrate improved nortriptyline efficacy would be difficult to explain and routine nortriptyline levels

Table 6
NORTRIPTYLINE DOSE PREDICTION TEST

24-hr Plasma nortriptyline conc. after 50 mg test dose (ng/mℓ)	Calculated daily dose required (mg)
<10	200
10—13	150
14—18	100
19—22	75
23—31	50
32—37	40
38—50	30
51—75	20
>76	10

might be considered irrelevant in patients without pharmacokinetic vulnerability factors. Using this paradigm, 90% of patients responded to nortriptyline. This rate of response for this severely depressed patient group is comparable to response data for ECT and recent European data using regular nortriptyline levels to change doses of nortriptyline and assess appropriate nortriptyline trial duration.

This response rate is greater than that reported for tricyclics or nortriptyline administered without regular nortriptyline monitoring. These data suggest the need to study on time in well-selected, homogenous groups of unipolar patients treated in, over, and under the nortriptyline window. A major recurring problem in comparing neurobiological research in different centers is that different centers may study different diagnostic groups or sub-types of diagnostic groups. With the development of the RDC and DSM III criteria, more consistent and clinically homogenous patient groups could be identified, treated, and studied. However, the problem of heterogeneity remains an important issue. One possible solution is to identify sub-types of unipolar depression by family history and biological abnormalities. Our data support the concept of a therapeutic window and TCA level monitoring to improve efficacy of nortriptyline in unipolar depressed patients. These data suggest that selection of patients may explain the lack of correlation and improvement data reported for nortriptyline by others.

XI. ADOLESCENT MAJOR DEPRESSIVE DISORDER

Childhood and adolescent depression has become a prominent focus of clinical and biologic psychiatric research. This research has identified the childhood depressive illness to be exactly like that found in adulthood or like that in adulthood but modified by developmental issues. These studies and more recent, better-controlled studies have indicated the effectiveness of antidepressant medication in the treatment of childhood and adolescent depression.

Our preliminary study with specific subgroups of patients focuses on the use of antidepressant medication with regular determination of plasma levels in the treatment of a group of adolescents with a diagnosis of major depressive disorder confirmed by a positive DST. A clinical assessment of the patient's depressive status using DSM III criteria and the clinical global impressions scale was conducted weekly. Patients completed a Children's Depression Inventory (CDI) twice weekly. A CDI score of greater than 16 was presumed to be significant for depression.

Pharmacotherapy consisted of nortriptyline with an initial test prediction dose of 50 mg at bedtime and dose adjustment as indicated. Plasma level determinations were performed twice weekly until the patient had maintained a plasma level between 50 ng/mℓ and 140 ng/mℓ, the therapeutic range, for at least 21 consecutive days. Plasma levels were then

performed on a once-weekly basis for the remainder of treatment. All patients received medication for at least 21 consecutive weeks at a dose that maintained plasma levels between 50 ng/mℓ and 140 ng/mℓ. An increase in dose of nortriptyline occurred at 25 mg increments when two consecutive plasma levels were below 50 ng/mℓ.

After 21 days of treatment at therapeutic plasma levels range, six of the eight patients had a marked and significant degree of clinical improvement of their depression receiving a clinical global impressions score of one or two. The other two patients revealed no change in clinical status. No patient experienced more than minimally severe orthostatic hypotension and dryness of mouth for longer than the first 1 to 2 weeks of treatment within the therapeutic plasma range. With a relatively low starting dose of nortriptyline, these adolescent patients quickly achieved a therapeutic plasma level with a minimum of undue side effects. As a result, there was complete compliance with the treatment by all patients.

The first significant finding from this study is a 75% response rate in depressed adolescents under carefully supervised inpatient conditions with full medical compliance documented by plasma levels. The second finding is that the adolescents required a relatively low dose to achieve levels in the therapeutic range. After the achievement of therapeutic plasma level, this level is maintained for at least 4 weeks of treatment on the same dose. Clinical improvement occurred in these patients within a time frame that suggests a significant role for the antidepressant medication. No patient experienced undue side effects during the course of treatment.

As seen in the two studies utilizing specific groups of depressed patients, nortriptyline with nortriptyline levels monitoring of antidepressant levels can improve efficacy. For carefully selected major depressives, response rates to antidepressants have been reported as low as 50 to 60% without monitoring of plasma levels and as high as 70 to 90% of adolescents and adults with monitoring of levels.[1-3,43] Many clinicians, including ourselves, find the monitoring of plasma levels at approximately weekly intervals quite useful, especially in the early weeks of dosage adjustment. It is especially useful in patients at the extremes of normal — those who require extremely low or extremely high dosage to achieve therapeutic effects.

XII. THERAPEUTIC DRUG MONITORING: ADDITIONAL COMMENTS

A. Antidepressant Levels

The use of standard dose regimens unrelated to plasma levels has been identified as a major source of antidepressant nonresponse. The reasons for this fact are numerous, but include pharmacokinetic, pharmacodynamic, and other factors.

Many clinicians have delayed use of the plasma levels because of suggestions in the past that all nonresponders merely require a higher dose of the antidepressant. To say that no depressant trial in the fact of nonresponse is complete without a period on high or very high doses is incorrect and dangerous, since some patients end up with extremely toxic levels. Some physicians feel that antidepressant levels are too expensive for routine use. However, given the much greater expense of a single hospital day, if the test decreases hospital length of stay by even 1 day, it is cost-effective, to say nothing of the risks of being on an antidepressant with substandard levels — the risks of not getting better, suicide, and suffering as well as the medical risks. Finally, psychiatrists have been similar to neurologists in their response to the introduction of medication levels. Neurologists once felt that clinical judgment was adequate in determining patient medication dosages and felt that anticonvulsant levels were an unnecessary expense. Now, while levels haven't eliminated judgment, very few neurologists fail to utilize these levels.

B. Why Blood Levels in Inpatients?

As was demonstrated in our studies mentioned above, antidepressant plasma level monitoring is clinically useful in the pharmacological treatment of depressed inpatients. In general inpatient psychiatry, the relationship between plasma antidepressant concentrations and therapeutic response is exploited to maximize response and reduce side effects and noncompliance and decrease length of hospital stays. This is of special importance for nortriptyline where use of dose prediction test, therapeutic window, and the defined trial (21 consecutive days at therapeutic levels) can bring response rate from 50 or 60% to 80 or 90%. Routine monitoring of plasma antidepressant concentrations in all medicated subjects is helpful and warranted in inpatients on both intellectual and cost-effectiveness grounds. Imipramine and desipramine also appear to have an adequately defined threshold which may be exploited to increase efficacy.

C. Reducing Toxicity?

Individuals who are at increased risk for toxic effects of antidepressants benefit from frequent plasma level monitoring. While most antidepressants have adverse effects, knowing plasma level-response relationships and using plasma levels can reduce or even eliminate side effects. In certain patients with cardiovascular disease, prolonged atrioventricular conduction times may lead to ventricular arrhythmias and potentially death. Consequently, any patient particularly at risk for toxic effects of antidepressants (e.g., elderly, cardiovascular disease, drug, and/or alcohol abuse history, liver disease, family or personal history of side effects at low doses of antidepressants) may be medicated with nortriptyline using concurrent frequent plasma level monitoring to remain within the lower limits of the therapeutic range to minimize any potential toxicity.

D. Why Blood Levels in Outpatients?

Tricyclic and other antidepressants may usually be used effectively in outpatients without frequent monitoring of plasma concentrations.

Greater than 50% of outpatients may be efficiently and appropriately treated by the simple use of standard doses of antidepressants, with a single blood level after dosage stabilization. In these patients, additional bi-weekly or weekly plasma level monitoring is unnecessary. However, weekly levels do ensure compliance and save the financial, familial, and personal cost of a relapse. If outpatients have not begun to experience a marked therapeutic benefit within 2 to 3 weeks, or seem to be sustaining unusually severe side effects, more frequent plasma levels determinations will be necessary. Dose adjustment may be reduced by the use of the nortriptyline dose prediction test.

Even some patients in clinical remission on maintenance antidepressants may benefit from plasma antidepressant concentration determinations. As noted above, a variety of exogenous factors may alter steady-state concentrations of antidepressant medications. For example, neuroleptics, methyphenidate, corticosteroids, disulfiram, dipropylacetamide, vitamins, and weight loss may all markedly increase plasma levels of antidepressant agents with "therapeutic windows". Conversely, barbiturates and tobacco smoking may markedly lower plasma tricyclic concentrations and allow relapse in patients treated with all classes of antidepressants. There are likely to be numerous other drug-drug interactions affecting tricyclic plasma concentrations in the outpatient and, when adding or deleting a concurrent medication to a patient's pharmacological regimen, a plasma level determination may be appropriate.

Finally, differences in bioequivalence among pharmaceutical preparations of the same tricyclic agent have resulted in changes in plasma tricyclic concentrations and caused clinical relapses or precipitated toxicity, and the clinician must be alert to this if outpatient changes pharmacies.

Table 7
ADEQUACY OF AN ANTIDEPRESSANT TRIAL

1. Dosage
2. Plasma Levels
3. Duration
4. Compliance

A Minimum Trial: 21 Consecutive days at therapeutic plasma levels

E. Compliance

It is well known that the majority of patients do not take medications prescribed. This is a fact in outpatient *and* inpatient psychopharmacology. Non- or partial compliance causes wide fluctuations in plasma levels and reduced response to treatment. Frequent monitoring of antidepressant levels is the best way to insure compliance and guarantee the integrity of the medications trial. Prevention of compliance problems is recommended to avoid wasted hospital time and risk of untreated severe depressions.

In summary, the use of levels can take much of the guesswork out of time-consuming clinical trials that involve gradually raising or lowering the initial dose. Without levels, one ordinarily begins a patient at a dosage somewhat lower than the anticipated average therapeutic dosage, observes the patient for side effects and response, and gradually raises the dose until response, or severe side effects, or frighteningly high dosages. With rise of plasma levels, the physician can sometimes maintain patients at low dosages and expect good results, sometimes raise the dosage quickly to a high amount safely, and sometimes cut down on the time involved in an unsuccessful trial. Perhaps most obvious and most important of all, the physician can monitor compliance. It has been well documented that many patients with depression, like patients with other illnesses, simply do not take their medication as prescribed.[1-4] In utilizing antidepressant levels, the clinician must be sure that laboratory has a sensitive and reliable assay. Several methods have been employed,[7] including high pressure liquid chromatography and GC/MS.[44] It is also important that results are available to the clinician quickly enough to be useful in adjusting dosage, within 1 to 2 days of drawing the blood sample.

Therapeutic plasma level monitoring has been useful in helping to define an adequate antidepressant trial. In light of the high proportion of treated depressives who have inadequate pharmacological treatment, criteria for adequacy are important. We define and consider an adequate antidepressant trial to consist of maintaining the patient at dosage adequate to achieve therapeutic plasma levels for a minimum of 21 days with documented compliance (Table 7).

F. Available Antidepressants and Variation in Side Effects

There are many antidepressants on the market currently. The commercially available tricyclic antidepressants consist of imipramine, desipramine, amitriptyline, nortriptyline, doxepin, protriptyline, and trimipramine. The new generation of antidepressants[1,45] includes maprotiline, trazodone, and amoxapine. Tranylcypromine, phenelzine, and isocardoxazid are the commercially available MAOI (see Chapter 7). Lithium is available in regular and slow-release forms. Carbamazepine[46] and alprazolam are also reported to have antidepressant effects.

G. Receptor Effects

All the tricyclics are reported to have about equal antidepressant effects, but wide variation in side effects.[1-3,47] Important side effects include sedation, anticholinergic effects, and

Table 8
RELATIVE ANTIHISTAMINE/HISTAMINE H_1/SEDATING POTENCIES OF ANTIDEPRESSANTS

Drug	Relative potency[a]
Doxepin (Adapin®, Sinequan®)	800
Trimipramine (Surmontil®)	250
Amitriptyline (Elavil®, Endep®)	190
Maprotiline (Ludiomil®)	25
Amoxapine (Asendin®)	4
Nortriptyline (Aventyl®, Pamelor®)	4
Imipramine (Janimine®, SK-Pramine®, Tofranil®)	2.5
Protriptyline (Vivactil®)	0.7
Trazodone (Desyrel®)	0.4
Desipramine (Norpramin®, Pertofrane®)	0.1
Diphenhydramine[b] (Benadryl®)	1

[a] Data modified from Ref. 45.
[b] Not an antidepressant; given here for comparison.

postural hypotension. These effects should be considered when making the initial choice for treatment and can often be tailored to a particular patient's requirements.

The degree to which sedation is produced by antidepressants corresponds to and is believed to result from H_1 histamine receptor blockade. Table 8 shows the relative potencies of the available antidepressants in blocking H_1 histamine receptors. As can be seen, many are more potent anthistamines than the standard antihistamine, diphenhydramine. Doxepin has the most potent antihistamine effects and is 800 times more potent than diphenhydramine. The rank order of these compounds correlates fairly well with their apparent sedative properties.

Desipramine is the least antihistaminic and is the least sedating of these compounds. For some patients, sedation may be a desirable side effect, particularly for those with extreme agitation and insomnia. Other patients are intolerant of these effects and may require a less-sedating agent. Other clinically important effects which may be mediated via H_1 receptor blockade include weight gain, possibly hypotension, and potentiation of the CNS depressant effects of alcohol, other sedative hypnotics, and CNS depressants.

Anticholinergic effects (dry mouth, constipation, urinary retention, blurred vision, increased heart rate) result from blockade of muscarinic receptors. As is shown in Table 9, there is a tremendous variation in the degree to which these effects are produced. Amitriptyline, the most potent in this regard, is about 1/10 as potent as atropine in blocking muscarinic receptors, and is 18,000 times more antihistaminic than the newly released trazodone. Anticholinergic effects can be quite significant clinically and should be considered when choosing an antidepressant agent. For patients with a history of narrow-angle glaucoma, agents which are highly anticholinergic should be avoided. Elderly patients may be at risk for anticholinergic delerium, urinary retention (especially in males with enlarged prostates), or constipation. Patients with a cardiac history may experience an excessive increase in heart rate from highly anticholinergic agents.

Orthostatic hypotension is probably the most frequently encountered adverse effect resulting from alpha adrenergic receptor blockade (Table 10). For patients who are sensitive to this effect, agents such as desipramine or protriptyline may be indicated, while highly anti-alpha-adrenergic agents such as doxepin, trimipramine, or amitriptyline should be avoided.

Amoxapine is a new antidepressant designated chemically as 2-chloro-11-(1-piperazinyl) dibenz (b, f)(1,4) oxazepine. The antidepressant activity of amoxapine is related to the blockade of norepinephrine and serotonin uptake. There are two major metabolites, 7-OH-

Table 9
RELATIVE ANTICHOLINERGIC POTENCIES OF ANTIDEPRESSANTS

Drug	Relative potency[a]
Amitriptyline (Elavil®, Endep®)	11.0
Protriptyline (Vivactil®)	8.0
Trimipramine (Surmontil®)	3.4
Doxepin (Adapin®, Sinequan®)	2.6
Imipramine (SK-Pramine®, Tofranil®)	2.2
Nortriptyline (Aventyl®, Pamelor®)	1.4
Desipramine (Norpramin®, Pertofrane®)	1.0
Maprotiline (Ludiomil®)	0.4
Amoxapine (Asendin®)	0.2
Trazodone (Desyrel®)	0.0006
Atropine[b]	100

[a] Data modified from Ref. 45.
[b] Not an antidepressant; given here for comparison.

Table 10
RELATIVE ANTI α ADRENERGIC/ HYPOTENSION-PRODUCING POTENCIES OF ANTIDEPRESSANTS

Drug	Relative potency[a]
Doxepin (Adapin®, Sinequan®)	5.0
Trimipramine (Surmontil®)	5.0
Amitriptyline (Elavil®, Endep®)	4.4
Trazodone (Desyrel®)	3.4
Amoxapine (Asendin®)	2.4
Nortriptyline (Aventyl®, Pamelor®)	1.9
Maprotiline (Ludiomil®)	1.3
Imipramine (SK-Pramine®, Tofranil®)	1.3
Protriptyline (Vivactil®)	0.9
Desipramine (Norpramin®, Pertofrane®)	0.9
Prazosin[b] (Minipress®)	2000

[a] Data modified from Ref. 45.
[b] Not an antidepressant; given here for comparison.

Amoxapine and 8-OH-Amoxapine, and it appears that these metabolites are responsible, more so than the parent compound, for pharmacological effects. 8-OH-Amoxapine is comparable to the parent compound's norepinephrine reuptake blocking properties; however it is extremely potent on serotonin reuptake blockade. It has been demonstrated that 7-OH-Amoxapine has significant dopamine receptor blockade in laboratory animals and as such its dopamine (DA) blocking and neuroleptic activity in humans should be studied. We have recent data in amoxapine-treated humans which demonstrated potent DA blocking effects in some patients and negligible effects in others. Plasma samples were obtained on 30 patients maintained on amoxapine therapy for at least 3 weeks. Plasma was assayed for 8-OH-Amoxapine by gas liquid chromatography and for dopamine receptor-blocking activity by a Neuroleptic Radio Receptor Assay (NRRA). Significant dopamine blocking activity was noted by NRRA in samples independent of plasma 8-OH-Amoxapine level. 7-OH-

Table 11
CLINICAL SIGNIFICANCE OF RECEPTOR ACTIVITY

	Property	Possible clinical consequence
1.	Blockade of norepinephrine uptake at nerve endings	Antidepressive effects; blockade of the antihypertensive effects of quanethidine, clonidine, and α-methyldopa
2.	Blockade of serotonin uptake at nerve endings	Antidepressive effects; ?postural hypotension
3.	Blockade of histamine H_1 receptors	Potentiation of alcohol, tranquilizers and other central depressant drugs; sedation, drowsiness; weight gain; hypotension
4.	Blockade of muscarinic receptors	Blurred vision, urinary retention, dry mouth, constipation, sinus tachycardia
5.	Blockade of α_1-adrenergic receptors	Potentiation of the antihypertensive effect of Prazosin (Minipress®); postural hypotension, reflex tachycardia
6.	Blockade of a_2-adrenergic receptors	Blockade of the antihypertensive effects of clonidine (Catapres®) and α-methyldopa (Aldomet®); ?antidepressive effects

Amoxapine concentrations correlate with dopamine blocking activity by NRRA. High concentrations of 7-OH-Amoxapine and NRRA activity may be correlated with akathisia, extrapyramidal symptoms (EPS), galactorrhea, antipsychotic efficacy. Occasional patients who are administered this compound on a chronic basis form high amounts of 7-OH-Amoxapine and may be at risk for tardive dyskinesia.

As the preceding discussion of receptor effects indicates, various antidepressant effects may vary widely from patient to patient. Using knowledge of these effects may help guide the initial choice and increase the likelihood of an adequate therapeutic trial with a minimum of unwanted effects (Table 11).

H. Other Effects

A recent and important finding is that tricyclics possess quinidine-like antiarrhythmic effects, and actually suppress premature ventricular contractions.[47] Many patients with cardiac disease can be treated safely with tricyclics if monitored closely.

Tricyclics can be lethal in overdosage.[3] Doxepin is alleged to be the safest in an overdose. Measurement of levels and EKG changes such as QRS widening are indicators of severity of overdoses. The ratio of tertiary to secondary and other metabolites can also be used for this purpose. Death can be from central nervous system or cardiorespiratory effects. Because of the possibility of serious overdose in depressed patients, no more than 1- to 2-weeks supply of an antidepressant should be prescribed at a time to outpatients.

XIII. DECISION TREES FOR PHARMACOLOGICAL TREATMENT OF MAJOR DEPRESSIVE DISORDERRS

A. Unipolar Depression (Nonpsychotic)

Antidepressants are the mainstay of the pharmacological treatment of uncomplicated, nonpsychotic, major unipolar depression.[1-3] The tricyclics are all effective antidepressants, with their main differences being side effects. Some researchers have tried to provide guidelines for choice of tricyclic based on potentiation of brain noradrenergic vs. serotonergic neurotransmission[27,48] or based on neurobiological markers. More research needs to be done in these areas. In view of the limiting anticholinergic and sedative effects of the tertiary tricyclics and the major advantages of a medication with a defined window, our first choice generally is the tricyclic nortriptyline (Table 12). In our experience it is generally well tolerated and therapeutic levels can be achieved and the trial established and maintained

Table 12
A DECISION TREE FOR PHARMACOTHERAPY OF MAJOR DEPRESSION

A. Unipolar Without Psychosis

1.	Antidepressant with minimal sedative/anticholinergic effects and as known therapeutic window (e.g., nortriptyline)	
2.	T-3 and/or lithium or tryosine potentiation	Exploit thereaputic window and pharmacokinetics to maximize response rate
3.	?Second tricyclic	Preserve the integrity of the antidepressant trial (21 consecutive days at therapeutic levels)
4.	MAOI	If limiting side effects try a "second generation antidepressant" (e.g., *maprotiline*)
5.	ECT	

without side effects. Low doses of benzodiazepines or neuroleptics can be added in unusual circumstances if needed for anxiety, agitation, or sleeplessness.[1-3] I would reserve the "second generation" antidepressants for patients who have real and severe low plasma-levels side effects. When there is better documentation that these newer antidepressants have efficacy equal to the tricyclics and efficacy equal to nortriptyline with nortriptyline levels, we will reconsider.

In an inpatient setting where primary vs. secondary diagnoses are made, neuroendocrine tests are used to confirm the diagnosis. A 21-day therapeutic level trial of nortryptyline will succeed in approximately 85% of cases of major depression. If an adequate nortriptyline trial is not successful, one may try at least one of two methods to potentiate the antidepressant effects of the tricyclic. Addition of triiodothyronine (T3) in subreplacement doses of 25 to 50 ng/day can convert a significant proportion of tricyclic nonresponders to responders.[9,10,49] Theoretical explanations of this "T3 potentiation" include correcting mild or subclinical hypothyroidism in some depressives, and effects of T3 on central norepinephrine receptor sensitivity. Addition of tyrosine 100 mg/kg/day to a NT trial, especially in low MHPG depressions, can convert nonresponders to responders. Both these techniques are simple, safe, and rapid. If they have not worked after 1 to 2 weeks, they probably will not work and they should be discontinued, along with the tricyclic, before going on to the next treatment approach. Similarly, there are several recent reports that adding lithium carbonate 900 to 1200 ng/day to the tricyclic regimen can convert nonresponders to responders.[11,12] The theoretical basis for lithium potentiation involves lithium's potentiation of serotonergic neurotransmission.

At this point, some psychiatrists would recommend trying a second tricyclic, some a "second generation" antidepressant, and others as MAOI. There has been renewed enthusiasm for MAOI over the last few years. Some literature suggests that patients with "atypical depressions" are more likely to benefit from MAOI. These include patients with hypersomnic, hyperphagic depressions, patients with prominent anxiety and characterological features, as well as patients described as "hysteroid dysphoric".[1] There are without doubt some depressives who do better on MAOI than on any other medications. There is also a very small proportion of depressives who do better on stimulants such as methylphenidate or dextroamphetamine than on any other medications.[1-3] Abuse potential must be weighed carefully in such patients. The amino acids tyrosine and tryptophan, precursors of norepinephrine and serotonin, respectively, have also been reported to be effective alone or as potentiators of antidepressant medications.[1,50,51] Tricyclics and MAOI have been combined to treat refractory depressions, though such patients need to be observed closely medically.[1-3]

Electroconvulsive therapy (ECT) is the most effective treatment available for the treatment

Table 13
A DECISION TREE FOR PHARMACOTHERAPY OF MAJOR DEPRESSION

B. Bipolar Without Psychosis

1. Lithium[a]
2. Lithium + tryptophan[a]
3. Lithium + tricyclic
4. Lithium + MAOI
5. ECT

[a] The FDA does not yet approve of lithium alone as a treatment for acute depression. For some depressed bipolar patients, lithium alone may, in the author's opinion, be an effective first-line treatment (see text.)

of major depression.[1-3,52,53] It is a safe and well-tolerated treatment as performed currently, with short-acting anesthesia and muscle blockade. The major side effect is transient memory loss and relapse. ECT can be the treatment of choice initially when life-threatening symptoms such as refusal to eat or drink or severe suicidality are present, or in the face of psychosis or severe agitation. Usually ECT is reserved for patients with clear depressive syndromes which are refractory to pharmacotherapy. One advantage of pharmacotherapy over ECT is that medication, if successful, can be continued after remission to have continued prophylactic effect. In addition, if the illness recurs, the patient can be treated with this medication instead of ECT. Social stigma sometimes mitigates against appropriate use of ECT. However, no seriously depressed patient should be thought of as a treatment failure unless they have had an adequate course of ECT.[53] In fact, there has been a renewed appreciation of ECT as an antidepressant over the past few years.

B. Bipolar Depression (Nonpsychotic)

Major depressive disorder, bipolar, simply refers to a depressive episode in a patient with a history of a manic episode — that is, the depressed phase of manic-depressive illness. About 50% of such patients will respond over the course of 1 month to lithium alone.[54] A trial of lithium alone in bipolar depression is perhaps less likely to have a clear antidepressant effect than a tricyclic or MAOI, but has certain advantages. First, it spares the patient the risk of antidepressant-induced mania or rapid mood cycling. Second, if a patient responds, then he is already on the medication most useful for prophylaxis of bipolar disorder. Thus, if patient and physician can afford to be patient for 3 to 4 weeks, a trial of lithium alone is a sensible, conservative approach (Table 13).

If severity of symptoms or other factors call for a pharmacological approach more likely to relieve the depression, and to do so more quickly, or if lithium alone is unsuccessful, then a trial of a less sedating tricyclic, such as nortriptyline or desipramine, usually in combination with lithium, is indicated. Particularly for bipolar depressives, who usually have psychomotor retardation, a very sedating tricyclic should be avoided. T3-potentiation of the tricyclic plus lithium combination can be tried. This may be especially helpful for patients with even early evidence of lithium-induced hypothyroidism, sometimes detectable by TRH testing only. If lithium plus a tricyclic (or second generation) antidepressant is not helpful, then strong consideration should be given to a trial of lithium plus an MAOI. Some clinicians and investigators have reported that bipolar depressed patients respond better to MAOI than to other antidepressants.[1-3] If pharmacological treatments are not successful, a bipolar depressed patient should have a course of ECT, usually along with lithium. Because lithium is the mainstay of treatment of manic-depressive illness, we usually recommend that bipolar patients be maintained on lithium while other additional treatments are tried.

Table 14
A DECISION TREE FOR PHARMACOTHERAPY OF MAJOR DEPRESSION

C. With Psychosis

1. Neuroleptic (antipsychotic)
2. Neuroleptic + tricyclic (and/or lithium in some bipolars)
3. ECT

C. Psychotic Depression

The term "psychotic depression" refers to a major depression with delusions or hallucinations.[5] These psychotic symptoms are usually depressive ones, such as delusional guilt or somatic delusions. A psychotic depression may be unipolar or bipolar. Psychotic depressions have been set aside in a separate category here because they have a different pattern of response to pharmacotherapy (Table 14). It has been clearly documented that psychotic depressions do not respond well to treatment with antidepressants alone.[55] In fact, they can become worse.

The initial pharmacological approach to the psychotic depressive is treatment with a neuroleptic (antipsychotic) medication in low to moderate doses. This usually results in significant calming and lessening of psychosis, but without clear remission. In most cases, a tricyclic antidepressant needs to be added to the neuroleptic for more complete recovery.[1-3,55] The physician needs to remember that patients will achieve much higher blood levels of a tricyclic on a given dose when also on a neuroleptic.[40] It is of interest that a small proportion of psychotic depressives have a virtually complete remission from neuroleptics alone. This ability of dopamine blockers to cause remissions in some clear-cut psychotic depressions is a challenge to the usual amine hypothesis of affective illness.

Because psychotic depressions tend to be more severe and sometimes life-threatening, some clinicians consider ECT the initial treatment of choice. ECT is quite effective in psychotic improvement as early as the first treatment.[52,53]

D. Changes in Neuroendocrine Tests and Prognosis

Both the DST and TRH test, when abnormal in depression, tend to normalize over the course of successful treatment. Patients in whom either of these tests has not normalized have a much higher probability of rapid relapse, despite clear clinical improvement.[13,14] Since most physicians, most patients, and even many psychiatrists do not believe psychiatry can help, demonstration of state-dependent changes reversed by treatment is of major importance. The DST and TRH test can be used to document biological state change with response to treatment, and to establish prognosis more accurately. The use of these tests before and after treatment may take some of the guesswork out of treatment decisions. For example, a course of ECT should probably be continued, within reason, until the DST and/or TRH test normalizes. Patients who seem to have recovered clinically, but have persistant DST or TRH test abnormalities, should probably be treated more aggressively, with prophylactic antidepressants maintained a longer time and more frequent outpatient follow-up.

E. Prophylactic Antidepressants

The use of antidepressants and lithium as prophylaxis against recurrent episodes of depression (or mania) is an application distinct from use of these agents in treating acute episodes.[56] Antidepressants are clearly superior to placebo in decreasing the likelihood of recurrent unipolar depression, as lithium is in decreasing the likelihood of recurrent depressions and manias in bipolar patients. Newer data suggest that lithium also has prophylactic effects in unipolar depressions.[57] Blood levels required for adequate prophylaxis have not been well

defined, but, for both antidepressants and lithium, it would seem reasonable to aim for levels in the lower regions of the therapeutic ranges established for acute treatment.

F. Other Uses for Antidepressants

There have been reports of several clinical uses of tricyclics and lithium other than in clear-cut affective disorders.[1-3] Tricyclics can be ffective in the treatment of patients with panic and phobic disorders, posessive compulsive disorders, chronic pain syndromes, as well as in the treatment of depression in schizophrenia and schizoaffective illness. Lithium (and carbamazepine) can be helpful in impulse control disorders in addition to mood disorders.

XIV. CONCLUSIONS

Given the high incidence of major depression in the population and the efficacy of appropriate pharmacotherapy in a high percentage of patients with this disorder, it behooves physicians and other health professionals to become familiar with the clinical use of antidepressant medications. These include tricyclics, MAOI, and lithium. This chapter has outlined a number of recent findings, the application of which can enhance antidepressant treatment. These include use of contemporary clinical nosology and neuroendocrine diagnostic test to identify candidates for pharmacotherapy and/or ECT, monitoring plasma levels of antidepressants to achieve therapeutic levels, potentiating tricyclic nonresponders with tricyclic or monoamine precursor (e.g., tryptophan, tyrosine) or lithium, and use of the "second generation" antidepressants, particularly in patients who cannot tolerate tricyclic side effects. The chapter has presented a decision-tree approach to the pharmacotherapy of major depression with an emphasis on sequential adequate medication trials with optimal clinical and laboratory monitoring of response.

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Chapter 5

THE SEROTONIN SUBTYPE OF DEPRESSION

Charles A. Dackis and Mark S. Gold

TABLE OF CONTENTS

INTRODUCTION

Since melancholia was first described by Freud in 1915,[1] there have been impressive gains in the treatment and understanding of this disorder. The modern, symptom-based approach has allowed for a more refined diagnosis of major depressive illness.[2] Furthermore, hereditary aspects of depressive illness are significant and point toward a biological, genetically transmitted etiology.[3] The biological nature of this disorder is underscored by the efficacy of somatic therapies, including a number of antidepressant medications which affect biogenic amines in the brain. Numerous abnormalities in neutrotransmitter function have been reported in affective disorders, particularly with regard to norepinephrine and serotonin function.[4] Attention has been increasingly focused upon abnormalities in brain physiology which might explain depressive illness. A substantial body of evidence has emerged which indicates that certain depressed patients have derangements in central serotonin activity. This has led to the indolamine theory of depression,[4,5] which states that a subset of major depressives have deficient serotonin neurotransmission as the biological basis of their disease. This section will review the evidence supporting serotonergic dysfunction in depression, as well as treatment considerations.

II. SEROTONIN BIOSYNTHESIS

Before proceeding to a discussion of abnormal serotonin function in depressive illness, some aspects of normal serotonin biochemistry will be reviewed. Serotonin is synthesized from the essential amino acid, tryptophan, by a sequence of two enzymatic conversions (see Figure 1). The first conversion is catalyzed by tryptophan hydroxylase, which is the rate-limiting step and occurs within the serotonergic neuron. The product of this conversion, 5-hydroxytryptophan, is rapidly converted to serotonin by tryptophan decarboxylase. When normal levels of the substrate, tryptophan, are in the brain, tryptophan hydroxylase is not saturated.[6] This lack of substrate saturation is extremely important because any increase in brain tryptophan levels is rapidly translated into increased serotonin concentration in the brain. Furthermore, brain tryptophan concentration is determined by the free plasma tryptophan level, which in turn determines the synthesis rate of central serotonin.[7]

Since brain serotonin content is physiolgically dependent upon free plasma tryptophan levels, it is important to understand some of the factors influencing plasma tryptophan. As an essential amino acid, tryptophan cannot be synthesized in the body and must be obtained from dietary sources such as milk, cereal, fruit, and protein. Once absorbed, tryptophan is largely bound loosely to serum albumen with only 10% occurring as unbound or "free" tryptophan.[8] Since only free plasma tryptophan is available for transport into the brain, drugs or plasma constituents which also bind albumin can displace the loosely bound tryptophan, leading to an elevation in free plasma tryptophan and hence increased cerebral serotonin.[7] For instance, elevations in plasma unesterfied fatty acids released during stress will displace tryptophan from its binding sites and increase brain serotonin.[9]

Plasma free tryptophan is also subject to shunting through metabolic pathways. One pathway involves the transformation of tryptophan by tryptophan pyrrolase in the liver, forming the kinurenine pathway to nicotinamide formation.[10] This major metabolic pathway metabolizes free tryptophan which would otherwise be available for transport into the central nervous system (CNS). Glucocorticoids, often elevated in depression,[11] increase tryptophan pyrrolase activity and thereby create a relative depletion of free plasma tryptophan.[12] Tryptophan also contributes to protein synthesis, as well as being converted peripherally to tryptamine by tryptophan decarboxylase.[13] Altered function of any of these multiple metabolic pathways can alter the concentration of free plasma tryptophan and brain serotonin.

The movement of plasma tryptophan across the blood brain barrier and into the CNS is

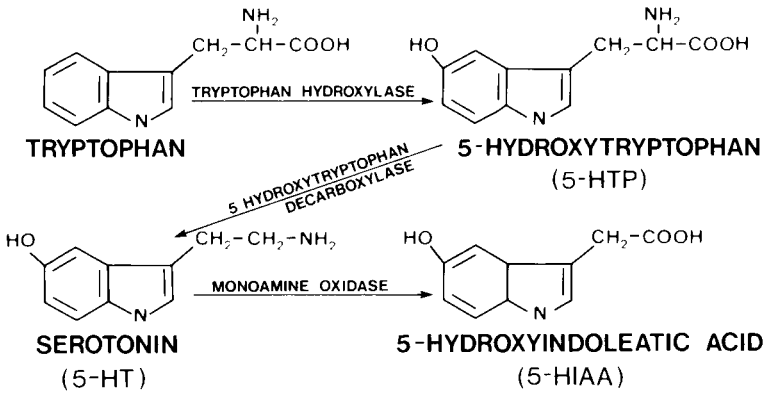

FIGURE 1. The biosynthesis and degradation of serotonin.

mediated through active transport by an energy-dependent, high-affinity pump.[14] Competing for this active transport site are other large, neutral amino acids including leucine, isoleucine, valine, tyrosine, and phenylalanine.[15] Since these other amino acids compete for the same transport site, their concentration correlates inversely with the amount of tryptophan transported from plasma to brain.[15] Therefore the ratio of plasma free tryptophan to the five competing amino acids (tryp/5-AA) is a useful measure of the plasma tryptophan which is available for serotonin synthesis. This ratio will be discussed later.

Once substrate has reached the brain, serotonin is rapidly synthesized and stored in secretory vesicles. The vesicle contents are released into the synapse upon depolarization of the serotonin neuron, and post-synaptic receptors are thereby stimulated. Synaptic serotonin is then largely transported back into the neuron by a high-affinity reuptake site. It is at this site that tricyclic antidepressants such as imipramine act to block the reuptake of serotonin.[16] Recently, tritiated imipramine has been used to identify binding sites in the brain which are closely associated with reuptake sites for serotonin.[17] Imipramine binding sites correspond to neuroanatomical areas of high serotonin concentrations such as the raphe nuclei.[18] These binding sites are also found on blood platelets,[19] which share many properties in common with serotonergic neurons.[20] Thus, the measurement of serotonin uptake by blood platelets can serve as a peripheral model of serotonin neuronal reuptake.[20] We will discuss recent findings with this measure in the next section.

Brain serotonin is metabolized in the serotonin neuron to the inactive metabolite 5-hydroxyindoleacetic acid (5-HIAA). This metabolite diffuses into the cerebrospinal fluid (CSF), is cleared through the choroid plexus, and eventually excreted in the urine. Serotonin is converted to 5-HIAA by the enzyme monoamine oxidase (MAO). CSF levels of 5-HIAA can be measured by lumbar puncture and serve as an indicator of serotonin turnover. However, since there are large individual variations in the clearance of 5-HIAA from the CSF, researchers have used the drug probenecid to inhibit the efflux of CSF 5-HIAA.[21] This allows for accumulation of 5-HIAA and more accurate measurement of central serotonin turnover. In fact, CSF tryptophan and 5-HIAA concentrations are strongly correlated in human subjects.[22] As we shall see, post-probenecid CSF 5-HIAA accumulation is a useful measure of serotonin dysfunction in depressive illness. This measure also increases with age, is greater in females than males,[23] and correlates inversely with height.[24]

This section has briefly dealt with some of the serotonin-related pathways which are known, as well as some of the measures used to quantify serotonin function. The biochemistry of tryptophan, serotonin, and 5-HIAA is more complex than this rather simplistic overview. Alterations in serotonin function can occur at any of several metabolic steps described, or

Table 1
ABNORMAL SEROTONIN MEASURES IN DEPRESSION

1. Low CSF 5-HIAA
2. Low post-probenecid CSF 5-HIAA
3. Low plasma free tryptophan
4. Low CSF tryptophan
5. Low tryptophan/5 amino acid (tryp/5-AA) ratio
6. Low brain serotonin
7. Reduced brain serotonin reuptake sites
8. Reduced platelet serotonin reuptake sites

in steps not discussed. In the next section we will review the major findings of serotonin dysfunction in a subset of depressive illness. One must also consider that heterogeneity of serotonin dysfunction may exist even in this subset of major depressive illness.

III. SEROTONIN DYSFUNCTION IN DEPRESSIVE ILLNESS

Depressive illness has been increasingly associated with biological abnormalities to genetic predisposition. As with other medical diseases, the understanding of the biology of psychiatric illness depends upon our ability to make quantitative measurements and thereby demonstrates alterations associated with the disease state. As our versatility in making laboratory measurements improves, we will gain a more sophisticated understanding of psychiatric illness and probably discover more effective somatic therapies. This section will deal with serotonin-related measurements which have been reported in depressed patients (see Table 1). Although the available measures of serotonin function are in the early stages of refinement, there are some interesting findings which have both theoretical and therapeutic implications.

Abnormal serotonin function was first implicated in depressive illness as early as 1960 with the discovery of low CSF 5-HIAA in depressed patients.[25] This suggested that certain depressed patients have a low turnover of CNS serotonin. Although this finding was replicated,[26] it was only after the use of probenecid that van Praag was able to demonstrate a bimodal distribution in CSF 5-HIAA levels in depressed patients.[27] This suggested that only a subset of depressives had low CNS serotonin turnover. Since that time, low CSF 5-HIAA has been found in a subgroup of depressives by numerous investigators.[28] Studies not reporting this finding have often failed to address the issue of bimodality.[29] Consistent findings of bimodality for low CSF 5-HIAA led researchers to question whether high and low serotonin depressions were distinguishable on clinical grounds. One interesting symptomatic difference was a higher incidence of suicidality in patients with low CSF serotonin metabolites.[30,31] This parameter will be discussed later in more detail. Low CSF 5-HIAA was also associated with a greater frequency of recurrent depressions[32] and perhaps with a family history of depression.[33] In addition, low CSF 5-HIAA has been reported not to normalize with recovery from depression,[34,35] suggesting it is a trait rather than state phenomenon. This would be consistent with the generic data for this measure presented by Sedvall et al.,[33] and might represent an inherited predisposition toward depression. It should be added, however, that low CSF 5-HIAA is not specific for depression as it has been reported in alcoholics,[36] criminals,[37] schizoaffective patients,[31] and nondepressed, suicidal patients.[38]

Low CSF serotonin metabolites could result from abnormalities anywhere between the absorption of dietary tryptophan in the gut and the final oxidation of serotonin by MAO. Van Praag has recently reviewed investigations of serotonin metabolic pathways in depressed patients,[39] which help to pinpont which metabolic impairments might exist. It has been

reported that depressed patients dying from natural causes have low brain raphe serotonin levels.[40] This suggests that low CSF 5-HIAA levels found in depressions reflect low serotonin levels, rather than decreased MAO activity (see Figure 1). It is also unlikely that reduced tryptophan hydroxylase activity would account for low serotonin turnover, because this unsaturated enzyme has substantial overcapacity.[7]

Since brain serotonin levels depend upon plasma free tryptophan concentration, this parameter has been extensively studied. Many investigators have reported free plasma tryptophan levels[41] and reduced CSF tryptophan levels[42] in depressed patients. There even has been reported a bimodal distribution of serum tryptophan.[43] However, several studies have also reported normal levels of plasma tryptophan in depressed patients.[22,44,45] Although these negative studies did not examine bimodality, there is considerable controversy over the existence of abnormal free plasma tryptophan levels in depressive illness.

Moller et al. have examined the ratio of free plasma tryptophan to other amino acids (tryp/5-AA) which compete for the same carrier to the brain.[46] The higher the tryp/5-AA ratio, the more successfully plasma tryptophan will compete for entry into the CNS to become substrate for serotonin synthesis. Moller et al. found this ratio to be decreased in some patients,[45] implying a functional plasma tryptophan deficiency in a subgroup of depressives. This decreased tryp/5-AA ratio could account for low CNS serotonin metabolites in some depressed patients because brain tryptophan levels correlate strongly with the CSF 5-HIAA concentration.[22] Such a deficiency of tryptophan relative to competing amino acids should be amenable to correction by tryptophan administration. The tryp/5-AA ratio would presumably serve as a convenient measure of the serotonergic subtype of depression and lumbar puncture could be avoided. Another abnormality of serotonin function which has been reported is decreased efflux of plasma tryptophan into the CNS.[44] Certain mechanisms have been proposed to account for this abnormality. For instance, Curzon and Bridges suggested that depressed patients shunt excessive tryptophan through the kynerenine pathway,[47] although this was not subsequently confirmed.[44] Peripheral alterations of tryptophan metabolism remain controversial and somewhat murky, awaiting further investigation.

Besides peripheral alterations in plasma tryptophan levels, there might also be central serotonin alterations in certain depressed patients. These alterations could result in decreased CSF 5-HIAA levels. One possible central cause of low CSF 5-HIAA would be a reduction of serotonin reuptake from the synapse. Traskman et al. have reported that the serotonin reuptake blocker chlorimipramine causes a decrease in CSF 5-HIAA levels.[48] Therefore, low CSF 5-HIAA levels in depressed patients might be explained by a deficiency in serotonin reuptake. In fact, there have been reported decreased number of reuptake sites (imipramine binding sites) in the brains of suicide patients.[49] We have already described how blood platelet serotonin uptake has been used as a model for serotonergic neuronal reuptake.[18] In fact, decreased uptake of serotonin by blood platelets has been reported in depressives when compared to normals.[50-52] We have obtained similar data in our own studies (see Figure 2). This has been shown to result from an actual decrease in the number of reuptake sites, rather than changes in affinity [50-52] Numerous other investigators have confirmed the finding of low platelet serotonin uptake in depressed patients.[53,54]

Platelet serotonin has been measured before and after recovery from depression. Coppen et al.[53] and Paul et al.[50] found that this measure does not normalize after treatment, although Scott et al. did report normalization.[54] If platelet serotonin uptake proves not to be dependent upon clinical state, it would represent a trait marker. This would be similar to the suggestion that CSF 5-HIAA accumulation is a trait marker for depressive illness.[34,35] These trait abnormalities of serotonin function might produce a vulnerability to depression, or to associated characteristics such as suicidality. In fact, such measures may eventually be found to reflect genetically transmitted abnormalities. Their use could predict incipient psychopathology and indicate prophylactic measures.

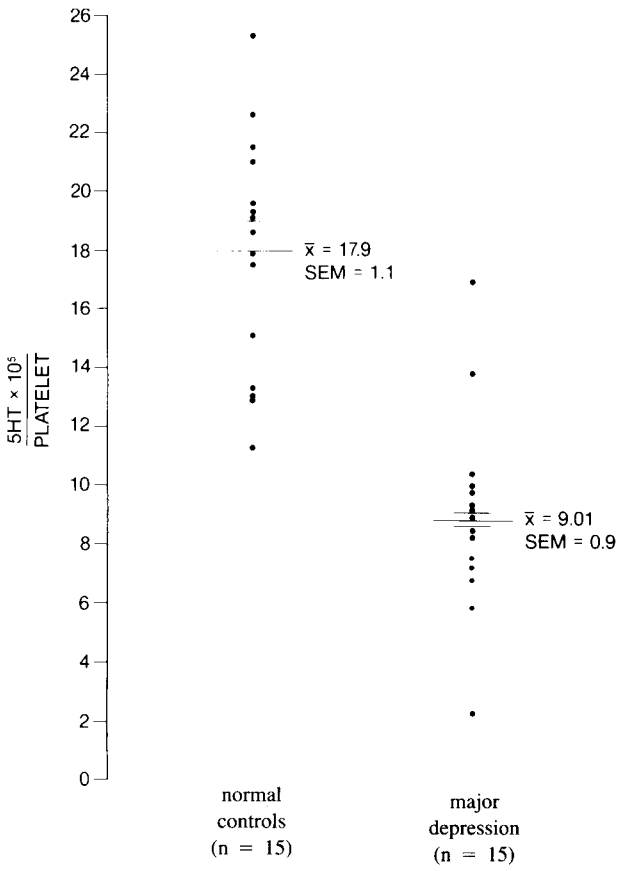

FIGURE 2. Platelet serotonin "transporter". Medication and drug-free patients with major unipolar depression have reduced platelet serotonin uptake.

IV. OTHER CLINICAL CORRELATES OF LOW SEROTONIN MEASURES

We have reviewed some of the literature regarding abnormal serotonin parameters in a subset of depressive patients. These patients have been distinguished by several measures, including low CSF 5-HIAA, low levels of precursor availability, and decreased numbers of platelet and brain serotonin uptake sites. It is not clear whether these different measures define the same population of patients since concomitant measures using the same patients have not been reported. Furthermore, it is probable that these various abnormalities are not specific for major depressive illness.[32,37,38] This section will review several characteristics of patients possessing deficient serotonin measures which do not necessarily correspond to diagnostic categories.

Perhaps the most significant clinical correlate to abnormal serotonin function is the presence of suicidality. Brains of patients who have committed suicide have been studied with respect to serotonin measures. Low concentrations of serotonin,[55] 5-HTP,[56,57] and 5-HIAA[55,57] have been reported in suicide patients with post-mortem studies. Consistent with these reports is the finding by Stanley et al. of decreased imipramine binding sites in the frontal cortex of suicide patients.[49] Studies on living patients have confirmed this finding. Asberg found that low baseline CSF 5-HIAA measures correlated with the frequency of suicidal behavior in depressed patients[58] and that these patients employed more aggressive means, such as

hanging, deep wrist slashing, and gas poisoning.[30] She found that 40% of low CSF 5-HIAA patients had made a suicide attempt, compared to 15% of patients without this finding.[30] The correlation between low CSF 5-HIAA accumulation and suicidality in depressed patients has also been reported by other investigators.[59,60] Traskman et al. found that, of 119 patients with low CSF 5-HIAA accumulation, 20% had killed themselves within a period of 1 year.[61] These patients were not exclusively depressed, suggesting that the serotonin abnormality correlates more with suicidality and violence than with depression.[61] Other investigators have found the correlation of low CSF 5-HIAA and suicidality in borderline patients,[62] mixed diagnostic groups,[63] psychotic illness,[64] and other nondepressed suicide victims.[38]

The relationship between suicidality and aggression has long been appreciated in clinical psychiatry. This relationship may have a biological basis. Brown et al. studied 26 military men with histories of significant aggression and found low CSF 5-HIAA as well as high CSF concentrations of 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG) after probenecid treatment.[65] This was consistent with reports of particularly violent suicide attempts in patients with low CSF serotonin metabolites.[58,61] Furthermore, criminals institutionalized for violence and aggression, who also had 47 XYY syndrome, were reported to show marked reductions in CSF 5-HIAA accumulation after probenecid.[37] Similarly, Agren found that unipolar and bipolar depressed patients with low CSF 5-HIAA level scored particularly high on the anger-related items of the SADS interview (Schedule for Affective Disorders and Schizophrenia).[66] Thus, as with suicidality, a predilection toward violence appears to correlate with this biological measure both with and without concomitant affective disease.

Genetic loading has been described for both suicidality[67] and aggression.[68] Sedvall et al. studied CSF 5-HIAA accumulation in a group of healthy volunteers.[33] They found that those with low values had significantly more affective illness in their families.[33] There has also been reported greater concordance in monozygotic than dizygotic twins for low CSF 5-HIAA accumulation.[69] Also consistent with genetic transmissibility of low CSF 5-HIAA accumulation is evidence that it represents a trait rather than state-related measure.[34,35] These findings suggest that this low serotonin measure is genetically determined and could indicate a genetic predisposition toward associated depression, suicidality, and aggressiveness. (See Table 2).

V. SEROTONIN-RELATED AGENTS AND THE TREATMENT OF DEPRESSION

We have reviewed the presence of serotonin dysfunction in depressive illness. The demonstration of serotonin deficiency in depression has led logically to the suggestion that precursor loading with tryptophan or 5-hydroxytryptophan (5-HTP) might prove to be an effective treatment for this disorder. Since a major finding in some depressions has been low CSF 5-HIAA,[27] and loading with either tryptophan or 5-HTP will elevate CSF 5-HIAA levels,[70] precursor treatment might constitute a form of replacement therapy.

There is a large body of literature reporting the treatment of depression with tryptophan alone or in combination with other antidepressant agents. Four controlled studies[71-74] compared the antidepressant efficacy of L-tryptophan with imipramine and found these to be equally effective with L-tryptophan doses ranging from 3 to 9 g/day. In one study, the patients with the highest levels of plasma tryptophan after treatment were most responsive to L-tryptophan therapy.[71] Treatment with L-tryptophan has also been found to be as effective as electroconvulsive therapy (ECT)[75] and as effective as amytriptyline.[76] Several other investigators, however, have found no efficacy with the use of L-tryptophan in depressive illness.[77,78] Contradictory findings could be explained by dose effects, sample sizes, and the probability of heterogeneity in depressives studied.

L-tryptophan has also been found effective in combination with tricyclic antidepressants.[71]

Table 2
CLINICAL CORRELATES OF LOW SEROTONIN MEASURES

1. Suicidality
2. Increased aggression
3. Genetic loading for depression
4. Increased anger
5. Vulnerability for recurrent depression

One possible explanation for the potentiation of L-tryptophan by tricyclic antidepressants is that these agents reduce plasma glucocorticoids[79] which in turn reduce tryptophan pyrrolase activity, leading to increased plasma tryptophan levels. Nicotinamide, which also inhibits the tryptophan pyrrolase shunt, has also been reported to enhance the antidepressant efficacy of L-tryptophan.[80] Numerous investigators have reported that L-tryptophan potentiates the antidepressant efficacy of monoamine oxidase inhibitors.[81,82] In addition, L-tryptophan has been reported to be effective in combination with lithium.[83] Interestingly, lithium enhances the neuronal uptake of tryptophan and could thereby increase serotonin synthesis.[84] The frequency by which L-tryptophan has been reported to be effective in depression appears to warrant its trial alone or in conjunction with other medications in treatment of refractory depression.

It is not clear why some clinical studies have failed to demonstrate efficacy for L-tryptophan in the treatment of depression. Van Praag[39] has discussed the heterogeneity of depressive disorders and the importance of pretreatment CSF 5-HIAA levels as a predictor of precursor response. Along these lines, Moller et al. have reported that patients with a low tryp/5-AA ratio recovered with L-tryptophan therapy, while patients with a high tryp/5-AA ratio had no response.[85] This implies that pretreatment measures of serotonin dysfunction can predict responsivity to serotonin precursor therapy. The use of serotonin measures to specify the choice of antidepressant is a critical clinical issue which requires further investigation. The lack of agreement regarding L-tryptophan efficacy in depression might be clarified by treating only patients with low pretreatment serotonin measures. Another factor involved in L-tryptophan efficacy could be dosage. Chouinard et al.[71] discussed the possibility of a "therapeutic window" for L-tryptophan plasma levels, and recommended that L-tryptophan doses not exceed 6 g/day. The concept of a therapeutic window for L-tryptophan has also been reviewed by Van Praag.[39] Further efficacy studies of L-tryptophan in depression should pay careful attention to dosage and patient selection.

The use of 5-hydroxytryptophan (5-HTP) in the treatment of depression appears to be more effective than L-tryptophan. Several investigators have reported significant efficacy of 5-HTP in depressive illness on the basis of controlled[86-88] and uncontrolled[89] studies. There have also been reported sudden and dramatic improvements with severe depressives.[90] Van Praag et al. have reported 5-HTP efficacy to be particularly significant in patients with low CSF 5-HIAA levels.[91] In addition, 5-HTP was found less effective than lithium in patients with high CSF 5-HIAA levels.[92] These reports support the notion of treatment specificity for subgroups of major depression. Other investigators have found 5-HTP to be as effective as imipramine[93] and to potentiate the effects of chlorimipramine.[94] Potentiation has also been reported with monoamine oxidase inhibitors.[95]

In addition to treatment efficacy, 5-HTP has been shown to have some prophylactic benefit for major depression. It appears that in patients with low serotonin CSF 5-HIAA relapse rates can be decreased with 5-HTP administration.[96] This treatment has also been reported to improve the intercurrent level of functioning in patients with recurrent depression.[32] Given the reported efficacy of 5-HTP in the treatment and prophylaxis of depression, and the lack

Table 3
TREATMENT IMPLICATIONS OF LOW SEROTONIN DEPRESSIONS

I. Criteria for consideration
   - A. Patients have one or more low serotonin measures on laboratory testing (see Table 1)
   - B. Patients have prominent clinical correlates of low serotonin depression (see Table 2)
   - C. Refractory depressions in which serotonin precursors have not been tried

II. Treatment Strategies
   - A. Precursor loading with L-tryptophan
     1. Without other medications
     2. With nicotinamide
     3. With tricyclic antidepressants
     4. With MAO inhibitors
     5. With lithium
     6. With ECT
   - B. Precursor loading with 5-hydroxytryptophan
     1. Without other medications
     2. With tricyclic antidepressants
     3. With MAO inhibitors
     4. With lithium
     5. With ECT
   - C. Antidepressants which are relatively serotonin specific
     1. Chlorimipramine
     2. MAO inhibitors
     3. Amitriptyline

of serious side effects,[97] one might wonder why this agent is not used more frequently. The few studies that have reported negative results with this agent used small doses for brief periods of time.[98,99] Interestingly, 5-HTP has even been reported to produce euphoria in normals.[100,101] More widespread use of 5-HTP seems indicated, particularly in depressed patients with abnormal pretreatment serotonin measure.

Tricyclic antidepressants have been used for years as the primary treatment for major depressive illness. These agents act by blocking neurotransmitter reuptake from the synapse[16] and affect both serotonin and norepinephrine neurons. Researchers have proposed the idea that these are two distinct subgroups of depression, characterized by norepinephrine or serotonin deficiencies, respectively.[45] Norepinephrine-deficient depressions have been associated with low CSF MHPG levels, while serotonin-deficient depressions are associated with low CSF 5-HIAA levels. The differentiation of these two subsets of depression has led investigators to explore their responsivity to specific tricyclic antidepressants. Pretreatment levels of CSF 5-HIAA and MHPG have been assessed with respect to predictability of response to antidepressants with either serotonin or norepinephrine mechanisms.

Chlorimipramine is a reuptake blocker which is relatively specific for serotonin neurons. Chlorimipramine has been found to decrease serotonin turnover and CSF levels of 5-HIAA, whereas the noradrenergic reupake blocker, nortriptyline, decreases CSF levels of MHPG.[102,103] Van Praag has reported that depressed patients with the best response to chlorimipramine had the lowest pretreatment levels of CSF 5-HIAA.[104] Consistent with this finding is the report that patients with high pretreatment levels of CSF 5-HIAA responded poorly to chlorimipramine.[105] Amytriptyline, which has serotonergic effects, was found to be more effective in patients with high CSF MHPG levels,[4,105] although these patients were not measured for CSF 5-HIAA levels. Other investigators, however, have failed to find a relationship between pretreatment CSF 5-HIAA levels and responsivity to chlorimipramine.[106] Furthermore, the use of biological markers for serotonin dysfunction, such as the tryp/5-AA ratio, platelet serotonin transporter, and plasma free tryptophan levels, have not been assessed with respect to tricyclic specificity. This area has great clinical importance because success in predicting antidepressant effectiveness could circumvent the frequent need for successive clinical trials of different antidepressants. (See Table 3).

VI. CONCLUSIONS

We have reviewed serotonin abnormalities that are associated with major depressive illness. We have seen how several different measures are abnormal in depressed patients. These biological markers may serve a diagnostic role in identifying a subset of depressive patients with certain characteristics. Such patients appear to have a greater tendency toward suicide and violence. These patients may also have a greater frequency of depressive episodes, as well as genetic loading for depression. Furthermore, the existence of serotonin-specific markers may imply a greater clinical response to particular antidepressant agents. Although the data are controversial, it appears that serotonin precursor therapy has a legitimate role in the treatment of certain depressive subgroups. The identification of which patients might benefit from precursor treatment or serotonin-specific agents depends upon our ability to measure serotonin function. As such laboratory measurements become more refined, it is likely that we will enhance our understanding of depression and our treatment efficacy.

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Chapter 6

LITHIUM: PREDICTING RESPONSE/MAXIMIZING EFFICACY

R. Bruce Lydiard and Rowland Pearsall

TABLE OF CONTENTS

I. INTRODUCTION

Lithium (Li^+) salts are one of the most important tools available to the general psychiatrist. Properly monitored, Li^+ therapy provides safe, effective treatment for acute mania and prophylaxis against recurrent mood swings. This chapter will briefly review the history and general pharmacology of the Li^+ ion. Guidelines for clinical and biological identification of Li^+ responders, pretreatment considerations, and suggestions for optimizing Li^+ therapy will be discussed. Additionally, a survey of drug interactions and unwanted effects of Li^+ will be presented.

II. HISTORY

The calming effects of Li^+ salts were first described centuries ago by Greek physician Seranus Ephesios. There is a high Li^+ content in the waters of many European springs where psychiatric patients used to take "cures" from the water. Perrier® water, said to have a soothing effect, contains Li^+ in a demonstrable concentration. During the 1800s, Li^+ was used unsuccessfully as a sedative and antiepileptic agent, as well as an experimental treatment for gout and urinary calculi. In the late 1940s, Australian John Cade recorded the profound reversal of mania in a chronically ill patient.[1] Around the same time in the U.S., Li^+ was being used in liberal amounts as a salt substitute, resulting in numerous toxic effects, including death from inadvertant poisoning. With the subsequent recognition that Li^+ can be used quite safely if serum levels are closely monitored, Li^+ has become a cornerstone in the treatment of affective disorders. In 1970 the Food and Drug Administration approved the use of Li^+ for treating acute mania and, in 1974, for prophylaxis against recurrent mania. The lifetime incidence of major affective disorder is between 10 and 20%,[2] and the use of Li^+ treatment is estimated to have saved at least 4 billion dollars to date as a direct result of its therapeutic effects.[3]

III. PHARMACOLOGY

A. Chemistry

Li^+ is an alkali existing in nature as a salt. It is a monovalent cation which is prescribed as Li^+ carbonate (Li_2Co_3). The usual dosage form is 300 mg (8.12 mEq) as a tablet or capsule. There is a slow-release form which allows for slower absorption and lower peak

serum levels. For patients who require very closely titrated dosage, a liquid preparation (Li^+ citrate) is available.

B. Pharmacokinetics

After oral administration, Li^+ blood levels peak between 1 and 3 hr, and absorption is completed by 8 hr.[4] The bio-availability of Li^+ may vary significantly from one brand to another. Li^+ enters the intracellular environment of different tissues at variable rates.[5] Excretion of Li^+ is primarily renal, much like sodium (Na^+). About 80% of filtered Li^+ is reabsorbed in the proximal tubule, and a very small proportion is reabsorbed in the loop of Henle. Unlike Na^+, the distal nephron does not reabsorb a significant amount of Li^+.[6] The half-life of Li^+ ranges from 12 to 30 hr, depending on various factors including the patient's age and renal status. A negligible amount of Li^+ exits via feces, saliva, sweat, and sperm.[7] Bone may retain Li^+ for some time following discontinuation of treatment.

C. Mechanism of Action

Numerous theories about how Li^+ exerts its mood-stabilizing effects have been proposed. It has numerous actions, including competition with cations (Na^+, K^+, Mg^{++}, Ca^{++}), altering biogenic amine turnover rates and receptor binding,[8,9] and interaction with various adenylate-cyclase nucleotide systems in the periphery and central nervous system (CNS).[10] In the CNS, it affects serotonin synthetic mechanisms, prevents development of supersensitivity of CNS amine receptors, and, in rodents, slows and alters circadian rhythms of alpha and beta adrenergic, acetycholine, dopamine, and benzodiazepine receptors.[11-13] There is also evidence that Li^+ alters the binding of opiates to the opiate receptor.[14] Whether any or all of these effects are important in the therapeutic action of Li^+ remains unclear.

IV. SELECTION OF LI^+-RESPONSIVE PATIENTS

The information currently available suggests that the best predictor of response to Li^+ is the diagnosis of bipolar affective disorder. This applies to the acute antidepressant and prophylactic effect of Li^+ as well as the acute antimanic effects in this subgroup of affective disorders. However, the literature contains many exceptions to this general rule.

Biological psychiatrists, for the most part, have centered their interest on the relationship of abnormalities in brain dopamine to amphetamine psychosis and schizophrenia. It is probably more appropriate to consider that acute administration of stimulants provides a model for euphoria and mania. The hypothesis that amphetamine psychosis is a model for mania with psychosis could thus be investigated in humans by cumulative administration of amphetamine after Li^+ pretreatment.

Cocaine- and amphetamine-induced states and naturally occurring manias appear similar clinically and can be blocked by Li^+. Although it has become fashionable to think of acute amphetamine-induced states as a model for paranoid schizophrenia, these states bear a close clinical resemblance to spontaneously occurring mania. Behavioral similarities and Li^+ blockade link these drug-induced and naturally occurring euphoric states.

A. Clinical Predictors of Acute Response to Li^+

About 70 to 80% of acutely manic patients respond well to Li^+.[15] Murphy and Biegel[16] reported that the subgroups of manic patients presenting with euphoric-grandiose features were more likely to respond acutely to Li^+ than were those with paranoid-destructive features. In contrast, Taylor and Abrams,[17] Steinbook and Chapman,[18] and others[19] have reported that irritability and psychotic features (paranoid delusions, visual and auditory hallucinations, catatonia, and first-rank Schneiderian symptoms) may respond well to Li^+ and are of no distinct prognostic value. Patients with atypical features such as delusions unrelated to mood

and chronic auditory hallucinations (which suggest schizoaffective disease), however, may do less well.[17] Depressed Li^+ responders tend to have "endogenous" symptom clusters which are consistent with the depressed phase of bipolar illness such as anergia, motor retardation, hypersomnia, and increased appetite. As a specific symptom, hypersomnia has been shown to predict acute antidepressant response to Li^+[20] or a response to the combination of Li^+/isocarboxizid[21] or Li^+/tranylcypromine.[22]

B. Other Demographic Features

Although Van der Velde[23] reported that patients under 40 tended to respond better than older patients, age has not been of consistent predictive value.[17,24] Sex and marital status seem similarly unhelpful.[17,24,25] Pyknic body habitus has been associated with antimanic response to Li^+[17] but body weight has no apparent relationship.[18]

C. Historical Features

Younger age (under 40) at onset of illness was suggested to predict a better antimanic response to Li^+ by Taylor and Abrams,[17] but they have recently failed to replicate their earlier finding.[25] Similarly, duration of illness[17,24,25] and the nature of the preceding affective episode (e.g., mania or depression) is unrelated to outcome of Li^+ treatment.[26] While the total number of previous affective episodes does not seem to provide predictive information, frequency of affective episodes may be helpful. Prien et al.[24] and Dunner and Fieve[27] (the latter used the criterion of at least four affective episodes per year) found that frequent cyclers tend to relapse more often during prophylactic treatment, but not all investigators share this view.[25] It may be that rapid cyclers have a more severe illness and may tend toward lower compliance with treatment. Along this line, Prien et al.,[24] Taylor and Abrams,[25] and Dunner et al.[26] all have agreed that noncompliance may be a major factor in both acute and prophylactic treatment with Li^+. Whether noncompliance relates to cycle frequency and illness severity or represents a nonbiologic factor is an important but still unanswered question. Alcoholism as a predictor of response to Li^+ has been examined. Prien et al.[24] reported that a history of alcoholism was associated with failure to respond to Li^+. Dunner and Fieve[27] found no correlation, and others suggested that alcoholism is found more frequently in Li^+ responders.[17]

D. Personality Characteristics

Premorbid cyclothymic personality traits in Li^+-treated patients have been associated with a good antimanic response, while those patients exhibiting depressive-withdrawn traits were more often nonresponders.[17] Kupfer et al.[28] identified two subtypes of personality characteristics in unipolar depressed patients. The groups which showed an antidepressant response to Li^+ exhibited more lability of mood in contrast to the nonresponders, who tended to exhibit a profile of chronic anxiety and obsessiveness. Minnesota Multiphasic Personality Inventory (MMPI) profiles studied by Donnelly et al.[29] and others[30] may have some empirical predictive value. High depression and psychasthenia scores predicted an antimanic response, as did a low score of the paranoid features profile. Donnelly et al.[29] developed a Li^+ Response Scale (LRS) derived from MMPI items. This scale was developed and cross-validated on a sample of patients presenting with a major depressive episode (unipolar and bipolar). House and Martin[30] found that severely depressed with elevations on certain conventional MMPI scales showed a response to the antidepressant effects of Li^+. Steinbook and Chapman[18] reported that acutely disturbed inpatients with a variety of psychiatric diagnoses who responded to Li^+ also had elevated scores on the MMPI Acquiescence scale prior to initiation of Li^+ treatment.

E. Family History

Mendelewicz et al.[31-33] and Schou et al.[34] have provided very strong evidence that the presence of bipolar illness in the first-degree relatives of the probands is a good predictor of response, although the absence of bipolar relatives does not necessarily predict poor response.[35] The relationship for unipolar illness is less convincing.[33] Dunner et al.[26] and Misra and Burns[36] failed to demonstrate a correlation between Li^+ response and family history. Twin studies further support the contention that Li^+ response is, at least in part, genetically determined in bipolar illness. Mendelwicz et al. showed that mono- or dizygotic bipolar twin pairs were highly concordant in their long-term response to Li^+, but did not find a similar concordance for twin pairs with unipolar depression.[37] Overall, the genetic data seem relatively consistent with a good prognosis for acute and long-term Li^+ response in patients with bipolar relatives.

F. Neuroendocrine Predictors of Li^+ Response

Making the correct diagnosis in situations where clinical presentations and syndromes can be identical is crucial to effectively treating patients with lithium. Patients with diagnoses such as schizophrenia, borderline personality disorder, schizoaffective disorder, major depression, and alcohol abuse have all, on a number of occasions, been found to be Li^+ responders and many are later diagnosed as true bipolars. Gathering a clinical history and a careful clinical interview are cornerstones to proper diagnosis; however, if clinical diagnoses alone were the only determinant of who got a lithium trial, large groups of potential responders would go untreated. Recent advances in neuroendocrinology and neurophysiology are providing additional important diagnostic information which relates to biological homogeneity and medication response. Just as the detection of small quantities of PCP, amphetamine, or cocaine in blood allows similarly appearing "manic or schizophrenic" patients to be appropriately diagnosed and treated, these newer tests are particularly useful in aiding the distinction between manic and schizophrenic states, as well as between unipolar and bipolar depression. Accurate diagnosis is critical in these cases to separate Li^+-responsive bipolar patients from schizophrenic and unipolar depressed patients. This section will review some of the newer laboratory tests that can help identify Li^+-responsive patients whether they qualify for DSM III bipolar diagnoses or are from other diagnostic subgroups.

1. TRH Test

The TRH test has been increasingly utilized as a sensitive and specific test which effectively rules out hypothyroidism in depressed patients.[38-41] In addition, it is useful as a confirmatory diagnostic test for major affective disorders.[42-44] The mechanics of the TRH test are summarized briefly below and are followed by some of the applications of the test as they pertain to diagnosis.

The TRH test[45] involves giving a small amount of the hypothalamic tripeptide hormone TRH (protirelin) after measurement of a pretest (baseline) TSH. TSH is then measured at 15, 30, 60, and 90 min after TRH infusion. In normal control subjects, the level of TSH increases within 60 min by 7 to 15 $\mu IU/\ell$ (micro international units per milliliter) over the baseline value. This peak minus the baseline TSH is called the Delta (Δ) TSH.

a. Mania vs. Schizophrenia

Use of the TRH test to distinguish manic states from schizophrenic episodes has been studied recently.[46,47] The TSH response to TRH stimulation, when measured in groups of manic and schizophrenic patients as well as normal volunteer controls, shows that manic patients have a decreased TSH response compared with normal controls and schizophrenic patients. Although the TSH response of schizophrenic patients showed some overlap with that of manic patients, the blunted TSH response in mania is 84% specific and did not seem

Table 1
TRH TEST[46]

	Δ TSH
Unipolar depression	↓
Bipolar depressed	↑
Manic Schizophrenia	↓
Alcoholism	↓
Amphetamine states	↓
Cocaine states	↓

to be the result of medication, thyroid disease, or demographic factors. Table 1 shows a summary of data from a study by Extein et al. on the use of the TRH test in distinguishing bipolar affective disorder, manic type, from schizophrenia.[46]

In clinical situations where patients present with psychosis characterized by delusional thinking with paranoid and grandiose ideation, the TRH test can offer an avenue to clarify the diagnosis in the face of a confused or unclear premorbid history. The finding of a blunted delta TSH in response to TRH infusion in such a patient would lend strong evidence to a diagnosis of bipolar affective disorder, manic type, and would suggest that Li^+ treatment might be useful.

b. Bipolar vs. Unipolar Depressed

TRH testing has been applied to the question of distinguishing unipolar depression from bipolar depression which might be Li^+-responsive.[44,48-50] Patients with unipolar depressions show a decreased or blunted response to TRH infusion while bipolar depressed patients show an augmented or increased delta TSH response. A patient presenting with symptoms of depression including sleep disturbance, appetite disturbance, decreased energy, hopelessness, and depressed mood, with either a prior history of similar previous episodes or a single episode, may in fact have a Li^+-responsive bipolar illness. There have been studies of bipolar patients during both the depressed and manic phases.[51] The TSH response to TRH infusion is increased in bipolar patients in the depressed phase, and decreased in bipolar patients in the manic phase. Although this finding has not proven useful in predicting the switch from depressed to manic phases in bipolar patients, it does support the idea of using the TRH test to distinguish bipolar patients from other diagnostic categories.

Research on the hypothalamic-pituitary-thyroid (HPT) axis and TRH test[52-54] during the past few years has provided insight into how the above clinical findings might be related to the norepinephrine hypothesis of affective illness.[55] In its simplest form, the norepinephrine hypothesis states that depression is characterized by a deficiency of central norepinephrine/dopamine (NE/DA), while mania is characterized by an increase in central NE/DA.[56] The central monoaminergic systems are also hypothesized to impact on the HPT neuroendocrine system via NE/DA stimulation of TRH release from the hypothalamus and serotonin inhibition of such release (see Figure 1).[57] Thus, if mania is characterized by increased central NE/DA activity, one might expect TRH release to be facilitated due to the increased NE/DA stimulation. In order to compensate and prevent dysregulation of thyroid function, the TRH receptors on the pituitary may become less sensitive and consequently, when TRH is infused, the TSH response is diminished relative to normal. The converse might be argued for the patient with bipolar depression who would be hypothesized to have a deficiency of central NE/DA. This would lead to decreased TRH output and a relative increase in the sensitivity of pituitary TRH receptors to maintain thyroid hormone homeostatsis. When stimulated by TRH infusion, such patients would be expected to show an increased TSH response due to the "supersensitive" pituitary TRH receptors.

The finding of blunted TSH response in unipolar depression might be hypothesized to

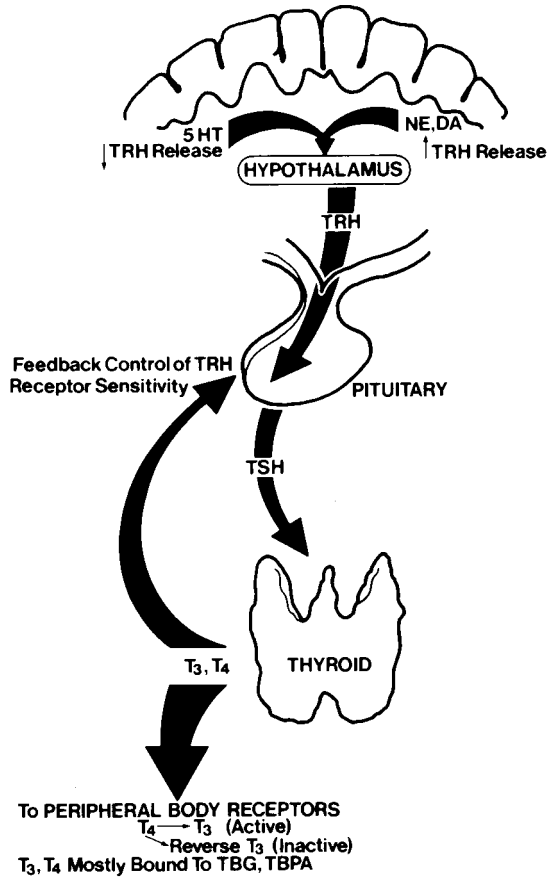

FIGURE 1. Regulation of TRH release and receptor sensitivity.

reflect a relative hypoactivity of CNS serotonergic activity which exerts an inhibitory effect on TRH release from the hypothalamus. There would be an increase of TRH at the pituitary receptors with a relative decrease in sensitivity reflected as a blunted response when stimulated by TRH infusion. The discussion of other neuroendocrine tests below lends credence to the concept that unipolar depression is a heterogenous illness. Depressed patients showing a blunted TSH response may represent a subgroup of these patients.

As noted earlier, both amphetamine- and cocaine-induced states have been noted to clinically resemble manic states.[14] Amphetamine and cocaine both increase central NE/DA activity and therefore would be expected to cause a blunted delta TSH on TRH testing. Studies of patients under the influence of amphetamine or cocaine have shown TRH test abnormalities consistent with this hypothesis.[58] The extent to which the norepinephrine hypothesis will hold true is unknown; however, for the present, the TRH test seems to be clinically useful and can provide important diagnostic information.

2. Dexamethasone Suppression Test

The dexamethasone suppression test (DST) is another neuroendocrine test which is especially helpful in confirming the diagnosis of a primary affective disorder. A positive TRH or DST can help the clinician confirm that the diagnosis is psychiatric and not secondary to another treatable medical illness. The mechanics of the DST have been discussed elsewhere and can be summarized briefly, as follows. Patients are given 1 mg of dexamethasone orally

at midnight and a pretest serum cortisol level is drawn. Subsequently, the serum cortisol level is measured at intervals through the following 24-hr period, usually 8 a.m., 4 p.m., and 11 p.m. The normal response pattern to dexamethasone is a suppression of the diurnal variation in cortisol to a level less than 5 μg/dℓ, and cortisol usually remains below the level for a period exceeding 24 hr. Patients with symptoms of depression and melancholia show an abnormal response to dexamethasone suppression and a return of cortisol levels to normal (greater than 5 μg/dℓ) before the end of the 24-hr period. Depressed patients show early escape from dexamethasone suppression in 67% of the cases (1 mg DST test) and the test is found to be 96% specific to depressive disorders as compared with other psychiatric diagnoses.[59]

The DST has been given to patients with widely varying psychiatric diagnoses and offers some consistent findings that may be helpful in predicting patients likely to respond to Li^+. Schizophrenic patients without evidence of depression show a normal suppression of cortisol in response to dexamethasone. Depressed patients, whether unipolar or bipolar, show early escape from dexamethasone suppression[60,61] and bipolar patients in the manic phase show normal dexamethasone suppression.[62,63] Longitudinal studies of bipolar patients have shown abnormal escape during the depressed phase of the illness with normal suppression during manic episodes.[63] The switch from mania to depression is often preceded by a switch from normal dexamethasone suppression to early escape during the few days prior to the change in mood.[61,63] Patients with schizoaffective illness show escape from dexamethasone suppression in a pattern more consistent with affective disorders than with schizophrenia. This may have implications as to how this diagnostic group is viewed in the future.[60]

Our studies indicate that the dexamethasone test can be extremely useful in confirming a diagnosis of depression in patients with melancholic symptoms, but is not by itself helpful in distinguishing between unipolar and bipolar depressed patients. The presence of an abnormal DST, even in a patient with psychotic features, strongly suggests an affective disorder and treatment should be consistent with this diagnosis. A positive DST in a depressed patient with a past history even remotely consistent with hypomania should suggest bipolar illness and the possibility of Li^+ treatment as well.

In an attempt to improve diagnostic accuracy, studies using both the DST and TRH tests in depressed patients have been done.[64] These show that there is an added diagnostic yield and that such combination testing is useful. One study of patients with unipolar depression showed that 50% of the patients failed to suppress in the DST and 64% had blunted TSH response to TRH. This study supported the notion that these two tests provide complimentary data about the depressed state, since 30% of the patients were identified by both tests, 34% by TRH test alone, 20% by DST only, and 16% by neither test (see Figure 2). Use of the combined TRH/DST testing across other diagnostic groups, for example, all patients with symptoms of depression, should also prove useful. The DST is helpful in confirming the presence of depression in the TRH may be helpful in distinguishing patients with bipolar depression who may benefit from Li^+ therapy from unipolar depressed patients who need treatment with a tricyclic antidepressant.

3. Diurnal Cortisol

The diurnal cortisol test (DCT) involves measuring the day-night variation in serum cortisol level over a 24-hr period. Control of cortisol secretion involves the hypothalamic secretion of corticotropin releasing factor (CRF) which stimulates release of adrenal corticotropic hormone (ACTH) from the pituitary gland. ACTH is released into the peripheral circulation and stimulates the adrenal glands to release cortisol. Studies of cortisol secretion over a 24-hr period indicate that secretion normally occurs in small, frequent bursts and that there is a typical pattern of increased secretion in the pre-dawn and early morning waking hours, followed by a period of decreased secretion in the evening and at night.[65] Measurement of

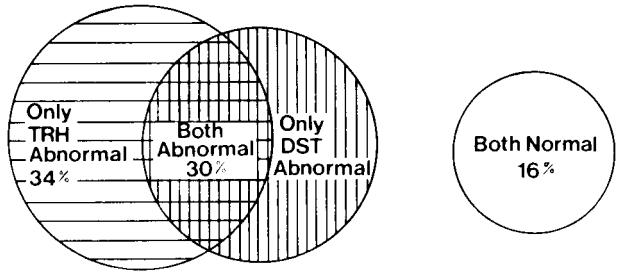

FIGURE 2. Relationship of DST and TRH test abnormalities in 50 inpatients with primary unipolar depression.

serum cortisol (hydrocortisone) at a minimum of four separate points during a 24-hr period gives an indication of the pattern of secretion for a given individual.

Studies of patients with clinical evidence of endogenous depression, either unipolar or bipolar, show an increase in cortisol secretion at each period of the day.[66,67] This hyperactivity of the hypothalamic pituitary adrenal (HPA) axis is the same phenomenon as observed in the DST; however, there is not a direct overlap between an abnormal diurnal cortisol and abnormal DST findings. Stress can cause some increase in the cortisol secretion; however, the findings in depression appear to be separate from any stress-related effects.[68] Patients with other types of psychiatric disorders, including schizophrenia, do not show a disturbance in 24-hr cortisol secretion.

Although the mechanisms that control secretion of CRF and ACTH are complicated, one can hypothesize that central monoaminergic systems play a role in their control. It has been suggested that serotonergic as well as noradrenergic and cholinergic systems all play a role in the neuronal regulation of CRF secretion and that possibly different systems play different roles in the basal secretion, 24-hr pattern of secretion, and secretion in response to stress.[69] The norepinephrine systems have been suggested to have an inhibitory effect on the production of CRF[70] and, if this were the case, it would be consistent with the norepinephrine hypothesis of depression. Decreased availability of norepinephrine at central neuronal sites would lead to a decrease in the inhibitory effect on CRF production and a subsequent increase in overall cortisol production. Studies with amphetamine, which can clinically mimic manic states and which stimulates central nervous system DA and NE activity, have shown a suppression of cortisol secretion also consistent with the norepinephrine model of mania and depression.[68]

The DCT finds its main use in psychiatric diagnosis to assist in the separation of primary from secondary depression and in the distinction of depressed states from other types of psychiatric disorders such as schizophrenia and borderline personality.

4. Growth Hormone Response to Insulin

As with other parts of the neuroendocrine system, the growth hormone (GH) response both in normal people and in psychiatric patients has been examined for possible diagnostic utility. Like cortisol, GH secretion varies over a 24-hr period with the highest levels of secretion during the early phases of sleep.[69] There is an increased release of GH in response to stress, anxiety, exercise, L-dopa, and insulin-induced hypoglycemia. Although not as useful as some of the previously discussed neuroendocrine tests, the response of GH to hypoglycemia induced by a controlled dose of insulin has been correlated with some psychiatric diagnoses and has some theoretical interest and possible utility.

Controlled induction of hypoglycemia using insulin at a dose of approximately 0.1 units per kilogram with measurement of the peak GH response has been used as a standardized

test of this neuroendocrine system.[71] When GH response to insulin is measured in patients with no evidence of psychiatric or emotional problems and across patients with evidence of various types of affective disorders, there are some characteristic changes found. Unipolar depressed patients show a decreased GH peak response when compared with normals.[72] Patients in manic and hypomanic states tend to show an increased peak GH response, while patients with bipolar depression show a normal to slightly increased peak response.[72,73]

As with other neuroendocrine abnormalities, the GH system can be theoretically related to the affective disorders. It is currently postulated that there are two hormones involved in the regulation of GH release. Growth hormone releasing factor (GHRF) and growth hormone inhibiting factor (GHIF or somatostatin) both seem to be important in controlling the release of GH from the anterior pituitary.[74] Neurotransmitter input into this system is complex; however, it is hypothesized that both serotonin and norepinephrine facilitate GHRF release through various inputs on cells in the hypothalamus.[73,75] A gluco-receptor cell is thought to respond to the decrease in serum glucose induced by insulin and this cell presumably interacts with the GHRF cell in the hypothalamic area. Actual release of GHRF to the anterior pituitary is facilitated by norepinephrine and serotonergic input and would presumably be decreased if there were a deficiency in either of these neurotransmitters. GHRF input at the anterior pituitary leads to subsequent GH release into the peripheral circulation. This is theoretically consistent with the norepinephrine hypothesis of depression in which a decrease of norepinephrine in the central nervous system leads to a decreased responsiveness of the GHRF cells to glucose stimulation and a subsequet decreased peak in GH. Interestingly, amphetamine tends to increase GH peak in normal patients. This is consistent with a facilitated norepinephrine response and is also consistent with the elevated GH peak seen in manic and hypomanic patients.

5. EEG Studies

Neurophysiologic studies of predictors of antimanic response have been disappointing. Several EEG studies have failed to correlate EEG patterns with acute Li^+ response.[76-78] Kupfer et al.[79] suggested that a sleep EEG pattern which showed decreased REM sleep and increased delta-wave sleep may be related to clinical response; others suggest that the EEG pattern is a result of drug treatment unrelated to response.[80] As a predictor of antidepressant response to Li^+, visual average evoked response (AER) studies have been more encouraging. An "augmenting" response indicates that there are relatively greater rates of increase of visual AER amplitude associated with increasing stimulus intensity. Baron et al.[81] reported that 23 depressed patients who were "augmenters" had a good clinical response, while nonresponders were "reducers".[82] Genetic studies suggest that the augmenting or reducing response may be a genetically determined response.[83] Augmenting responses may be associated with the tendency to seek sensory input.[84] Buchsbaum et al.[82,85] suggested that "augmentors", whether depressed or manic, tend to be bipolar patients. Their data suggest a possible association between AER response and bipolar status; whether AER is specifically a predictor for Li^+ response in unipolar patients awaits further study.

6. Red Blood Cell Membrane Studies

Recently there has been considerable interest in the cell membrane as a possible experimental model for events taking place at the membrane level of neurons in the central nervous system. One of the most accessible sources of cell membranes is blood cells, in particular the red blood cell (RBC). The RBC membrane in patients with a history of bipolar affective illness has been studied using a variety of techniques, and the results may someday provide us with a trait marker for these patients.

One method used to study RBC membranes in affectively ill patients is the RBC to plasma Li^+ ratio. This value is obtained by measuring the Li^+ concentration in the RBC and dividing

it by the Li^+ concentration in plasma or surrounding solution. Generally this ratio is considerably less than 1 and is indicative of some type of active transport process which allows Li^+ to be moved against a diffusion gradient out of RBCs and into the surrounding plasma. When RBC to plasma Li^+ ratios are measured in bipolar patients and in normal controls, there is a higher Li^+ ratio in bipolar patients.[62] This means that there is relatively more Li^+ in the RBCs of bipolars and may imply some defect in the active transport process that generally extrudes Li^+.

Erythrocyte (RBC) to plasma Li^+ ratios have received a great deal of attention since Mendels and Frazer reported that an elevated ratio predicts an antidepressant response to Li^+ treatment.[86] Others have found similarly that a high ratio predicts a good antidepressant response to Li^+.[87,88] Unfortunately, the initial enthusiasm was premature. Several other groups failed to demonstrate that the Li^+ ratio has predictive value for either acute or maintenance treatment response or Li^+.[89-92] In fact, Mendels et al.[93] were unable to duplicate their original finding. This complicated area has been extensively and critically reviewed by Carroll,[89] who concluded that no predictive value from the RBC to plasma Li^+ ratio was appreciable across a broad range of studies. Carman et al. (personal communication) found that the lithium ratio had significant predictive power in manic or psychotic patients receiving lithium. They also reported significant differences by race in the lithium ratio and suggest that this might be one of the difficulties encountered in replicating the original predictive experiments. However, a high RBC to plasma Li^+ ratio may be helpful in identifying those patients who may be susceptible to Li^+-induced neurotoxicity.[94] Li^+ efflux is another technique used to study membrane abnormalities in affectively ill patients. It involves the measurement of the rate of transport of Li^+ out of the RBCs. Li^+ kinetics across RBC membranes are complex and involve both influx and efflux with a presumed active transport process involved in the removal of Li^+. Li^+ efflux can be expressed as a rate constant (K_0) and reflects Li^+ accumulation in a Ringer's solution after 1 hr divided by the mean concentration of Li^+ in the RBC during the incubation period. Some data indicate that bipolar patients show a lower rate of Li^+ efflux from RBCs than do unipolar or schizophrenic patients and normal controls.[95] Generally speaking, bipolar patients also are Li^+ responders. Interestingly, giving Li^+ seems to effect a change in Li^+ efflux and results in an increase in the Li^+ ratio or a decrease in Li^+ efflux.[96] This change occurs within 1 to 2 weeks after the beginning of Li^+ treatment and lasts for 1 to 2 weeks after Li^+ is discontinued. Several explanations for this change in the Li^+ ratio or Li^+ efflux have been proposed. The most likely seems to be the induction of some type of endogenous regulator which controls the rate of Li^+ movement across the cell membranes. Whether abnormalities in the levels or activity of such an endogenous regulator have any clinical implications is unknown at present. As has been noted, there is increasing evidence that patients with affective disorders may have membrane alterations which are genetically determined.[97-100] Differences in Li^+ ratios as well as in efflux rates from RBCs and various other tissues may be a function of these membrane abnormalities or differences. Total body elimination rates of Li^+ may vary in effectively ill subgroups also. Serry[101,102] reported that acutely manic patients who retained Li^+ after an oral loading dose showed a good response to Li^+, while excretors had poor response to Li^+. The methodology used has been criticized and others have been unable to replicate the initial finding.[89] It does, however, appear that the egress of Li^+ is slowed in manic patients relative to normal controls.[103-106] A recent study by Goodnick et al.[107] suggests that the half-life of Li^+ in RBCs, plasma, and urine is associated with different subgroups of affective disorder. Euthymic bipolar patients showed slower elimination of Li^+ than did unipolar patients, and both groups showed longer Li^+ elimination half-lives than normal controls. While RBC to plasma Li^+ ratios and efflux measures may be of potential value in identifying the various types of affective disorders, they do not currently appear to be

clinically useful measures for predicting individual, acute or long-term outcome of Li^+ treatment.

a. Other Membrane Markers

Fluorescence spectroscopy of red blood cell membranes has been investigated recently.[108] This involves the use of "probes", i.e., substances with a known affinity for particular areas of the cell membrane. RBC membranes labeled in this way and undergoing fluorescence spectroscopic analysis with measurement of emission spectrum show characteristic changes. Results show that hydrocarbon regions of membranes are altered in bipolar patients. This seems to be independent of their clinical symptoms and medications. This may represent a possible trait marker and also as a possible pre-symptomatic diagnostic test for bipolar disorders. Surface HLA antigen sub-typing has also been investigated as a possible predictor of Li^+ response, and preliminary findings suggest that patients with the HLA-A3 antigen respond less well than those who did not carry this antigen.[109,110] ABO blood type has been studied and apparently differs between unipolar and bipolar patients,[111] but has not been studied as a predictive variable.

b. Divalent Cations

Carman and associates reported that an antidepressant response to Li^+ may be predicted by the ratio of serum calcium (Ca^{++}) to magnesium (Mg^{++}). A ratio greater than 2.62 was associated with a good response.[112] They also noted that an increase in Mg^{++} over the first 5 days of treatment was associated with a good response, while a decrease was seen in nonresponders. They suggested that divalent cation displacement may be related to the mode of action of Li^+ as an antidepressant. Indeed, significant increases in serum total Ca^{++} and Mg^{++} were noted during the first 5 days of treatment in the 60% of endogenously depressed patients who subsequently responded to Li^+. While neither ion was altered significantly in the nonresponders, increases in serum Mg^{++} and Ca^{++} were very specific (100%) but relatively insensitive (66%) predictors of antidepressant response in the 42 patients studied. Moreover, those patients who became temporarily hypomanic early in the course of Li^+ treatment exhibited much greater increases in serum Ca^{++} but no significant changes in Mg^{++}. An isolated hypermagnesemia early in treatment may predict development of a neurotoxic reaction to Li^+.

c. Biogenic Amine Neurotransmitter Metabolites

The catecholamine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) has been widely studied as an index of CNS norepinephrine (NE) activity. The MHPG metabolite derives both from CNS and peripheral metabolism of NE and the ratio of contribution to urinary MHPG excretion is unclear.[113,114] However, even if the majority of MHPG is derived from peripheral sources, determination of urinary MHPG could still empirically be a useful clinical tool.[114,115] MHPG excretion in the urine is most reliably measured by collecting a 24-hr urine sample after the patient has been on a low monoamine diet. Studies over the past few years have also attempted to measure plasma MHPG concentrations. Both plasma and urine MHPG levels appear to change and correlate with mood changes in affective states.[116]

Clinical studies have shown a variable of MHPG responses in different diagnostic subgroups. MHPG levels may have some value in distinguishing among affective subtypes. It is generally agreed that MHPG seems to be decreased in bipolar depressed patients compared to normals,[113,114] and in some studies was noted to be increased in manic patients.[117,118] Serial determinations of urinary MHPG in bipolar patients over time indicates a fluctuation with mood and, at least in one study, changes in mood were accompanied by concurrent changes in MHPG.[119] There is some evidence that bipolar depressed patients have lower MHPG levels than unipolar depressed patients.[115]

MHPG levels in unipolar depressed patients have provided a wide variety of data. There have been reports of increased,[120] decreased,[121,122] and normal[123] levels of MHPG excretion in patients exhibiting symptoms consistent with unipolar depression. One way to view these data is that there is a spectrum of MHPG responses, perhaps reflecting different underlying neurotransmitter pathology in the various types of unipolar depression (see discussion in Chapter 4). Patients with a low MHPG excretion rate presumably have decreased NE activity in the CNS, and reportedly respond well to antidepressant therapy with imipramine.[124,125] There have also been some reports that blunting of the TSH response to TRH may be associated with low urinary MHPG excretion.[126] Normal MHPG excretion suggests normal CNS NE activity and may be associated with depressions involving disorders of serotonin metabolism. High MHPG excretion suggests increased norepinephrine activity or output in the CNS, and has been suggested to occur in patients showing hypersecretion of cortisol.[126,127] These MHPG findings lend support to the concept of abnormal neurotransmitter turnover rates in affective disorders and may be of help in classifying unipolar depression and discriminating between unipolar and bipolar depression.

Variou investigators have attempted to identify a relationship between Li^+ response and cerebrospinal fluid (CSF) and urinary biogenic amine neurotransmitter metabolite concentations. Goodwin et al.[128] reported that patients who exhibited low CSF 5 hydroxyindoleactic acid (5 HIAA) accumulation following blockade of transport from CSF by probenecid showed an antidepressant response to Li^+. This suggests that serotonin (5-HT) turnover-deficient patients may respond to Li^+. Others failed to substantiate the findings of Goodwin et al.[129] Fyro et al.[130] found that Li^+ treatment was accompanied by a lowering of 5 HIAA and an increase in the dopamine metabolite homovanillic acid (HVA), but could discern no correlation between therapeutic effects and these biochemical data. Beckmann et al.[131] studied MHPG excretion in depressed patients treated with Li^+. Those patients with initially low 24-hr urinary MHPG levels tended to benefit most. They also found that, as these patients responded, the urinary MHPG levels gradually increased. Since low CSF 5-HIAA, low 24-hr urinary MHPG accumulation, and a tendency for a good antidepressant response to Li^+ are all associated with bipolar status, it has been suggested that these biochemical data may be more helpful in identifying bipolars than in predicting response to Li^+.[89,131,132] The predictive value of these data awaits further study, especially in various subgroups of affectively ill patients.

7. Enzyme Studies

The enzymes regulating the degradation of biogenic amines have been measured in samples of various patient populations in the search for prognostic indicators of Li^+ response. Little clinically useful information has resulted from these efforts. Platelet monoamine oxidase activity (MAO) was observed to be associated with a poor antimanic response in 6 of 24 patients.[133] Some investigators have found that low platelet MAO is associated with bipolar status,[134,135] while others have failed to find a similar association.[136] Van Kammen and Murphy[137] found no relationship between platelet MAO levels and antidepressant effects of Li^+ treatment. Low platelet MAO activity is probably not specific to bipolar patients — Buchsbaum et al.[138] have suggested that low platelet MAO is associated with a general predisposition to psychopathology. Erythrocyte catechol-o-methyltransferase (COMT) levels may be lower in unipolar than in bipolar women[139] but has no discriminable predictive value.[81]

8. Pharmacologic Predictors

In a preliminary report, Van Kammen and Murphy[137] observed that an acute antidepressant response to an oral *d*-amphetamine challenge predicted an antidepressant response to Li^+ in depressed unipolar but not bipolar women. Surprisingly, a prior history of positive Li^+

response does not predict future Li^+ response.[89] The reasons for this are unclear and are, as yet, incompletely investigated. A previous history of a "switch" from depression to mania — spontaneously, during antidepressant treatment, following ECT, or following use of CNS stimulants (e.g., cocaine, amphetamine, methylphenidate) — would suggest a bipolar diathesis, and therefore an increased likelihood of response to Li^+.[14] Physostigmine infusion also has been studied as predictor of Li^+ response. The depressogenic response to intravenous infusion of physostigmine has been suggested by one group[140,141] as a correlate or predictor of ultimate response to Li^+.

V. PRESCRIBING LITHIUM

Following the appropriate neuropsychiatric evaluation, Li^+ may be indicated. As a general rule, before initiating Li^+ therapy, a complete physical examination should have recently been performed. Baseline serum electrolytes, complete blood count (CBC) urinalysis, and baseline renal and thyroid function should be measured and recorded. (Serum Ca^{++} and Mg^{++} determinations may be helpful for possible response prediction in some cases.) Renal function testing should include BUN, creatinine, and measurement or estimate of 24-hr creatinine clearance.[142] Renal function should be reassessed every 6 months (or more frequently in patients with compromised renal function). Thyroid function testing should include (ideally a pre-lithium TRH or) TSH, T_4, T_3RU, and T_4I. TSH should be repeated every 3 months for the first year as an early indicator of decreasing thyroid function and every 6 months thereafter. TRH testing, if feasible, would be the most sensitive early indicator of decreasing thyroid function. (Further comments on renal and thyroid function are included in the Cautions and Guidelines section below).

A. Treatment Considerations

1. Acute Mania

For acute mania, the treatment of choice is Li^+ (see Figure 3). Since the antimanic effect of Li^+ usually does not become evident for 7 to 10 days, it is common practice to treat the highly activated patient with adjunctive antipsychotic medication. The hospitalized patient who can be carefully monitored may be given Li^+ fairly aggressively. Usually dosages of 1200 to 1800 mg/day may be given initially, provided no serious adverse effects appear early in treatment. As levels approach 1.0 meq/ℓ, the clinician may choose to decrease the daily dosage slightly and, with careful monitoring, titrate the level upward to the 1.1 to 1.4 meq/ℓ range. Frequent monitoring of Li^+ levels should be continued until the Li^+ level is stable. As the antimanic effect appears, the level may be lowered slowly to a range closer to 0.9 to 1.1 meq/ℓ. The need for antipsychotic medication treatment is dictated primarily by the clinical situation. For patients who are very agitated and potentially dangerous, rapid control of symptoms may be necessary by rapid neuroleptization (see chapter 8). For less activated patients, a low dosage of antipsychotic medication may suffice. As manic symptoms abate, the antipsychotic may be slowly decreased and discontinued. Even if treatment is optimal, an estimated 20 to 30% of acutely manic patients will fail to respond[143] or may experience toxicity before therapeutic levels are attained. ECT may be considered at this point, but is often refused by patients. Recent studies indicate that carbamazepine (Tegretol®) may be helpful for Li^+-treated patients who either fail to respond or respond incompletely. Ballenger and Post[144] treated a series of manic patients with a divided dosage of 600 to 1600 mg carbamazepine per day with resulting blood levels of 8 to 12 μg/mℓ. Antimanic effects were apparent between 2 and 7 days — 8 of 11 manics improved markedly. Four patients who had not responded to Li^+ had a dramatic response. Interestingly, these investigators also observed significant antidepressant effects in 50% of patients after 2 to 4 weeks of a similar regimen. A synergistic action between Li^+ and carbamazepine in incompletely

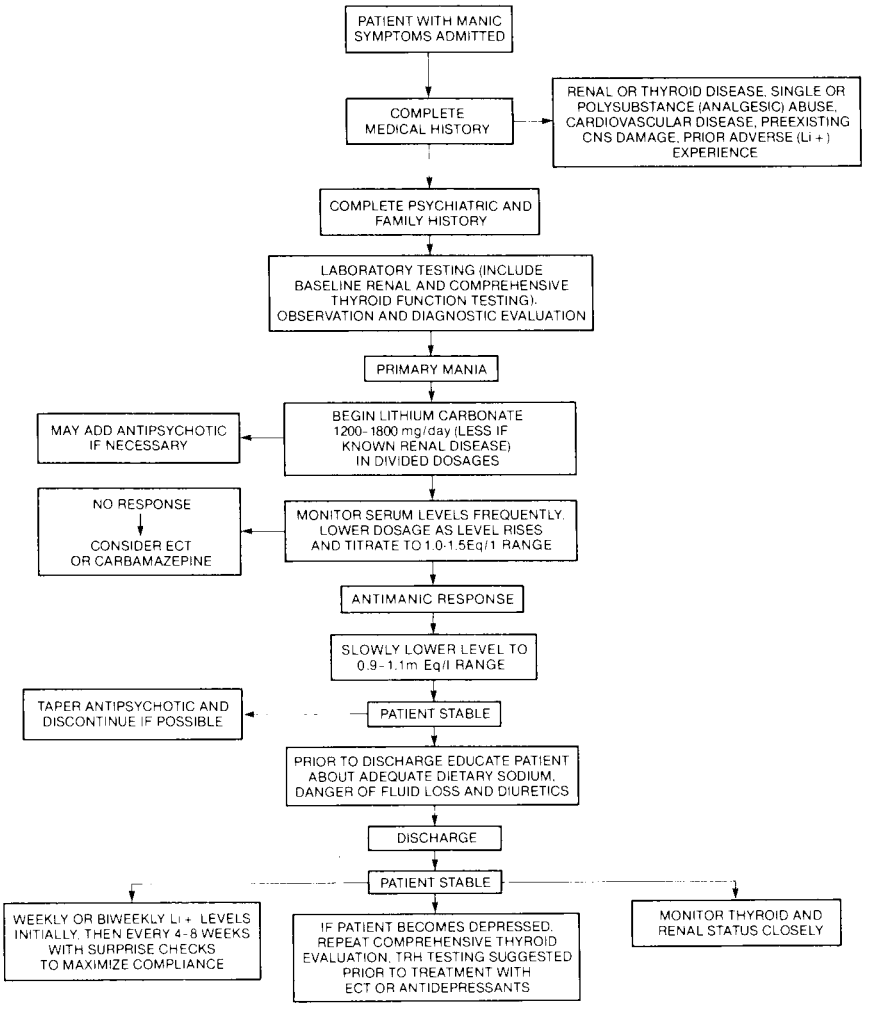

FIGURE 3. Flow diagram for initiating lithium treatment in acute mania.

responding manics may exist.[145] There is some evidence that the addition of L-tryptophan, the amino acid precursor to serotonin, may have some mood-stabilizing effects when added to Li^+. Another alternative approach to poorly Li^+-responsive rapid cyclers is the addition of low-dose L-thyroxine. Cooper et al. have devised a nomogram which enables the clinician to predict, with greater than 95% accuracy, the daily dose needed to maintain serum lithium concentrations between 0.6 and 1.2 meq/ℓ. This same test predicts doses necessary for treating acute mania and depression, despite the higher levels warranted in these conditions, with an accuracy of greater than 90% (Carman et al., personal communication).

2. Acute Depression

There is good evidence that Li^+ has acute antidepressant effects for some patients.[89,146-148] For patients who have failed to respond to or cannot tolerate other forms of antidepressant treatment, Li^+ may be a consideration. However, FDA has not yet approved the use of Li^+ as an antidepressant. As was noted earlier, Friedel[20] suggested that those patients most likely to respond are those most resembling bipolar depressed patients with anergic, hypersomnia, and increased appetite. Treatment of acute depression with Li^+ is currently more a point of

theoretical interest and should be considered as an adjunct rather than as a first-line treatment consideration.

3. Prophylaxis

Prophylactic or maintenance Li^+ treatment requires a complex clinical decision. Multiple factors such as the frequency and past severity or affective episodes, the impact of relapse on the patient and his or her job and family, the therapeutic alliance and the likelihood of compliance must all be counterbalanced. As previously noted, compliance may be a key factor in both acute and prophylactic treatment response — it may be the most decisive factor in a successful trial of Li^+ maintenance. During prolonged maintenance, one should be aware of sudden reductions in serum Li^+ levels since this may signal either noncompliance or an impending exacerbation unrelated to compliance. Frequency of episodes is also important. Grof et al.[149] suggested that patients who have experienced two or more episodes within 2 years may derive the most benefit from long-term treatment, but there is no universally accepted "rule of thumb". It is clear that, for bipolar illness, prophylaxis is most beneficial for preventing recurrent mania and also has a lesser but substantial prophylactic benefit for bipolar depression. Bipolar patients run a high risk of antidepressant-induced "switches" into mania.[150] Wehr and Goodwin[151] have shown that rapid cycling can occur in bipolar patients taking tricyclics. Quitkin et al.[152] showed that 25% of Bipolar I patients on Li^+ plus imipramine prophylaxis had manic relapses vs. 10% in the Li^+ group alone. Prien et al.[150,153] noted manic relapse in 67% of bipolar patients on imipramine — twice the spontaneous rate in a comparable placebo group. The combination of antidepressants and Li^+, then, should be avoided for prophylaxis in this group. Davis[154] summarized the data available prior to 1976 on the efficacy of Li^+ prophylaxis for both bipolar and unipolar illness. He concluded that both patients with bipolar and unipolar illness derive substantial benefit from maintenance therapy. The statistical significance of data for prophylaxis of bipolar illness was so apparent that he suggested that no further studies on this issue were warranted. While the diagnostic issues for unipolar depression remain murky (i.e., some presumed unipolar patients eventually experience hypomania or mania and obtain a new diagnosis), the data indicated that unipolar patients also derive significant benefit from maintenance Li^+ treatment. However, there are alternate forms of prophylaxis for depression — such as antidepressant medication and maintenance ECT. On the medicolegal side, Li^+ still lacks FDA approval for maintenance treatment for unipolar depression. It is therefore up to the clinician to decide which maintenance treatment to choose for the individual patient. Recent reviews bear out Davis' view that Li^+ alone is an effective maintenance treatment for unipolar depression.[35,89,148,155] Nearly equal efficacy has been shown for treatment with antidepressant medication alone, Li^+ alone, or the combination.[156-158] For patients with recurrent unipolar depression who have been treated unsuccessfully with preventive antidepressant medication or ECT maintenance or cannot tolerate these treatments, a case can definitely be made for considering Li^+ as an alternative maintenance treatment.

Euthymic patients (usually outpatients) for whom prophylactic Li^+ is being initiated, a dose prediction test has been developed by Cooper et al.[159] It consists of a 600-mg oral dose of Li_2CO_3 and measurement of serum Li^+ concentration after 24 hr. A logarithmic relationship between the 24-hr blood level and the maintenance dose can be obtained from a nomogram. The patient can then be treated with the appropriate dosage (ranging from 600 to 1500 mg/day in divided doses, usually about 900 to 1200 mg/day) as soon as possible. After initial dosage, Li^+ levels should be drawn at least weekly, and after a stable level is achieved, repeat levels may be checked every 4 to 8 weeks at a minimum. Surprise Li^+ level checks may allow the clinician to optimize compliance (an important factor, as was noted earlier). The optimal maintenance Li^+ level must be individualized for each patient. Effective levels range from about 0.5 to 1.2 meq/ℓ.[160-164] Most often, levels in the 0.7 to

1.0 meq/ℓ range are used for maintenance. The proper duration of a trial of Li^+ prophylaxis remains an important and as yet unanswered clinical question. The cycle length of patients is often inconsistent. For patients with a history of two or more cycles over the past 2 years, assessment of prophylactic efficacy may require at least this period of time (or even longer). The additional question of how long to maintain a patient who has derived prophylactic benefit is difficult to assess. Angst[165] found that 12% of bipolar patients and about one third of unipolar patients over 65 years old experienced a symptom-free period of over 5 years. On the other hand, about 88% and 70%, respectively, of bipolar and unipolar patients will experience relapse. At the present time, there are no clinical predictors of relapse with which to identify the individual at risk. It seems most prudent, then, to review the cases of patients who have been maintained symptom-free for several years, calculate the potential risks and benefits of discontinuation, and make the decision jointly with the patient. For patients who do not do well on Li^+ maintenance therapy, there is preliminary evidence that carbamazepine may have some prophylactic benefit, but further study is needed to assess the true efficacy of carbamazepine as a prophylactic agent for affective disorders.[145]

4. Schizophrenia and Schizoaffective Disorders

Beneficial effects of Li^+ treatment for schizophrenia and schizoaffective disorders have been reported by various investigators. A problem in interpreting many of these studies is the lack of consistency in diagnostic criteria used as well as variability in criteria for measuring improvement. It is generally accepted that mania can mimic schizophrenia, including the presence of Schneiderian symptoms.[166] Some feel that a positive response in a schizophrenic patient suggests that the illness is actually an atypical affective disorder,[167-169] while others feel there is a pure schizophrenic subgroup which is responsive to Li^+.[170-174] Open trials have shown schizophrenic patients responding poorly to antipsychotics can have a positive response to Li^+.[172] Alexander et al.[173] conducted a placebo-controlled study showing that psychosis ratings in 7 of 13 schizophrenic patients given Li^+ alone improved within the first week of treatment. Four of these patients worsened after withdrawal of Li^+. These authors urged caution in prematurely applying this to current clinical practice. Interestingly, in this study the Ca^{++} to Mg^{++} ratios were higher in the responders than in the nonresponders (see Divalent Cation section in this chapter). Van Kammen et al.[174] also demonstrated a modest reduction in schizophrenic psychosis following treatment with Li^+. A positive response to Li^+ was predicted by an acute increase in psychosis after *d*-amphetamine administration prior to Li^+ treatment. Edelstein et al.[175] recently reported the effects of physostigmine intravenous administration of Li^+ in 11 schizophrenic patients. A rapid antipsychotic effect was observed in those patients who had a good response to Li^+ at 2 weeks. Shopsin et al.[176] reported that schizophrenics may be more sensitive to the neurotoxic effects of Li^+ at usually well-tolerated levels (average 0.75 meq/ℓ).

With the advent of helpful laboratory testing, such as the presence of a blunted TSH response to TRH, more accurate diagnosis may be able to help identify manic patients who appear to be schizophrenic and hasten early and appropriate treatment with Li^+. However, there seems to be some evidence that, for truly schizophrenic patients, a minor but measurable benefit may result from the addition of Li^+ to an antipsychotic regimen. While Li^+ may have some beneficial effects in schizophrenic disorders, it is clearly not the first drug choice and should be considered only for patients who respond incompletely to antipsychotic medication.

Schizo-affective illness is a poorly understood condition with both prominent schizophrenic and affective components. Only fairly recently have research (RDC) criteria been used to classify these patients on a continuum from mainly schizophrenic to mainly manic. Johnson et al.[177,178] compared Li^+ and chlorpromazine in a double-blind study of 17 schizo-affectives and indicated that chlorpromazine was superior to Li^+ in this patient group. In a larger

study, Prien et al.[179] found that chlorpromazine was more effective than Li^+ in highly activated schizo-affective patients, but that both treatments were equally effective in a mildly activated group. Biederman et al.[180] used a continuum of primarily affective to primarily schizophrenic to classify 36 schizo-affective patients and compared a combination of Li^+ and haloperidol to haloperidol alone. In each of the extreme groups (i.e., mainly schizophrenic or mainly manic) the combination had a better effect than haloperidol alone. These data suggest that there may be a place for Li^+ in the treatment of schizo-affective patients. It is commonly felt that Li^+ has only been effective in reducing the affective component of this disease, but these data suggest that Li^+ may reduce nonaffective symptoms as well. Annitto et al.[181,182] have speculated about the issue of specificity of Li^+ action. They suggest that Li^+ may not have a true specificity for affective symptoms but that it may reduce any psychopathology that is "cyclic, episodic and fully remitting." With the advent of more sophisticated laboratory diagnosis testing, the identification of subtypes of schizophrenic and affective disorders may become easier. In the meantime, Li^+ may be a helpful adjunct in some schizoaffective patients and, to a lesser extent, in some incompletely responding schizophrenic patients. From a practical point of view, the studies which have shown benefits of a trial of Li^+ carbonate generally indicate that any beneficial effects are likely to occur early in treatment. Therefore, if Li^+ is used for these disorders, a lack of response after 1 month of treatment would be a probable indication for discontinuation of Li^+.

5. Other Syndromes

Premenstrual tension, a syndrome characterized by premenstrual agitation, affective symptoms (irritability, crying, lethargy, insomnia) has been reported to be ameliorated by Li^+ in several open studies and case reports.[183-185] Double-blind studies, however, have not supported the usefulness of Li^+ for this syndrome.[186] Emotionally unstable character disorder (EUCD) as described by Rifkin et al.[187] is a condition of brief depressive and manic-like mood swings lasting hours or days, which are independent of environmental events. In a double-blind, crossover study of 21 such patients, they found a therapeutic benefit from Li^+ treatment. They ascribed this benefit to a possible relationship of EUCD to affective illness, and suggest that it is an alternative to antipsychotic treatment for this group of patients. Whether this subgroup of patients actually represents a distinct diagnostic entity or a poorly characterized subgroup of rapidly cycling, affectively ill patients requires further clarification. Li^+ has also been suggested as a treatment for episodic aggression. It seems possible that aggressive behavior may in some patients be a symptom of mania and may thus be a Li^+-responsive symptom. Sheard[188] conducted a double-blind trial of Li^+ in inmates convicted of serious aggressive crimes (murder, assault, rape) who had continued to engage in aggressive behavior while incarcerated. He noted that a significant reduction in violent behavior occurred in some Li^+-treated prisoners. An open study by Tupin et al.[189] also suggested a possible beneficial effect of Li^+ on chronically violent inmates. Whether this effect of Li^+ is a specific anti-aggressive affect or simply a treatment of occult affective disorders remains unclear, but merits further double-blind study.

6. Substance Abuse

Alcoholism and alcohol abuse are common in affectively ill patients and their first degree relatives.[190] Substance abuse in general may represent an inappropriate attempt by some individuals to treat unrecognized affective illness, although substance abuse is certainly not unique to affectively ill patients. Kline et al.[191] showed a reduction in readmissions to an alcohol detoxification unit in a 1-year, placebo-controlled study of Li^+ maintenance in detoxified alcoholics. Sixteen Li^+ patients had nine rehospitalizations compared with 36 in the year prior to Li^+ treatment. Four patients accounted for all nine of these admissions. Fourteen placebo-treated patients had a rate of 34 hospitalizations for both years. Merry et

al.[192] conducted a double-blind study showing some reduction in recidivism in those alcoholic patients with symptoms of depression, while those without mood disturbances did not appear to benefit from Li^+ treatment. Judd et al.[193] explored the possibility that Li^+ may reduce alcohol-induced euphoria. In a controlled study of 23 normal males, this group failed to find any anti-euphoric affect of Li^+ after alcohol administration. Other clinical studies have suggested a possible role for Li^+ in treating other types of substance abuse, most notably CNS stimulant abuse. Gold and Byck[14] discussed the similarity between amphetamine and cocaine-induced euphoria and manic states, suggesting that they may be mediated by similar mechanisms. Case reports suggest that Li^+ can attenuate euphoria induced by amphetamines and cocaine.[14,194] In one double-blind study of depressed patients, Van Kammen and Murphy[195] noted that the attenuation of the euphoric affects of *d*- and + l-amphetamine were attenuated by Li^+ pretreatment. Li^+ treatment of opiate abusers has been less promising. Although Li^+ has been shown to antagonize morphine-facilitated intracranial stimulation in rodents,[196] Altamura et al.[197] did not find that it was helpful in reducing recurrent opium use in 20 opium addicts.

Li^+ may have a role in substance abuse disorders in two different ways: first, for those patients with occult affective disorders who are inappropriately self-administering any of a variety of drugs, it may obviate the need for destructive self-administration. Secondly, the scanty data available indicate that it may also be helpful in blocking or attenuating the euphoric (and hence reinforcing) effects of CNS stimulants in nonaffectively ill patients. This is an area of research that has been under-explored and further studies are required to provide any clear guidelines for the future. There is a clear need for increased knowledge and research in treating this chronically undertreated and difficult patient population.

VI. SOME CAUTIONS AND GUIDELINES FOR LI^+ TREATMENT

A. Central Nervous System

After the initiation of treatment with Li^+, patients complain most frequently of lethargy, cognitive blunting, and tremor. Symptoms of lethargy and cognitive blunting[198] usually subside as the patient accommodates to treatment (and may accompany the disappearance of the affective symptoms of mania which patients enjoy). Tremor often also subsides but may persist in some patients or appear during the period of peak serum Li^+ levels.[199,200] Lowering the Li^+ level may provide relief; if this is not clinically feasible, propranalol in divided doses of 20 to 160 mg/day often provides substantial relief.[201] Persons with preexisting action tremor (familial, senile) may be at greater risk for bothersome tremor. Signs of CNS toxicity may be observed at Li^+ concentrations over 1.5 meq/ℓ and include muscular fasciculations, increased tremor, dysarthria, ataxia, visual disturbance, extrapyramidal symptoms, and confusional states.[202] At levels greater than 3.0 meq/ℓ, serious neurotoxic symptoms appear, and in addition to the above signs, seizures, coma, brain damage, and death have been reported.[203] There is conflicting data as to whether Li^+ has epileptogenic potential,[204-206] but Li^+ may selectively increase temporal lobe seizures.[207] In general, however, patients with seizure disorders can tolerate Li^+ well. Patients with preexisting CNS pathology may be at increased risk for neurotoxic effects from Li^+, and elderly patients or patients taking other psychoactive medication may experience some of the above symptoms at lower Li^+ levels.[208,209] (See Tables 2 and 3.)

B. Renal Effects

Renal effects are common in Li^+-treated patients. Polyuria and polydipsia, usually benign and reversible, result from a Li^+-induced anti-ADH effect at the renal tubule.[210] Nephrogenic diabetes insipidus (NDI) characterized by massive urine output (up to 9 ℓ/day) may rarely occur, and usually responds to lowering Li^+ levels.[211] For patients at serious risk for affective

Table 2
ADVERSE CLINICAL EFFECTS OF LITHIUM

Early Adverse Effects

Effect	Comment
Cognitive blunting, fatigue, lethargy	Seen early, often resolve over time
Fine action tremor	Occurs at peak blood levels, often resolves. May reduce Li^+ level if possible or use propranolol
Polyuria and thirst (under 2 ℓ/day)	Benign and reversible
Indigestion, abdominal cramping, loose stools, or diarrhea	Usually early in treatment or with rising Li^+ level after dose. May try divided dosages, taking with meals, different brand, slow release forms
Leukocytosis	Benign, may recheck CBC later
ECG changes	Benign. Yearly ECG (more frequently for older or cardiac patient)

Later Adverse Effects

Persistent tremor	Lower Li^+ level if possible; propranolol
Increased polyuria and thirst or frank NDI; possible late morphologic changes	Monitor renal function every 6 months. Reassess need for Li^+ if severe. Cautiously add thiazide. NDI usually reversible if Li^+ is stopped
Antithyroid effects	Regularly monitor thyroid function. Ask about more subtle symptoms of hypothyroidism
Weight gain	Dietary discretion — caloric restriction
Acne	Tetracycline
Edema	Short-term diuretics with careful monitoring of Li^+ level
Leukocytosis	Usually benign

Table 3
LITHIUM TOXICITY

Lithium — Toxic Symptoms (early)

Effect	Comment
Slurred speech	Check Li^+ level
Muscle weakness or irritability	If these occur in a previously stable patient, consider sodium loss, new medication, medical illness, overdose. Treat as indicated
Stupor or increased lethargy	
Coarse tremor	
Ataxia	
Diarrhea, nausea, vomiting	

Lithium poisoning (late)

Impaired sensorium	Stop Li^+
Hyperactive reflexes	Immediate medical attention indicated
Gross ataxia	
Extrapyramidal movements	
Seizures, coma, death	

relapse at lower Li^+ levels, thiazide diuretics may also be used. They paradoxically reduce polyuria by a poorly understood mechanism.[212] The question of whether Li^+ causes serious renal damage has been studied recently.[213-219] The accumulated evidence suggests that some degree of focal glomerular atrophy and interstitial fibrosis are associated with long-term Li^+ administration. There is no evidence to date suggesting that carefully monitored Li^+ treatment has resulted in irreversible renal failure. The degree of morphologic change correlates with

Table 4
RENAL CONSIDERATIONS

Prelithium
- UA
- BUN
- Creatinine
- Electrolytes
- 24-hr Creatinine clearance
- History of analgesic use or abuse, renal disease, or family history of renal disease, risk factors (diabetes, hypertension), other medications (diuretics)
- Instruct patient to use adequate dietary Na^+, replace fluid loss during exercise or GI illness

During treatment
- Reassess every 6 months
- If renal function declines (Creatinine or BUN rising; 2 ℓ/day urine output) reconsider need for Li^+ and use lowest effective level
- Divided dosages avoid unnecessarily high levels after dosing and possible renal toxicity

the degree to which concentrating defects occur,[213] and polyuria (over 2 ℓ/day) may be an early sign of renal lesions.[219] However, even patients with seriously impaired renal function can be quite safely maintained on Li^+ with proper monitoring. A recent study of Li^+-naive, affectively ill patients found significant concentrating deficits, raising the possibility that patients with affective illness are at risk for renal damage.[217] Also, previous studies in this area have not always scrupulously excluded other causes of nephropathy (urinary obstruction, analgesic abuse). Patients should be screened for preexisting renal pathology, risk factors such as diabetes and hypertension. It is conceivable that some Li^+-related renal changes may result from frequent, short exposure to high Li^+ levels in the renal tubule during routine treatment. Therefore, divided dosage and selection of the lowest effective level of Li^+ should be determined individually. Since Li^+ and sodium are interchangeable, a decreased supply of Na^+ to the kidney could cause increased Li^+ retention and toxicity. Patients should therefore be advised to use adequate dietary Na^+. Replacement of Na^+ loss and fluid replacement during dieting, exercise, or GI illness (diarrhea, vomiting), should be encouraged to avoid possible Li^+ toxicity. Table 4 summarizes renal considerations for Li^+ therapy. Occasionally patients receiving Li^+ will require diuretics. This will be discussed in the drug interactions section below.

C. Thyroid Effects

It is well known that Li^+ has potent anti-thyroid properties.[4,220-224] At least 5% of patients receiving Li^+ develop Grade 1 hypothyroidism, 3% nontoxic goiter, and up to 30% develop Grade 2 hypothyroidism. All of these anti-thyroid effects are eventually reversible upon discontinuation of Li^+. It has been common practice to follow thyroid stimulating hormone (TSH) as an indicator of failing thyroid function in patients receiving Li^+. Although it is not currently being used routinely, it may be that the thyrotropin releasing hormone (TRH) test could be a more sensitive and early indicator of impaired thyroid function. Takahashi et al.[222] measured TSH response to TRH in eight manic patients prior to and after 4 weeks of Li^+ treatment at therapeutic levels. All of the patients appeared to be clinically euthyroid at retesting. Basal TSH levels were slightly but not significantly elevated in these patients, and serum thyroxine levels were essentially unchanged. However, the TSH response to TRH had become markedly elevated in these patients. Lazarus et al.[223] found abnormal TRH tests in 36 (49%) of 73 patients who had received Li^+ for approximately 3 years. Twenty-one of these 36 patients had basal TSH levels in the normal range. Epstein et al.[224] found exaggerated TSH responses to TRH in two of nine clinically euthyroid Li^+-treated patients. They were able to reverse this abnormality by treatment with T3. These data indicate that

Table 5
THYROID FUNCTION CONSIDERATIONS

Prelithium
- TRH test (if possible)
- TSH (basal)
- T4
- T3RU
- T4I
- History for prior thyroid disease or family history

During treatment
- Repeat: TRH (if possible) every 3 months during first year through every 6 months. If TRH becomes abnormal, follow patient closely for possible hypothyroid symptoms (anergia, fatigue, dry skin, constipation) and consider thyroid replacement therapy if they emerge

or TSH every 3 months for 1 year, then every 6 months. If TSH level rises, full thyroid function studies are indicated. Consider replacement therapy
- All other studies at least yearly
- If Grade 2 or Grade 1 hypothyroidism develops, replacement therapy is indicated. Follow Grade 3 carefully

TRH test abnormalities precede basal TSH elevation or peripheral thyroid hormone changes and can thus provide a more sensitive and early indicator of decreasing thyroid function. TRH testing could alert the clinician to compromised thyroid function and we would suggest this as a preferable substitute for basal TSH and follow-up TSH measures. It is not always feasible to obtain TRH testing, so at a minimum, basal TSH levels should be obtained prior to treatment every 3 to 6 months thereafter (see Table 5). If abnormal TRH or TSH tests are found, the patent should be carefully followed for clinical evidence of hypothyroidism. Some clinicians may choose to use replacement therapy even in patients who are clinically euthyroid. Patients with any clinical symptoms of hypothyroidism should, of course, receive appropriate replacement therapy. This can usually be accomplished without discontinuing Li^+. If a patient who has been taking Li^+ should become depressed, careful measures of thyroid function should be included in the evaluation process. Similarly, patients who become depressed soon after discontinuing Li^+ may actually be experiencing sub-clinical hypothyroidism from the lingering anti-thyroid effects of Li^+. Although this has not been studied, it would be of great interest to know if such patients would respond to thyroid replacement therapy instead of antidepressants.

D. Other Endocrine Effects

Other endocrine effects, such as interference with carbohydrate metabolism and adrenal cortical effects, are not usually important clinically.[225] Some reports of $Li.^+$-associated elevations in serum parathyroid hormone (PTH) and Ca^{++} have appeared and suggest possible Li^+-induced "biochemical hyperparathyroidism".[226,227] Accordingly, patients with known abnormalities of Ca^{++} regulation may be at risk for an acceleration of hyperparathyroid conditions. For patients with no such history, routine measurement of PTH and Ca^{++} do not seem warranted.

E. Cardiovascular Effects

Although some unwanted effects may occur, serious cardiotoxicity resulting from Li^+ is rare. The most common electrocardiographic (ECG) effect is t-wave flattening or inversion (Table 2). Occasional reports of conduction disturbances, arrythmias (atrial and ventricular), and cardiomyopathy have appeared in the literature. Approximately 20% of patients show a benign, reversible t-wave change, likely due to partial displacement of intracellular potassium.[228] S-T depression during exercise stress tests does not increase in noncardiac pa-

tients.[229] Conduction disturbances have also been reported in association with Li^+ treatment. Reversible sinoatrial node dysfunction[230] and first-degree heart block[231] have been noted in previously healthy individuals. Most serious problems have occurred in elderly patients, but if Li^+ is absolutely indicated, pacemaker insertion can reduce the danger of irregular sinus pauses or bradycardia. Atrial and ventricular arrythmias have been reported occasionally in Li^+-treated patients with no cardiac history,[230] but it is unclear whether this is a causal association. In acute Li^+-toxic states, however, refractory ventricular tachycardia has been reported.[232] Cardiomyopathy and congestive heart failure have been reported in a few cases,[233,234] but, again, a causal relationship is unclear. While Li^+ may cause edema,[235] it has no apparent myocardial depressant effects.[236]

F. Gastrointestinal Effects

Gastrointestinal (GI) distress is often encountered during the initiation of Li^+ therapy, manifested by nausea or vomiting, loose bowel movements (or occasionally diarrhea), and abdominal cramping (Tables 2 and 3). These symptoms typically accompany rising serum Li^+ levels and occur usually during the initiation of treatment or following a dose of Li^+. The occasional patient may experience symptoms severe enough to warrant discontinuation of treatment. Usually, increasing the frequency of the divided dosages, taking medication with meals, or using slow-release forms provide adequate relief from these symptoms. It should be remembered that GI symptoms appearing in a previously stable regimen may herald the onset of Li^+ toxicity, and a Li^+ level should be promptly obtained in such cases.

G. Developmental and Reproductive Effects

Li^+ probably has teratogenic effects in man, the most sensitive period being the first trimester of pregnancy. The majority of abnormalities in newborns exposed to Li^+ *in utero* are abnormalities of the heart and great vessels,[237] with the frequency of Ebstein's anomaly[238] being dramatically increased over the expected incidence. Thus, the cardiovascular system is probably most Li^+-sensitive developing organ system. Although the actual risk of insult to the developing fetus may be overestimated due to more frequent reports of problematic than untroubled pregnancies, it is best to avoid use of Li^+ in pregnancy (especially early in pregnancy) until further data are available. For pregnant mothers who are receiving Li^+, the renal clearance of Li^+ may increase up to 100% during pregnancy and then drastically fall at term, thus exposing both the mother and fetus to potential Li^+-toxic states. Li^+ should be discontinued if at all possible or should at least be decreased to pre-pregnancy dosages prior to delivery.[239] Since Li^+ is excreted in milk and the potential danger to the nursling is unknown, lactating mothers taking Li^+ should avoid breast feeding.[240]

H. Other Effects

The most common hematologic effect accompanying Li^+ treatment is a benign leukocytosis resulting from a Li^+-induced stimulation of granulocyte production (up to 12 to 15,000 WBC/mm^3) (Table 2). This may either persist or decline over time and should not raise undue concern. There are sporadic case reports of leukemia associated with Li^+ treatment, raising concerns that it may be leukemogenic. However, a recent review suggests that there is no epidemiologic reason for concern at this time.[241] Dermatologic effects may include an increase in or appearance of acne which responds to standard treatment (tetracyclines, others), exacerbation of preexisting psoriasis, appearance of psoriasis *de novo*, and drug allergy rash.[242] Edema may occur in some patients and the mechanism for this is unclear. After ruling out other causes, e.g., congestive heart failure (CHF), hypothyroidism, etc., short-term diuretic therapy may be helpful for some individuals. Weight gain is experienced in 20 to 60% of patients.[243,244] This may accompany normalizing eating patterns in previously ill patients or may result from using high-calorie beverages to relieve Li^+-

induced thirst. Weight maintenance or reduction can be achieved through dietary discretion — caloric restriction in most patients will suffice.[245]

I. Drug Interactions

Some patients with hypertension or CHF may need to take both Li^+ and a diuretic, or diuretics may be used to treat an occasional patient who has excessive edema or NDI. Thiozide diuretics can cause an abrupt, potentially toxic accumulation of Li^+ by altering renal reabsorption mechanisms.[246,247] If a thiazide is added, Li^+ should be decreased immediately and serum levels should be carefully followed. Potassium-sparing diuretics like spironolactone and trimamterine may cause a very gradual rise in Li^+ levels due to slow Na^+ wasting.[248,249] Loop diuretics like furosemide and ethacrynic acid do not seem to alter Li^+ levels significantly.[250] Osmotic diuretics and carbonic anyhydrase inhibitors may increase Li^+ excretion and lower levels.[251]

Antipsychotic drugs and Li^+ are frequently co-administered. There have been reports of a possible toxic interaction between the butyrophenone haloperidol and Li^+ in several case reports — in some cases, apparent permanent CNS damage was reported.[252-254] Though a rare, toxic synergism cannot be excluded, several of these were elderly patients with preexisting CNS pathology, and others had fever, electrolyte imbalance, and elevated liver enzymes, thus allowing for other possible etiologies. It may be that some of these cases were variable combinations of Li^+ toxicity and neuroleptic malignant syndrome.[255] It should be remembered that a great many patients have received both haloperidol and Li^+ simultaneously with no difficulty, and there seems to be no medical contraindication to using this combination. Somnombulism has been reported in patients receiving both antipsychotics and Li^+.[256] Usually this improves when antipsychotics are discontinued. Antipsychotics may increase intracellular Li^+ concentration and possibly predispose patients taking both drugs to neurotoxic effects at usually therapeutic serum Li^+ levels.[257] Antipsychotic drugs may decrease urine concentrating capacity and amplify this side effect of Li^+.[213,215] Chlorpromazine may increase Li^+ excretion,[258] and one report indicated Li^+ may decrease chlorpromazine levels.[259] In general, the combination is safe and the incidence of adverse effects in patients taking Li^+-antipsychotic combinations are the sum of those expected from either alone.

Various other drug interactions have been reported and appear in Table 6. Many are isolated case reports and must be considered as potential interactions which require further clarification and study.

J. Lithium Poisoning

The seriousness of Li^+ intoxication is directly related to the concentration and duration of exposure. Shock, electrolyte disturbances, and renal failure may follow acute CNS depression and cardiovascular collapse during Li^+-toxic states. Treatment of acute Li^+ poisoning is based on standard principles of managing toxic ingestions: accurate diagnosis, vital support, limiting absorption, and promoting excretion. There is no specific antidote for Li^+ overdose. In acute overdose, absorption is delayed by emptying the stomach. Patients who are alert may be given emetics; for patients whose level of consciousness is impaired, endotracheal intubation and nasal gastric suction may be required.

Since renal clearance of Li^+ may be slowed considerably in Li^+-toxic patients, promoting excretion is also important. If sodium depletion is responsible for or aggravates Li^+ toxicity, replenishing sodium stores may enhance excretion of Li^+. Dialysis has also been used to hasten excretion.[260] For patients with a serum Li^+ concentration greater than 4.0 meq/ℓ, dialysis is indicated; between 2.0 and 4.0 meq/ℓ, dialysis may be indicated if the clinical condition is poor. Clearance of Li^+ by peritoneal dialysis is about 15 mℓ/hr, while hemodialysis provides up to 50 mℓ/hr. Following dialysis, redistribution of Li^+ from tissue stores may occur, causing a second rise in serum Li^+ levels.

Table 6
DRUG INTERACTIONS WITH LITHIUM

Drug	Effect	Comment
Diuretics		
Thiazide (hydrochlorothiazide, chlorothiazide)	Abrupt ↑ in Li^+ level	Adjust Li^+ dose down when adding diuretic; use lower dose of Li^+ than usual when adding to thiazides. Monitor levels closely
Potassium-sparing (spironolactone, triamtrine)	Slow ↑ Li^+ level	Monitor Li^+ levels and adjust accordingly
Loop (furosemide, ethacrynic acid)	Little effect	Little infomation to date. Monitor levels closely
Osmotic or carbonic anyhydrase inhibitors	May ↓ Li^+ level	Monitor levels closely
Antipsychotics		
	??Rare toxic synergism with haloperidol	Recognize and treat neuroleptic malignant syndrome and Li^+ toxicity of present
	Somnambulism	Lower or discontinue antipsychotic
	↑ Intracellular (Li^+)	May theoretically cause Li^+ toxicity at lower Li^+ level
	↓ CPZ level	Little information
	↓ Li^+ level by CPZ	Little information
Methyldopa	Symptoms of Li^+ toxicity emerged	2 Cases, resolved when methyldopa was discontinued
Neuromuscular junction (NMJ) blockers (pancuronium, succinylcholine)	Prolonged NMJ blockade	Caution in surgical procedures advised
Prostaglandin synthatase inhibitors (phenybutazone, indomethacin)	↑ Li^+ levels	Monitor levels closely
Baclofen	Combined with Li^+, dyskinetic movements in Huntington's disease	2 Patients reported
Xanthines	↓ Li^+ level via diuretic effect. Li^+ level, is high intake abruptly stopped	
Anticonvulsants (phenytoin, carbamazepine)	Tremor, polydipsia, polyuria developed at previously tolerated Li^+ levels when added to Li^+ regimen	Few cases reported. Remitted when drug stopped
CNS stimulants (amphetamine/cocaine)	May block euphoric effects	
ECT	May cause increased Li^+ toxicity if coadministered	Avoid combination if possible

VII. SUMMARY

Sifting through the clinical and biochemical data on identification of potential Li^+ responders, it becomes clear that no single reliable prognostic indicator for either acute or long-term response has been identified.

The likelihood of a good Li^+ response is probably greatest in bipolar I, bipolar II, and (as an antidepressant) unipolar patients, respectively. Schizoaffective illness responds variably. The more "classic" features of bipolar illness observed or obtained by history and neuroendocrine testing (see Table 7), the greater the likelihood of a good treatment response to Li^+. The literature, however, is replete with exceptions to this general trend. Therefore, an empirical trial of Li^+ is still required to answer the important question of whether a

Table 7
CLINICAL AND BIOLOGICAL FACTORS POSSIBLY ASSOCIATED WITH A POSITIVE RESPONSE TO LITHIUM

Mania or hypomania associated with grandiosity or elation
No atypical (schizoaffective) symptoms
History of or current depressive symptoms of anergia, hypersomnia, increased appetite
Less than 4 cycles per year
History of compliance with treatment in the past
First-degree relative with bipolar illness
? History of "switch" to mania, spontaneously, after antidepressnts or CNS stimulants
? Serum [Li^+] 1.0 meq/ℓ
? High Ca^{++}/Mg^{++} ratio
? Low MHPG (depressed)
? Augmenting AER response
? Augmented TSH response to TRH in depressed bipolar patients
? Any periodic, fully-remitting psychopathology

Note: There are no absolute predictors of Li^+ response. The items in this list represent traits consistent with bipolar illness (manic or depressed), reports in the literature noted in this chapter and the opinion of the authors. Those with question marks are highly speculative or incompletely investigated items which we feel deserve further study.

patient will respond to Li^+. Careful attention to monitoring of blood levels, adverse effects, and maximizing compliance cannot be overemphasized.

Li^+ is a relatively safe drug — it has been shown that no increase in mortality in a group of patients receiving Li^+ for up to 10 years was noted in one epidemiologic study.[261] It is worth noting that the risk of suicide in patients with untreated affective disorder is 30 times that of the general population.[262] Why certain patients respond while others do not and whether these are "state" or "trait" variables will require significantly more information than is presently available. In the meantime, good clinical judgment combined with a thorough physical, neurologic, and laboratory examination of patients with suspected mood disorders will provide the basis for optimal Li^+ therapy.

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Chapter 7

MAO INHIBITORS: PREDICTING RESPONSE/MAXIMIZING EFFICACY

Robert Moreines and Mark S. Gold

TABLE OF CONTENTS

I. INTRODUCTION

The history of the use of monoamine oxidase inhibitors (MAOI) for the treatment of affective and anxiety disorders is one of the most fascinating and controversial chapters in modern psychopharmacology. It began when several investigators creatively took advantage of the serendipitous observation that the anti-tuberculosis drug iproniazid had mood elevating effects[1] and it grew with enthusiastic reports of special efficacy of MAOI for certain subgroups of patients described as suffering atypical depressions.[2,3] MAOIs were rescued from premature condemnation by keen detective work in the elucidation of the "cheese reaction" as responsible for reports of serious hypertensive reactions.[4] Over the past decade MAOI therapy has stood at the center of more rigorous attempts to define specific medication responsive homogeneous subgroups among patients presenting with varying depressive syndromes.[5-9]

The MAOIs are a class of antidepressant medication which has been proven effective in the treatment of depressive episodes and panic-anxiety disorders.[10,11] They can be used quite safely if patients are carefully counseled regarding the potentially dangerous food and drug interactions that must be avoided.[12] Use of the laboratory for therapeutic drug monitoring can reduce side effects and improve efficacy. There is clear evidence that to be effective they must be prescribed in adequate dosage that results in 80 to 90% inhibition of monoamine oxidase as measured in platelet assays.[13-15] In general, they are indicated for patients with major depression or panic disorders who either did not respond to prior treatment with tricyclic antidepressants or for whom such drugs are contraindicated due to anticholinergic or cardiotoxic side effects. While evidence is still suggestive, we would also recommend their consideration as first-line medications for certain other depressed patient groups — those with family history of response to MAOI[16] or those presenting with certain atypical features.[11]

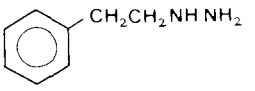
II. PHARMACOLOGY

Monoamine oxidase (MAO) is the enzyme predominantly responsible for intraneuronal metabolism (oxidative deamination) of biogenic amine neurotransmitters. Inhibition of this enzyme increases intracellular stores of these neurotransmitters and is thought to potentiate their action through release of increased amounts into the synaptic cleft. The resulting enhancement of serotonin and norepinephrine activity is shared with the tricyclic antidepressants (TCA) which exert their effects, at least in part, by inhibiting presynaptic reuptake of the neurotransmitters from the synaptic cleft. (This is a bit oversimplified and important secondary receptor actions have also been identified.) While they act in different ways, both classes of drugs provide general support for the monoamine theory of depression and, theoretically, should synergistically enhance one another's effects[1] (see combined MAOI-TCA treatment section).

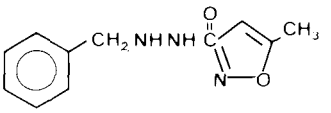
The MAOIs used in current clinical practice may themselves be subdivided into two classes. The types of MAOI currently in use in this country are the hydrazines, (phenelzine and isocarboxazid) and the nonhydrazine, tranylcypromine. The hydrazines irreversibly inhibit MAO, and therefore their effects last beyond termination of drug administration, until enzyme resynthesis occurs. This has been found to take 203 weeks for full restoration of pretreatment levels.[1] Tranylcypromine produces a reversible inhibition of MAO. Its effects have a briefer time of onset and duration.[1] All are equally effective at adequate dosage; tranylcypromine (which resembles amphetamine structurally) is thought to be more activating[1] (see Figure 1).

Currently, studies are underway examining the effectiveness of selective MAO inhibitors.

HYDRAZINES

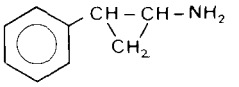


PHENELZINE



ISOCARBOXAZID

NON-HYDRAZINE



TRANYLCYPROMINE

FIGURE 1. Chemical structures of monoamine oxidase inhibitors.

MAO is present throughout the body and exists in two forms: MAOA and MAOB. The currently used MAOIs, phenelzine, isocarboxazid, and tranylcypromine, effectively inhibit both forms. This work is of theoretical interest because MAOA acts selectively on serotonin and norepinephrine (NE) and MAOB on dopamine and phenylethylamine. Differential clinical effects in different conditions between the selective MAOIs would further clarify the role of specific neurotransmitters in subtypes of depression.

MAOA is the predominant form of the enzyme in intestine; MAOB is the enzyme present in platelets; both MAOA and MAOB are present in brain. In animal experiments, it has been found that MAOI effects follow a similar time course in brain as in human peripheral measurements of enzyme inhibition.[17] Recently it has been demonstrated that MAOA inhibition can also be monitored peripherally by measuring changes in plasma MHPG;[18] oxidative deamination by MAOA is a necessary step in the metabolism of NE to MHPG. In the absence of MAO, NE is metabolized to normetanephrine. This not only provides a means of monitoring therapeutic levels of selective MAOI (Type A), but also the extent of alteration of NE activity when using the nonselective MAOIs as well. Finally, Pickar et al.[19] have provided evidence that the increased pressor response to tyramine is more complicated than previously thought. Tyramine is a substrate for both MAOA and MAOB. It was previously thought that the hypertensive reaction to tyramine-containing substances is a result of inhibitory effects on MAOA in gut which permits increased absorption of tyramine. However, intravenous infusions of tyramine had much greater effects following MAOA inhibition than after MAOB inhibition. This suggests there is probably an interaction peripherally, directly at the site of blood pressure regulation which is altered by MAOA but not MAOB inhibition, and probably involves norepinephrine which is selectively affected by MAOA.

III. CLINICAL USE

Over the past 3 decades, research in the affective disorders has sought to establish a nosology of subtypes of depression.[20,21] While there is still considerable controversy, it will be most useful for the discussion of the therapeutic value of MAO inhibitors if we make some basic distinctions. (Please refer to Chapter 1 on DSM III for a more complete discussion). Let us look separately at the evidence for effectiveness of MAOI in "endogenous" and "atypical" depressions. We are specifically choosing these terms, which do not appear in this usage in DSM III, because they capture the basic dichotomy that has been addressed historically in the literature. Unfortunately, the subtypes that have been used in this research do not neatly correspond to the DSM III classifications.[22]

"Endogenous" often has been used loosely to refer to the more seriously impaired, hospitalized patient population. Sometimes it has included criteria of typical vegetative symptoms (anorexia, early morning awakening, diurnal mood variation) or nonreactivity of mood (as would better correlate with the DSM III subtype "melancholia").[22] In general it includes the group of patients who have the highest rate of response to tricyclic antidepressants or ECT. Early studies, in particular that of the respected British Medical Research Council[23] and an NIMH collaborative study,[24] found MAO inhibitors not to be significantly better than placebo in this population. However, these early studies suffer the compelling criticism that they did not employ a sufficiently high dose of phenelzine (they used a standard dose of 45 mg/day). More current research has demonstrated that a minimum dose of 60 mg/day is necessary to achieve platelet (and by extension, brain) MAO inhibition greater than 80% in a majority of patients.[15] This degree of enzyme inhibition is highly correlated with therapeutic response.[15] Unfortunately, there is no way to predict effective dosage for a specific individual without using laboratory assays for platelet MAO inhibition. Yet, these findings do suggest that a standard dose of 45 mg/day of phenelzine was inadequate for the majority of patients in this and other early studies.

More recent studies[25-27] in this patient population, using appropriate doses, have demonstrated effectiveness of MAOI comparable to TCA. Davidson et al.[25] treated 43 inpatient depressives (although some had a primary diagnosis of anxiety) with phenelzine (up to 90 mg/day) or imipramine (up to 150 mg/day). They found both to be equally effective. In particular, a separate analysis limited to those patients with documented therapeutic dosages (imipramine + desipramine blood level — greater than 200 ng/mℓ or platelet MAO inhibition — greater than 80%) also found both treatments equivalent. Moreover, the trial followed a 1-week washout period which permitted exclusion of those patients showing a placebo response; thus there was some indication of nonreactivity of mood in the patients treated.

Similarly, Paykel et al.[26] and Ravaris et al.[27] found phenelzine and amitriptyline to be equally effective in outpatient groups characterized as suffering major depressive disorders. Although these studies did not present their data in a way that illustrates the number of individuals meeting a designated level of recovery, they do demonstrate significant and meaningful pre- and post-treatment differences in mean intensity of symptoms. They can be criticized for using a relatively low maximum dose of amitriptyline, choosing a TCA with excessive side effects and without definitive therapeutic blood levels, and not measuring platelet enzyme inhibition (although the dose of phenelzine they used is relatively more adequate than that of amitryptyline). For these reasons generalizability of results is limited. In conclusion, however, it has been impossible to define consistent differences in response to MAOI and TCA when both are used inadequate dosage. There is now substantial evidence that MAOI are effective in endogenous depression.[10] We would recommend an initial medication trial with TCA in this group. MAOI remain an effective second line of treatment in those patients that fail to respond.

A. Atypical Depression

Studies of MAOI effectiveness in atypical depression have provided the predominant initial and persisting enthusiasm for these drugs. These patients have been thought to receive a preferential benefit from MAOI greater than that afforded by TCA. Since the initial report by West and Dally in 1959,[3] research groups have defined this group in a confusing multiplicity of ways, and variously labeled them neurotic, phobic-anxious, nonendogenous, hysteroid dysphoric, subacute, etc.

Defining subtypes of atypical depression remains a very controversial issue,[5,8,28,29] DSM III even chose not to use the term atypical in this historic sense but retained it only as a residual category.[22] For the purposes of the present discussion, we should like to endorse the separation of atypical depressions used by Davidson et al.[5] into two subtypes: that accompanied by prominent anxiety and depression characterized by reversal of vegetative symptoms (overeating, oversleeping, worsening of symptoms in the evening). We feel that the atypical population described in past studies basically fit one or the other category. In those studies, MAOI has consistently been significantly better than placebo and at least equivalent (sometimes superior) to TCA.[10]

A question remains as to whether these patients should be approached differently from the general approach to the moderately depressed outpatient. There we recommended use of MAOI after a trial of TCA failed to provide adequate improvement. There is no doubt that MAOI are efficacious drugs.[10] However, is there some way to describe the patient for whom the initial drug of choice is MAOI? In this regard we find that the most recent studies have failed to demonstrate *consistent* superiority of MAOI over TCA for any specific constellation of symptoms.[26-31]

B. Predictors of Response to MAOI

We will include a list of those symptoms that various authors have found to predict MAOI responsiveness, so that the reader will appreciate the tempting, but thus far elusive, historic thread of commonality. However, we believe that all we can say, like Quitkin, Rifkin, and Klein,[11] is that the patients (1) lacking typical vegetative disturbance and (2) retaining reactivity of mood should be considered for an initial treatment with MAOI. If in addition they seem to display some of these other symptoms to be mentioned, then the case for MAOI is even more compelling. In the end, until more reliable biochemical or phenomenological predictors are developed, and in the absence of past personal or family history of response to MAOI, the clinician will have to be guided by his overall impression of the patient. Additionally, in making the decision to use MAOI he must consider also the patient's reliability in observing the necessary diet and medication restrictions.

The first suggestion that atypical depressives responded best to MAOI was a series of studies by Sargant[2] and his colleagues West and Dally.[3] They pointed to evening worsening (reversed diurnal variation), initial insomnia, hysterical symptoms, tremor, fatigue, anxiety, and absence of impaired premorbid personality as predictors of response to MAOI.

Robinson et al.[15] developed a diagnostic index with relative positive and negative weighting of endogenous and nonendogenous symptoms, respectively. Highest positive items thought to correlate with endogenous depression were suicidal ideation, weight loss, depressed mood, agitation, psychomotor retardation, guilt, delusions, loss of insight, and depersonalization. Highest negative items correlated with atypical depression were psychic anxiety, somatic anxiety, initial insomnia, somatic complaints, communication of suicide attempts, weight gain, having suffered a personal loss, longstanding phobia, self-pity, and hysterical personality. High negative scores implied atypical depression while high positive scores were more indicative of endogenous depression. They observed a significant correlation of negative items with responsiveness to MAOI when contrasted with endogenous patients with high

positive scores. However, more recent studies have failed to duplicate the suggestion of preferential response to MAOI greater than TCA.[25,26]

Giller et al.[13] found that those patients who responded best to isocarboxazid had mild to moderate severity of depression and measurable anxiety and somatic complaints. Similarly, Raft et al.[14] found a marked response to phenelzine in a pain clinic population who also met criteria for major depression. This too is consistent with the association of somatic complaints and MAOI responsivity.

Liebowitz and Klein and colleagues[7] have defined an atypical depression syndrome they call "hysteroid dysphoria." These patients are characterized by traits of rejection sensitivity (leading to frequent brief depressive episodes), self-esteem dependent on external approval, hystrionic and narcissistic personality features, impulsivity, and substance abuse. Prominent symptoms during episodes of depression include responsivity of depressed mood, overeating, oversleeping, social withdrawal, and fatigue. These patients are often normally expansive, find praise stimulating, and enjoy (and may abuse) stimulants. Liebowitz and Klein describe a positive response to MAOI, in these patients, and note that sedating TCA often makes these patients worse. (They advise use of an activating TCA like desipramine if that class of drug is prescribed.)

C. Anxiety Disorders

The early British studies[2,3] did not clearly distinguish primary anxiety disorder with depressed features from primary depression. Rather than view the symptoms as forming a single syndrome of phobic-anxious-depression, it would be more precise to divide them into separate disorders. Recent studies have demonstrated an efficacy of MAOI in panic disorder equal to or superior to TCA.[32-34] Moreover, in a sample of patients with panic disorder, extensive secondary psychopathology is found: agoraphobia and other phobic symptoms, depression, psychosomatic complaints, and obsessive-compulsive traits. The coexistence of such symptoms illustrates the ease with which prior studies probably contaminated their atypical depressed populations with endogenous anxiety syndromes.

MAOI, like TCA, treats the panic disorder directly. Often patients will subsequently have to deal with residual phobic and avoidant behavior. Depressive and somatic symptoms are more likely to spontaneously disappear after MAOI or TCA. In this regard, Sheehan et al.[33] have noted a slight preference for MAOI over TCA in energizing patients to resume normal living. An additional advantage for the use of MAOI is the lack of sensitivity to extremely low dosages, as is sometimes seen in these patients with imipramine. On prescribing MAOI for panic disorder, full antidepressant dosage usually must be employed.

D. Other Conditions

Ashford and Ford[35] treated a small sample of depressed elderly patients with trenylcypramine 20 to 30 mg/day or phenelzine 30 to 60 mg/day. They found a high success rate, especially in those patients with associated dementia. They found the MAOIs to be well tolerated and suggested an advantage over TCA with less side effects and potential use in the face of cardiac conduction abnormalities. They advise caution with concomitant use of neuroleptics as they observed several cases of movement disorder.

Walsh et al.[36] report six cases of patients with bulimia and atypical depression who responded dramtically to MAOI. While their findings are consistent with the effectiveness of MAOI in atypical depression; e.g., hysteroid dysphoria, they suggest a possible benefit for bulimia in the absence of depression as well.

The findings of Wyatt et al.[37] in demonstrating nearly total suppression of REM sleep with MAOI suggests a benefit for these medications in the treatment of narcolepsy. Furthermore, REM sleep deprivation itself seems to have some benefit in treating depression.

Finally, MAOI can be used in place of TCA in other conditions where antidepressants

Table 1
INDICATIONS FOR MAOI

1. Endogenous depression, not responsive to TCA and TCA plus adjuncts (T_3, Ritalin®, tryptophan, etc.)
2. Atypical depression:
   a. Negative neuroendocrine testing
   b. Anxiety or somatic symptoms present
   c. Lack of vegetative symptoms
3. Bipolar depression
4. Subsyndromes of borderline personality disorder: subaffective dysthymia, hysteroid dysphoria
5. Panic disorder
6. Narcolepsy
7. Other:
   a. Schizoaffective with neuroleptics
   b. Depression associated with schizophrenia
   c. Residual depressive disorders not responsive to TCA

are indicated; e.g., schizoaffective disorder or delusonal depression in conjunction with neuroleptics. At this time, no particular advantage has been described for MAOI in these conditions.

Table 1 lists the conditions for which MAOI are indicated and the accompanying flow chart (Figure 2) describes the evaluation process leading to the determination of the diagnostic categories. The first step in the assessment of a patient presenting with symptoms of depressed mood is to rule out a primary medical condition or primary anxiety disorder. If a primary depression is present, the next step is to distinguish a major depressive episode from one of the subacute chronic conditions. Major depressive episode could then be characterized as bipolar or unipolar. If unipolar, it would be further defined as endogenous (with melancholia) or atypical. Those diagnostic categories with numbers are treatable with MAOI, and correspond to the numbered indications for MAOI in Table 1.

IV. TREATMENT CONSIDERATIONS

A number of research groups have demonstrated a clear-cut correlation of degree of MAO inhibition (as measured in platelet assays) and therapeutic response to MAOI. In retrospect, many of the early studies in the literature used dosages which are generally inadequate for inhibiting MAO in brain. This fact may be responsible for equal or less efficacy than TCA as reported in the older literature. As noted by Raft, Davidson,et al.,[14] animal and human studies indicate that 85% inhibition of brain MAO is required for significant changes in monoamine activity.

Ravaris et al.,[30] compared phenelzine treatment doses of 60 and 30 mg/day. They found 60 mg provided a mean platelet MAO inhibition of 83% and response rate of 10/14 (70%) of patients definitely improved. Phenelzine (30 mg/day) had a mean platelet MAO inhibition of 59% and was no better than placebo. When inadequate doses are used with low platelet MAO inhibition, the risks patients are exposed to are much greater than the potential benefit of the medication. Similarly Raft, Davidson et al.[14] treated patients with 90 mg phenelzine and found that after 4 weeks on this dosage, average platelet MAO inhibition was 85% and clinical response was significantly greater than placebo. Moreover, after 5 weeks, the MAO inhibition averaged 92% and MAOI-treated patients demonstrated a superior response compared to those receiving amitriptyline as well. Finally, Robinson et al.[9] note that, on a regimen of 60 mg/day of phenelzine, those patients with platelet inhibition greater than 80% at week four had significantly greater improvement in measures of depression from those with lower platelet MAO inhibition.

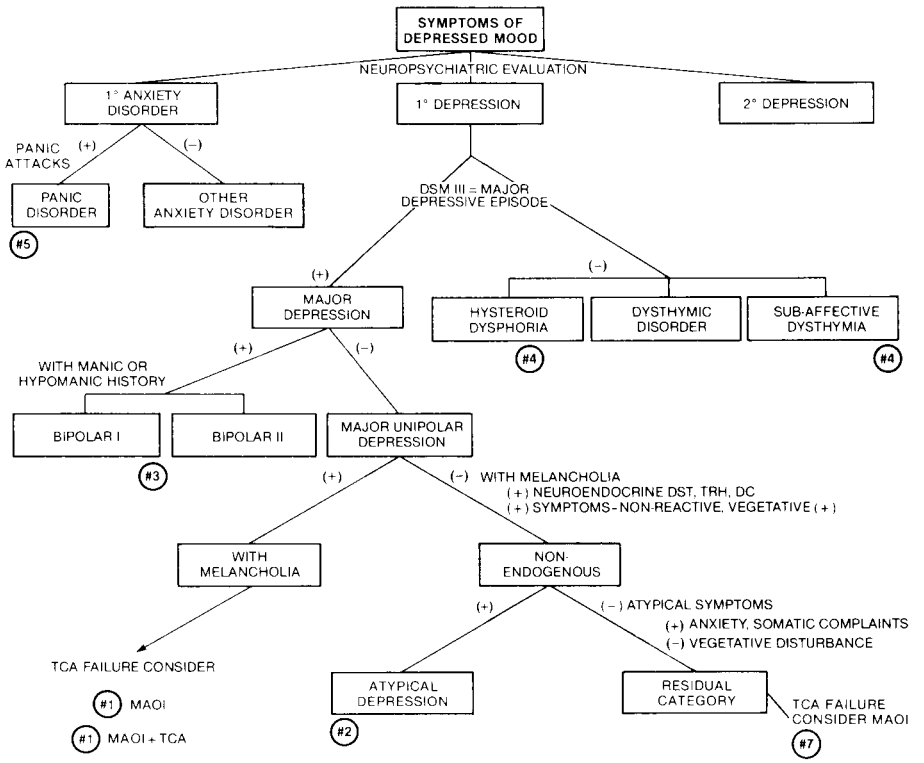


FIGURE 2. Flow chart for use of monoamine oxidase inhibitors (see Table 1 and text).

With tranylcypromine, the relationship of degree of MAO inhibition and clinical response is more complex, because platelet enzyme inhibition seems to precede clinical response (this is also seen with some of the newer experimental MAOIs). Moreover, the clinically determined effective dose is 20 to 50 mg/day, which is higher than that causing 80 to 90% platelet inhibition. The same is true for isocarboxazid; Giller et al.[13] demonstrated an average 88% platelet MAO inhibition by the end of week one, but significant improvement in depression not occurring until week three. Overall, 92% of patients receiving isocarboxazid improved, while only 27% of the patients on placebo improved.

Wyatt et al.[37] and Dunleavy and Oswald[38] correlated mood response with abolition of REM sleep in patients taking phenelzine. Doses of 75 and 90 mg/day abolished REM sleep in about 8 days; a 60-mg dose had a 16-day delay.[38] Elevation of mood seemed to begin about 2 days before abolition of REM sleep, but at a point when REM had already decreased to less than 5% of total sleep. Thus the delay to beginning of mood response was 1 to 2 weeks, and response reached a plateau after an additional week.

There is some inconsistency in the findings as to duration of time needed to attain adequate platelet MAO inhibition. Raft et al.[14] noted a 4-week delay while Ravaris et al.[30] and Dunleavy and Oswald[38] suggest a 2-week period. Moreover the work of Dunleavy and Oswald[38] suggests there is no additional lag in brain MAO response, at least as measured by REM suppression from demonstrated enzyme inhibition in platelets. The time course of clinical response seems to parallel MAO inhibition. Robinson et al.[9] note that, at 2 weeks, 60% of the ultimate improvement is attained.

A. Prescribing MAOI

Some authors suggest a dosage of 1 mg/kg phenelzine or approximately 60 mg/day as a

Table 2
MAOI PRETREATMENT EVALUATION

1. Pre-drug history and physical with attention to the following:
   a. Hepatic involvement; e.g., hepatitis, cirrhosis (avoid hydrazine class)
   b. Cardiovascular status: tolerance of hypotension, interaction with medications (digoxin, anticoagulants, antihypertensives); (MAOI preferred over TCA in first degree heart block)
   c. Renal function and dose adjustment
   d. Contraindicated conditions: pheochromocytoma, carcinoid, active asthma, impaired cardiac output
   e. Possible interactions with other current medications and potential treatments for existing conditions (Parkinsonism, diabetes mellitus, thyroid disorder, seizure disorder, chronic respiratory disease)
2. Laboratory studies:
   a. UA, CBC, blood chemistry (SMA22), ECG, thyroid function
3. Baseline platelet MAO

Note: Adapted from Sheehan et al.[66]

rough guide to adequate treatment. Yet, in a report by Robinson et al.,[15] over 25% of the patients treated with 60 mg/day (13/49) had inadequate platelet enzyme inhibition (less than 80%) and inferior clinical response. Thus, the use of the laboratory in monitoring degree of platelet inhibition provides a critical increase in attaining proper dosage schedules for the individual patient, and assurance that risk to benefit ratio is in order.

We recommend measuring baseline platelet MAO activity as part of the pretreatment evaluation in all patients to receive MAOI. In addition, the work up should attend to preexisting conditions that would be affected by the medication (see Table 2). We then prescribe a dose of phenelzine (30 mg/day) to start (see Table 3). Dose can be increased by 15 mg every 5 days to 60 mg/day by the end of the first 2 weeks. At the end of the fourth week (2 weeks at 60 mg/day) platelet enzyme inhibition is again measured and dose adjusted to achieve 85 to 90% inhibition. Patients should remain at the adjusted dose for an additional 2 weeks. If adequate clinical response has not been achieved at that time, dose can be raised an additional 15 mg/week up to 90 mg/day. Caution should be taken not to exceed 95% platelet inhibition as that raises the probability of hazardous drug and food interactions. (In particular, there have been reports of adverse interactions with L-tryptophan in patients taking very high doses of MAOI; yet the addition of tryptophan to MAOI is a recognized, effective adjunct in partial responders).

If phenelzine provides a partial response only, or if there is oversedation, a trial of tranylcypromine may be useful. There are many reports of patients responding to one but not another MAOI, and, when tranylcypromine was temporarily taken off the market, a number of responders relapsed and did not respond to phenelzine[10] (although dosage may have been inadequate). Tranylcypromine often has a more activating effect (it is structurally related to amphetamine). We recommend starting with a dose of 10 mg bid (both doses given before 12 noon). Dosage can be raised by 10 mg/week up to 50 to 60 mg/day. At these higher dosages, we recommend measuring platelet enzyme inhibition to avoid 100% enzyme inhibition and increased risk of diet and drug interactions. When switching from phenelzine to tranylcypromine, it is very important that a 2- to 3-week medication-free period be observed to prevent serious hypertensive interactions. In switching from TCA to MAOI, a 1-week medication-free period is sufficient.

B. Acetylator Status

Acetylator status has been suggested as a possible factor in the differential response of patients to phenelzine. As other hydrazine compounds are found to be metabolized by liver acetylation, this has been assumed to be the metabolic route for phenelzine (although there

Table 3
MAOI PRESCRIBING INSTRUCTIONS

1. Start with phenelzine 15 mg bid
2. Increase by 15 mg/day every 5 days to total dose of 60 mg/day at end of 2nd week
3. Maintain at 60 mg/day for 2 weeks and measure degree of platelet inhibition
4. Adjust dose to achieve 85 to 90% platelet enzyme inhibition
5. Maintain that dose for additional 2 weeks
6. Dose may be raised by 15 mg/week to 90 mg/day; caution is indicated not to totally inhibit enzyme acivity
7. In partial responders lithium carbonate can be added — start at 300 mg bid and adjust dose to blood level 0.6 to 0.8. Response should be seen within 2 to 3 weeks
8. In partial responders gradually add L-tryptophan — up to 5 g/day (compatible with MAOI + lithium)
9. After 2 weeks if no response, discontinue medication
10. 2-Week period medication free
11. Consider trial of TCA, TCA + MAOI, or tranylcypromine depending on prior drug trials

is controversy, and the presumed metabolite has never been recovered).[39] When patient populations are tested for rate of acetylation (by giving a test dose of sulfamethazine and measuring the percent that is acetylated), there appears to be a genetically determined bimodal distribution of fast and slow acetylators.[40] It has therefore been hypothesized that slow acetylators would be exposed to higher active drug concentration and would evidence greater therapeutic effects (as well as increased side effects).

A number of studies have shown that not only does acetylator status not correlate with clinical response, it does not even correlate with degree of platelet MAO inhibition.[40,41] It has been shown that effective dose, as measured by platelet MAO inhibition, is by far the most important factor in determining drug response.

We concur with the conclusion of Rose[42] in a recent review of the literature. Of the limited number of published studies, only two found a relationship between acetylator status and therapeutic effect; the other five did not. Furthermore there are a number of shortcomings in all of these studies which therefore leave a definitive answer to this question lacking. Unlike laboratory measurement of platelet MAO activity, determination of acetylator status makes no proven contribution to treatment strategy at this time.

C. Combination Treatments

1. MAOI Plus Tryptophan

A number of studies have indicated that the addition of L-tryptophan, the precursor of serotonin, may enhance the antidepressant effects of MAOI. Theoretically they should potentiate one another as they increase brain serotonin concentrations in different ways.

Coppen et al.[43] found that the addition of high doses of DL-tryptophan (214 mg/kg or about 14 g/day) to tranylcypromine (30 to 50 mg/day) significantly increased clinical response, in a double-blind, placebo-controlled study of an older, endogenously depressed patient group. Glassman and Platman[44] also report a significant benefit in a similar patient population. They combined phenelzine 60 mg/day with 12 to 18 g of DL-tryptophan per day (in three divided doses) or placebo in a double-blind study. In the tryptophan group, 60% had markedly improved outcome, while, in the placebo group, only 20% responded well.

Support for the efficacy of this combined treatment also comes from Gutierrez and Alino[45] who combined (IV) nialamide with tryptophan, in a severely depressed, hospitalized group. They reported a 79% satisfactory response for combination treatment, as contrasted with 53% for MAOI alone. In a more indirect way, Pare[46] and Shopsin et al.[47] provide support for combined treatment. Pare administered tryptophan to a group of patients that had responded to MAOI but had relapsed when dosage was decreased. Of 14 patients, 6 promptly recovered on tryptophan but relapsed again when placebo was substituted. Shopsin et al.[47] noted that addition of small doses of parachlorophenylanine (PCPA), a serotonin synthesis

inhibitor, caused relapse in depressed patients who had responded to tranylcypromine. This adds support to the involvement of serotonin in MAOI antidepressant effects and the expectation that tryptophan, its precursor, should potentiate MAOI treatment.

The studies described above used relatively high doses of tryptophan and did report significant side effects. In Pare's study,[46] 6 of 14 patients had to discontinue the combination. Side effects included drowsiness, feeling drunk, nausea, muscle twitching, and dizziness. While the equivalent of up to 9 g (in divided doses) L-tryptophan has been used, we would recommend addition of tryptophan gradually and in smaller amounts (start with 500 mg bid) to partial responders. Care must be taken, however, because there are isolated reports of serious side effects when high degree of MAO inhibition is present. We would recommend an upper limit of 5 g L-tryptophan per day.

2. MAOI Plus Lithium

Most clinical experience with MAOI suggests an incidence of inducing manic or hypomanic episodes similar to that seen with TCA. In approximately 10% to 15% of patients with depression and in 35 to 60% of patients with bipolar illness, either antidepressant can precipitate a switch to mania.[48,49] Recently it has been suggested by Potter et al.[50] that low doses of clorgyline, a selection MAOA inhibitor, have beneficial effects on previously intractable bipolar illness. It was used alone or in combination with lithium. Similarly Quitkin et al.[51] and Himmelhoch et al.[52] report successful treatment of a number of bipolar depressed patients that had been resistant to TCA, with usual therapeutic doses of phenelzine or relatively low doses of tranylcypromine. Himmelhoch et al.[52] report nearly 20% induced paranoid/manic state. At this time we would suggest cautious use of either TCA or MAOI in bipolar depression that is resistant to lithium alone. The antidepressant should be added to the lithium, relatively lower doses should be tried first, and it should be tapered as soon as mood improvement occurs. It should also be noted that induction of mania or rapid cycling can occur, even after the MAOI has been discontinued.

In unipolar depression, Zall[53] and Nelson and Byck[54] report several case studies where lithium plus isocarboxazid and phenelzine, respectively, provided marked improvement. Nelson and Byck[54] further assert that the sequence of medications is important. They found that addition of lithium to phenelzine caused a very rapid response (within a few days after lithium was started) which was thought to involve some priming effect of the MAOI (and not simply an additive effect of the antidepressant activity of lithium). They suggest that lithium is acting presynaptically in a synergistic fashion, similar to the effect postulated in combination with TCA, which cause postsynaptic serotonin supersensitivity.

3. MAOI Plus TCA

Amid all of the controversy surrounding the dangers of MAOI treatment, the most extreme warning (and prohibition) has been reserved for combined treatment with tricyclic antidepresants. In part, there has been hesitation to combine two medications which each have significant potential for toxicity; it is also a reaction to anecdotal reports of serious interactions. As closer analysis of the involved cases and more sophisticated understanding of the mechanisms of action of the medications have been forwarded, prudent clinicians have concluded that the alarm is unwarranted. Recently, a review by White and Simpson[55] noted that in all the thousands of trials of combined MAOI-TCA treatment there has *never* been a serious drug interaction when they were prescribed in a safe manner. The severe toxic reactions have followed either addition of TCA to a preexisting MAOI regimen, use of parenteral route, overdosage, or accompanying diet and drug indiscretion. The latter two reactions would be seen with improper use of MAOI alone, and it is well recognized that overdosage with either drug alone is extremely serious. Thus there seems to be no significant additive danger in properly using combined treatment. Moreover in well-controlled as well

as retrospective studies of combined treatment, the side effects noted are generally only slightly more severe than those associated with either drug alone. (There is actually a theoretical and demonstrated advantage of combination treatment in lessening the adverse sympathomimetic-MAOI interaction.)[56]

The consensus of experienced clinicians is that combination treatment is safest if the following protocol is adhered to.[55] The patient should be free from either medication for 2 weeks. Both medications are then started simultaneously, at a low dose. For example, the TCA would be started at an equivalent of 25 mg amitriptyline h.s. and the MAOI started the next morning at 15 mg for phenelzine (10 mg for tranylcypromine or isocarboxazid). Every week the dose of each would be raised by an additional tablet; thus on day eight, 50 mg TCA would be given at h.s. and on day nine, 15 mg phenelzine at a.m. and noon. The total dose of TCA can be given h.s.; the dose of MAOI should be split during the morning (to avoid insomnia). Dosage can be raised weekly in this fashion to three pills MAOI, three pills TCA at which time 2 weeks should be permitted to elapse, to observe the patient for beneficial response. (Frequently, lower dosages are effective in combination treatment.)

If the patient has still not responded, the TCA could be increased by one additional tablet per week. Currently, dose equivalents of 45 mg phenelzine and 75 to 150 mg TCA (amitriptyline) have been recommended as therapeutic doses. If the patient still has not responded, consideration should be given to further increases. In particular, one might seek to attain 85% platelet MAO inhibition while avoiding severe suppression of the enzyme (greater than 95%) and the use of the laboratory would be particularly helpful in this case.

There are some reports that, in combination treatment, amitriptyline and triimipramine have relatively greater safety among TCA, and imipramine less; phenelzine and isocarboxazid are thought to be safer than tranylcypromine. However, it must be stressed that the schedule and route of drug administration is infinitely more important than the specific agent used. Further, it should be reiterated that the evidence for the above folk wisdom comes from drug interactions observed when they were not prescribed in the recommended manner, and from megadose animal experiments. Their relevance for recommended usage is limited.

The indications for use of combined treatment at this time are basically for patients refractory to a single drug. It has been more difficult to define a group of patients where combined treatment might be indicated as less than treatment of last resort or better than ECT. We would recommend TCA-MAOI combination for endogenous depressives after trials of two different classes of TCA, TCA + T_3, TCA + Ritalin®, a subsequent trial of MAOI alone, MAOI + lithium or MAOI + tryptophan, and who refused ECT or in whom ECT failed.

Gander[57] reported an open study of 90 patients treated with combined therapy after prior treatments had had minimal benefit. A significant percent of patients (62/83) who tolerated treatment greatly improved. Equally important, there appeared to be an equal number of side effects reported as with prior, single-medication treatments, and they were managed by adjusting dosage. Depressive features associated with recovery were weight loss and anorexia, anxiety, and somatic complaints. Dosage used was up to 45 mg phenelzine + 150 mg amitriptyline. None of the serious side effects now recognized as due to overdose or improper dosing schedule were observed. However, weight gain was much more pronounced in combined treatment.

Davidson et al.[58] compared ECT with the combination treatment phenelzine + amitriptyline in a small population with history of prior unresponsiveness to adequate single-medication trial. They report that the dosage tolerated was, in fact, limited by side effects. They found ECT to be significantly superior. However they don't clearly describe their patient population and frequently were forced to use inadequate doses of medication (average dose amitriptyline 71 mg/day, phenelzine 34 mg/day). Schuckit et al.,[59] in a review of the literature, and Spiker and Pugh,[60] in a chart review, found a similar incidence and severity

of side effects in combined treatment as in single-drug treatment. Winston[61] described results in 20 previously refractory patients treated from a practice of 273 new patients. Two thirds showed considerable or marked improvement on combination treatment even though he used low doses in a different schedule from that recommended. He suggests possible benefit as follow-up maintenance for relapsing patients that had responded to ECT. He also notes that a transient response to one drug predicted those patients that went on to respond to the combination.

Sethna[62] successfully treated with MAOI-TCA a group of patients that had failed to respond to single-drug treatments or quickly relapsed with ECT. In general, the responsive patients demonstrated anxiety and lacked the endogenous vegetative symptom patterns. They also had a chronic course with frequent exacerbations; none had experienced complete symptom-free intervals. Additionally the group had striking incidence of personality disorders. While there was no control population, patients did serve as their own controls in that they had failed in prior treatments. This is suggestive, because this chronic group of patients has been most refractory to single treatments, including ECT; it is a group where combined treatment might prove more efficacious than ECT. Follow-up was a mean of 16 months and the description of improvements was impressive; 9/12 were considered nearly free of depression symptoms. Side effects again were reported as no greater than for either medication alone. Parasthesias and mouth ulcers were found in nearly half the cases, but were mild. Toxic psychokinetic reaction was seen in two cases and has been reported with MAOI alone.[63] It is different from hypomania in that it involves an excited state without mood elevation, has a toxic, confusional quality, and promptly responds to discontinuation of medication. Weight gain was also noted and was worse with combined treatment.

White et al.[64] reported a prospective study comparing (a) amitriptyline up to 300 mg with (b) tranylcypromine up to 40 mg and (c) combination (up to 150 mg and 20 mg, respectively) of amitriptyline + tranylcypromine for 4-week treatment. They report equal improvement across groups in a hospitalized patient population, meeting RCD criteria for major or minor depression. Combination treatment is noted to only have had an increase in minor side effects without any additional cases needing to discontinue treatment.

In sum, these controlled studies and open trials have suggested that a significant number of refractory patients that have failed on single medication trials are responsive to combined MAOI-TCA treatment. There is a suggestion that nonendogenous symptoms and prominent anxiety distinguish the responsive group. As White and Simpson[55] note, given the fact that it has been so difficult to describe a subgroup that responds preferentially to MAOI over TCA and the longstanding hesitancy to use combined treatment, it is unlikely that a subgroup defined by shared symptoms will be demonstrated to preferentially respond to combined treatment. Perhaps more important is the fact that there are now recorded thousands of cases where combined treatment, prescribed in the forementioned prudent fashion, has had no serious side effects. It should certainly be considered for refractory patients.

D. MAOI Side Effects

Adverse effects suffered by patients taking MAOI fall into two categories; those resulting from interactions with other ingested foodstuffs and medications, and those associated with use of the drug itself. The former has been the source of the reputation for extreme dangerousness that this class of antidepressants has undeservedly suffered, and we will discuss that first.

The hypertensive reaction that follows interaction with certain compounds is now understood to be mediated by the increased activity of biogenic amines that escape degradation due to inhibition of MAO throughout the body. The most severe reactions are found in interaction with the indirect acting sympathomimetics, e.g., tyramine, amphetamine, and pseudephedrine. When ingested, they also escape metabolism by MAO normally present,

Table 4
DIETARY INSTRUCTIONS FOR PATIENTS TAKING MAOI

Follow these instructions for 2 weeks after stopping medication

Foods and beverages which *must be avoided*:

1. All matured or aged cheese — for example blue, cheddar, Swiss, parmesan, mozzarella,, American, and other processed or hard cheeses; popular foods like pizza, fondues, many Italian dishes, and salad dressings are prohibited. (Only cottage cheese, farmer cheese and cream cheese are permitted).
2. All fermented, aged, and tenderized meats, fish and poultry — these include sausages, bologna, salami, pepperoni, corned beef, and pastrami; game meats; any meat that is not fresh, freshly canned, or freshly frozen (left overs). It also includes pickled herring, smoked fish (e.g. lox), and dried salted fish.
3. Liver — beef or chicken or pork; liverwurst, liver paté.
4. Broad bean pods — e.g. Chinese pea pods, Italian green beans, fava beans.
5. Yeast or meat extracts — for example, Brewer's yeast vitamin supplement and Bovril and Marmite, especially when consumed as a drink. (Use of yeast in baked products is safe).
6. All wine, except white wine. Red wine (Chianti in particular), rosé, sherry, vermouth, and champagne are prohibited.
7. All beer and ale.

Foods which may be used in moderation; some individuals may be sensitive to large amounts:

1. Caffeine-containing beverages: coffee, tea, cola.
2. Sour cream and yogurt may be eaten in moderation only if produced by a reliable manufacturer.
3. Bananas, avocado, figs; (cooked banana skins must be avoided).
4. Soy sauce, MSG.
5. Alcohol; dangerous because of additive effects in producing intoxication; distilled liquors (vodka, gin, rye, scotch, and white wine are permitted in very small quantities.
6. Chocolate.

Note: Adapted from Klein et al.[10] and McCabe and Tsuang.[12]

but now inhibited, in the small gut, liver, and elsewhere throughout the body. These stimulants release the increased cellular amine concentrations (norepinephrine and epinephrine) from adrenal medulla and other peripheral nerve endings. The transmitters then act directly on the receptors mediating blood pressure regulation to cause the hypertensive reaction.

In advising patients regarding the foods and medications that must be avoided, a mixture of clarity and caution is most important. We advise the use of a printed set of instructions (examples of which are included in Tables 4 and 5). It is reviewed with the patient in the office and the patient is then advised to carry it at all times. It is helpful to discuss with the patient his normal eating habits, to pinpoint the potentially offending foods requiring attention.[12] He should be told that the responsible substance is tyramine, an amino acid, which increases in concentration in foodstuffs as a result of aging and fermentation. In this way the reasons underlying the prohibition of certain categories of foods can be better understood. One should then explicitly note that cheeses, aged or treated meats and fish, and wines are prohibited. Separately, the residual foods of liver, broad beans, yeast extract, and overripe fruit should be noted as additional items that must be avoided. We find that organizing the foods into a limited number of categories and liberally discussing examples within each group provides the patients with a better understanding of the rules and avoids overwhelming them with a long, meaningless list. One should then note that certain additional foods are to be taken with caution and in moderation; in response to this latter group of substances individual variations in sensitivity exist. It is useful to explain to patients that lack of reaction to one of the prohibited foods (either taken by accident or as a test) is not evidence that it is safe for them. Differences in food preparation and gastric emptying can fortuitously cause minimal response on one occasion, only to be followed at a later time by hypertensive crisis.

Table 5
MEDICATION INSTRUCTIONS FOR PATIENTS TAKING MAOI

Do not take any medicines or nonprescription drugs, without first contacting your doctor.

Medications which *must be avoided*:

1. Cold medications — Nasal decongestants, sinus medicine (tablets, drops or spray) and cough suppressants (dextromethorphan). Aspirin, acetaminophen, guaifenesin, and menthol lozenges are safe).
2. Hay fever and allergy medication.
3. Anti-asthmatic sympathomimetic medications (including inhalants). (Pure steroid inhalants like beclomethasone (Vanceril®) are safe).
4. Narcotic Analgesics — Meperidine (Demerol®) in particular is of special danger. (Nonsteroidal anti-inflammatory agents are safe).
5. Anti-appetite medications — Amphetamine is particularly dangerous; pep pills, phenylpropranolamine in OTC preparations.
6. Other anti-depressants (MAOI may be used with TCA only when prescribed in the specific sequence as described in text).
7. Illicit drugs — cocaine and amphetamine are particularly dangerous; LSD; PCP.
8. L-Dopa (for Parkinsonism).
9. Anti-hypertensives — Methyldopa (Aldomet®), guanethidine, reserpine.
10. Local anesthesia containing epinephrine (as in dental work or "stitches"). (Lidocaine (Xylocaine®) and procaine (Novocain®) are safe when used alone).
11. Spinal anesthesia.

Medications that may be used with caution, if necessary:

1. URI — terpin hydrate with codeine.
2. Allergy — antihistamines; e.g., chlorpheniramine.
3. Antihypertensive — propranolol, hydralazine.
4. Narcotic analgesic — morphine and codeine.
5. Sedative hypnotics.

Medications that may need dose decreased:

1. Insulin and oral hypoglycemics.
2. Oral anticoagulants.
3. Thiazide diuretics.
4. Anticholinergic (anti-parkinson) agents.
5. Muscle relaxants, succinylcholine.

Note: Adapted from Klein et. al.[10] and Gelenberg.[65]

E. MAOI-Drug Interactions

In reviewing the medications to be avoided, we advise the patient not to take anything (except aspirin or acetaminophen and antibiotics) without first contacting us. In addition, it is stressed that he must take the initiative in telling any other physician or dentist he may consult of his use of MAOI. We note that this prohibition includes over-the-counter (e.g., diet aids) and illicit drugs; we specifically draw attention to cold and anti-appetite medications, amphetamine, and cocaine as particularly hazardous. We will carefully review treatments for any existing medical conditions and discuss alternatives in their regimen. A medic alert bracelet is a consideration for additional safety.

The indications of the hypertensive reaction can be described as a clearly identifiable, severe, throbbing headache, usually occipital with sudden onset. It is frequently accompanied by palpitations, tachycardia, sweating, nausea, and vomiting. The patient will often experience fright, stiff neck, pallor, and chills. The reaction may begin within minutes after ingestion of tyramine or after a delay of a couple of hours. The patient should be advised to go immediately to an emergency room for evaluation and treatment. He should be warned not to lie down for relief as this may further increase the blood pressure. We agree with Sheehan et al.[66] that it is hazardous to instruct patients to carry chlorpromazine or phento-

lamine and to take it in case of attack; anxious patients may misinterpret a hypotensive reaction as the hypertensive reaction and dangerously further lower blood pressure. It is also prudent to discontinue MAOI if a patient should plan an extended trip to an area lacking medical facilities. Emergency medical treatment consists of administering either a vasodilator; e.g., diazoxide or nitroprusside, or the alpha adrenergic blockers phentolamine, or chlorpromazine. If cardiac arrhythmias should occur, propranolol is recommended but can only be used *after* alpha adrenergic blockade.[68] Diuretic (e.g., furosemide slowly, IV) should also be added to decrease fluid retention.[66]

MAOI interactions with other medications fall into two main categories: more dangerous synergistic syndromes and simple potentiation of primary effects. The following medications are *prohibited:*

1. Indirect-acting sympathomimetics like amphetamine, Ritalin®, and phenylephrine — they will cause hypertensive crisis. Patients with residual attention deficit disorder, weight reduction programs, or URI congestion will need special consideration. Antihistamines are safe.[65]
2. Other MAOI simultaneously — furazolidone, an antibacterial, is an MAOI.[67] When switchingfrom one MAOI to another, one must observe a 2-week, medication-free interval, and still remain cautious. Hypertensive reaction to a sympathomimetic drug has been reported 2 weeks after discontinuing phenelzine.[69]
3. Simple addition of tricyclic antidepressant or switching to TCA — a 2-week interval must also be observed. Combination treatment with MAOI-TCA is safe if the two medications are started simultaneously at low dose and gradually increased together. Carbamazepine may have similar dangerous effects due to structural resemblance to TCA.[67]
4. Precursors of biogenic amines: L-dopa, 5 hydroxytryptophan, tryptophan — they can lead to malignant hypertension or hyperpyrexic syndromes, if degree of MAO inhibition is excessive (greater than 95%) and if used in high dosage (e.g., L-tryptophan greater than 7 g). Combination of L-tryptophan and MAOI has been found to be a useful combination in partial responders to MAOI alone (see text).
5. Meperidine (Demerol®) and dextromethorphan have been known to produce a dangerous syndrome with "excitement, agitation, hypertension, restlessness, rigidity, headache, hyperpyrexia, and convulsions."[70] It is thought to be due to excessive serotonergic activity, and treatment should include IV steroids, alpha blockers (phentolamine), and cooling.[70]
6. The antihypertensives guanthedine, alpha methyl dopa, and reserpine[65,70] are contraindicated as they may cause serious excitation and hypertension in combination with MAOI. Propranalol has also been associated with this effect;[70] although other authors report it as safe,[65] we recommend avoidance.

The second group of medications to be described should be used with caution because their effects will be potentiated.

1. Narcotic analgesics — morphine and codeine may be used safely but should be administered in approximately one quarter the usual dosage.[66,70] Hypotension, respiratory depression, and coma are possible due to inhibition of hepatic enzymes responsible for metabolism.
2. Sedative hypnotics such as barbiturates and chloral hydrate will be potentiated. Effects on benzodiazepines may be similar.[70]
3. With inhalant anesthetic agents, increased caution is necessary in the management of intra-operative hypotension. Fluids, plasma expanders, and corticosteroids are recommended,[65,66] although direct-acting sympathomimetics are less dangerous than the

indirect-acting agents (which are prohibited) because the direct acting compounds (norepinephrine) are degraded by the enzyme COMT (catechol-o-methyl-transferase). However, caution is indicated because there are anecdotal reports of hypertensive reactions, possibly due to denervation supersensitivity.[70] Spinal anesthesia should be avoided.[65]

4. Other antihypertensive agents; hydralazine, diuretics, may be potentiated.[70]
5. Insulin and hypoglycemic agents will have to be regulated (dosage reduced) due to possible additive effects.[66]
6. Neuroleptics may be potentiated but are safe if used moderately.[67]
7. Epinephrine should be avoided in combination with local anesthetics (although there is probably less danger than when used with TCA).[70]
8. Anticholinergic agents will be potentiated[66] with the possibility of organic brain syndrome.
9. Other — digoxin, oral anticoagulants may be potentiated.[70]

F. Overdosage

Overdose with MAOI presents a complicated and very serious situation.[1,66]Lethal dosage represents approximately a 1-week supply of the normal therapeutic dose. Symptoms may appear only after a delay and may be long lasting with the irreversible hydrazine inhibitors; e.g., phenelzine (these patients should be observed in the hospital for 1 week). Prominent symptoms include agitation, hallucinations, hyperreflexia, hyperpyrexia, confusion, and convulsions. Either severe hypotension or hypertension may occur. Gastric emptying by emesis and lavage and dialysis can markedly decrease amount of drug exposure. The potential dangers associated with regulating blood pressure require close monitoring with IV management. Hyperpyrexia must be aggressively addressed with external cooling, antipyretics, and perhaps curarization to reduce heat output from overactive musculature. Other supportive measures (fluids, electrolytes, ventilation) are also necessary. Management may also be complicated by concomitant ingestion of other psychotropic drugs (e.g., TCA) and pressor agents (including prohibited tyramine-containing foodstuffs).

G. Direct MAOI Side Effects

A wide range of side effects attributed to MAOI can be grouped into several categories. Liver toxicity has been associated with the hydrazine class (phenelzine and isocarboxazid; others have been removed from the market due to higher incidences). It takes the form of hepatocellular jaundice; higher susceptibility is seen in carriers of hepatitis virus. Onset presents with rash, nausea, fever, eosinophilia, and enzyme elevation. Incidence is thought to be between 1/3000 and 1/10,000 cases.[10] It is recommended that liver function tests be repeated at 3- to 6-month intervals for surveillance.

A large number of side effects are similar to the anticholinergic side effects seen with TCA. Included are postural hypotension, urinary retention, dry mouth, constipation, loss of visual accommodation, and impaired sexual function.[67,71,72] Usually they can be managed with reassurance, supportive measures, and decreased dosage. If more troublesome, the following interventions may be taken. For orthostatic hypotension, taking medication with meals or the mild pressor effects of caffeine may suffice. Surgical elastic stockings and fludrocortisone acetate (Florinef®) can be used in more difficult cases. Urinary retention and sexual dysfunction have been found to respond to bethanechol.[73] In particular, disorders of ejaculation or orgasm may be treated with bethanechol at bedtime (start with 10 mg and gradually increase the dose). For dry mouth, sugarless gum or candy can be relieving; oral pilocarpine is also effective. Constipation responds to water-retaining or bulk-producing laxatives like Milk of Magnesia® or Metamucil®. Pilocarpine eye drops can be used for visual accommodation problems.

Other complaints without clear etiology include weight gain with carbohydrate craving, muscle twitching (myoclonus)[74] or cramps, tinnitus, sweating, flushing, and chills.[10,66] A peripheral neuropathy has been described which responds to pyridoxine.[66] Hypocalcemia has also been reported.

A number of behavioral effects have been described. Some patients note decreased sleep (often without fatigue) and this may respond to a.m. dosing or switching from tranylcypromine to phenelzine.[66] A disinhibition syndrome has been described[75] and interpreted as increased emotional arousal; on psychological tests increased dim and aggressive responses were found. As previously noted, Ayd[63] has described a toxic psychokinetic reaction that superficially resembles mania. Additionally, hypomania,[48] and manic and paranoid delusions[48,75] can be precipitated or worsened. Finally, tranylcypromine has been found to be a potential drug of abuse.[76,77] One must be particularly cautious with patients who have a prior history of abuse of stimulants.

Cardiovascular side effects are limited to orthostatic hypotension, although decreased heart rate can also be seen with phenelzine.[78,79] There is no inotropic effect and arrhythmias are rare, although tranylcypromine may have direct amphetamine-like effects on the heart. MAOI are preferable to TCA in cases of first-degree heart block.

MAOI are effective antidepressant medications when used properly and with the appropriate laboratory monitoring of platelet MAO inhibition. Although they are not usually a first-line treatment, they may be indicated in certain patients with a prior history or family history of response intolerance of other antidepressants (e.g., cardiac patients or sensitivity to anticholinergic effects). If used with the proper dietary precautions and awareness of drug interactions, they represent an important pharmacologic class of antidepressants.

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Chapter 8

ANTIPSYCHOTICS: PREDICTING RESPONSE/MAXIMIZING EFFICACY

R. Bruce Lydiard, John S. Carman, and Mark S. Gold

TABLE OF CONTENTS

I. INTRODUCTION

Prescribing antipsychotic medication is frequently necessary in the general practice of psychiatry. These agents are remarkably effective in treating various types of psychoses including acute mania, psychotic depression, and organic psychoses. They are the only currently effective pharmacologic treatment available for many of the manifestations of an acute or chronic schizophrenic illness.[1] In addition to understanding who will benefit from antipsychotic medication, it also is important for the practitioner to be aware of potential adverse effects. Concern over the risk of long-term exposure to antipsychotics — especially tardive dyskinesia[2] — has made it increasingly important to minimize the risks and maximize the benefits of antipsychotic medication treatment for each individual patient. It is likewise important to identify those patients for whom medication is not helpful.

This chapter will discuss the use of antipsychotic medication in a general psychiatric practice. Following a brief historical overview and a discussion of the mechanism of action of antipsychotic drugs, the potential clinical and biochemical predictors of response to antipsychotic medication will be reviewed. The current status and use of neuroleptic blood levels as a tool for optimization of antipsychotic medication treatment will be discussed. Finally, guidelines for the use of antipsychotic drugs, a survey of their adverse effects, and drug interactions will be presented.

II. HISTORICAL OVERVIEW

Although the Rauwolfia alkaloids (reserpine) were the earliest effective antipsychotic drugs, it was not until the early 1950s that the true age of chemotherapy for psychosis came into being. Around that time chlorpromazine, a phenothiazine dye derivative with potent antihistaminic properties, was being used to potentiate barbiturate sedation for excited psychotic patients. It was soon noticed that it was quite an effective antipsychotic by itself.[3] Since that time, a number of new phenothiazines and other structurally unrelated compounds have been developed, all of which share the ability to reduce psychotic symptoms. Figures 1-4 show the structures of agents from each of these chemical classes of antipsychotic drugs.

III. MECHANISM OF ACTION

A. Antipsychotics and Dopamine

Despite the structural dissimilarity of the various antipsychotic agents, they share in common the ability to interfere with neuronal functions mediated by the neurotransmitter dopamine (DA). It is now known that these agents all have the capacity to bind DA receptors in the brain, and that their affinity for binding DA receptors roughly parallels their clinical antipsychotic potency.[4,5] Unfortunately, the currently available antipsychotics are not particularly selective in their DA receptor-blocking actions and produce a number of additional unwanted antidopaminergic effects. Table 1 shows the four important sites of action of the antipsychotic drugs. Extrapyramidal symptoms (EPS) are caused by reducing DA activity in the nigrostriatal DA system, resulting in EPS, including the "pseudoparkinsonian" syndrome.[6] After prolonged DA receptor blockade, supersensitive DA receptors may cause dyskinetic movements which are manifested clinically as tardive dyskinesia.[7] The tuberoinfundibular DA system contains neurons with cell bodies in the hypothalamus which release DA into the hypophyseal portal system and tonically inhibit the release of prolactin from the posterior lobe of the pituitary.[8] Tuberoinfundibular DA receptor blockade abolishes the usual inhibitory effect on prolactin secretion and prolactin levels rise. The mesolimbic and mesocortical DA systems are currently thought to be the most important in mediating the antipsychotic effects of DA receptor-blocking drugs.[9] While no currently available antipsychotics are strictly selective for the mesolimbic and mesocortical DA receptors, clozapine, an antipsychotic which is currently being evaluated for clinical use, shows promise in this regard. Unlike most other antipsychotic drugs, it does not appear to cause significant EPS.[10,11] Furthermore, this lack of EPS seems to be due to selective DA receptor binding effects rather than balancing of striatal DA receptor blockade via anticholinergic effects.[12] There is some suggestion that thioridazine may have a similarly selective binding profile which spares the striatal DA system relative to other currently available antipsychotic drugs.[12,13] As more DA-blocking agents are developed, it seems possible that truly selective DA blocking agents could be developed in the future. This would not only mean less discomfort for patients in the form of EPS, but raises the optimistic possibility that such agents may carry a lower risk of producing the long-term, irreversible effect of tardive dyskinesia in those patients who require chronic maintenance treatment.[14]

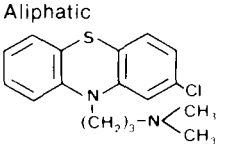
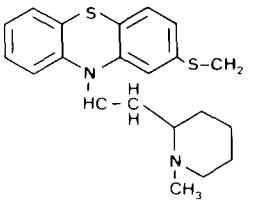
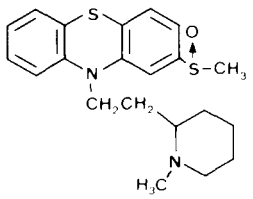
CHEMICAL STRUCTURE	GENERIC NAME	TRADE NAME
PHENOTHIAZINES		
Aliphatic 	Chlorpromazine	Thorazine
Piperidine 	Thioridazine	Mellaril
	Mesoridazine	Serentil

FIGURE 1. Chemical structure of aliphatic and piperdine phenothiazine antipsychotics.

Antipsychotic drugs also bind to a number of other amine receptors — muscarinic, α-adrenergic and histamine (H_1 and H_2) — in the CNS and periphery. These other receptor affects mediate various side effects discussed later in this chapter. It is possible that in the future antipsychotic agents which are selective for *only* DA recptors can be developed, thus reducing other unwanted adverse effects while maintaining antipsychotic efficacy.

B. Antipsychotics and Schizophrenia

As was noted above, antipsychotic drugs probably exert their therapeutic effect via DA receptor blockade. In the 1960s Connell[15] and others[16] observed that amphetamine, a drug with potent DA-releasing properties, could cause psychotic symptoms in normal individuals. The symptoms — thought disorder, auditory hallucinations, and paranoid delusions — were remarkably similar to those observed in schizophrenic illness. Furthermore, these symptoms were quickly abolished by antipsychotic medication.[17] These observations collectively contributed to the "dopamine hypothesis" of schizophrenia.[9] Simply stated, the hypothesis postulates that excessive DA activity underlies schizophrenic illness. It is supported by indirect pharmacologic evidence that agents which cause an increase in dopaminergic activity (i.e., amphetamine, methylphenidate, L-dopa) induce an exacerbation of schizophrenic symptoms, and drugs causing a reduction of dopaminergic activity (i.e., DA receptors blockers, DA release, or synthesis inhibitors) result in a diminution of schizophrenic symptoms. There is considerable evidence to indicate that the DA hypothesis has significant merit as a model for studying psychotic states. However, as with any simplified theory, there are many problems with the DA hypothesis for schizophrenia. It is known, for example, that some schizophrenic patients are quite resistant to the expected worsening after administration of

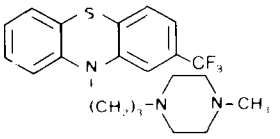
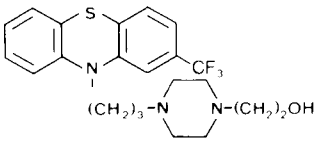
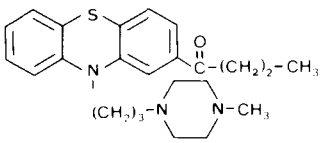
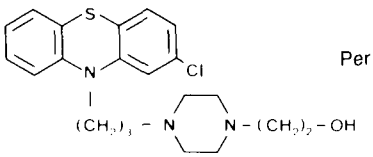
CHEMICAL STRUCTURE	GENERIC NAME	TRADE NAME
PHENOTHIAZINES (continued) Piperazine		
	Trifluoperazine	Stelazine
	Fluphenazine HCl	Prolixin HCl
	Butaperazine	Repoise
	Perphenazine	Trilafon

FIGURE 2. Chemical structure of piperazine antipsychotics.

d-amphetamine.[18,19] Some investigators have even shown an *improvement* in psychosis after amphetamine[19] or L-dopa[20,21] was given to schizophrenic patients. Additionally, some schizophrenic patients either do not respond to antipsychotic medication[22] or become worse[23] after drug treatment. There are no truly antischizophrenic drugs, i.e., no cures for schizophrenia. There are treatments (i.e., antipsychotic drugs) for certain *symptoms of psychosis* which often accompany schizophrenic and other psychoses. While the final common pathway in many schizophrenic and other psychotic illnesses may be an overactive DA system in the brain, there are probably many ways to arrive at that neurochemical state. Numerous etiologies for schizophrenia have been proposed, and include alterations in the function of amine neurotransmitters (DA, norepinephrine, serotonin), CNS peptides (endorphins and others), viral infections, autoimmune disease, production of endogenous psychotogens, and others.[9] Over 40 postulated neurotransmitters and neuromodulators coexist in the CNS and interact in a complex and poorly understood fashion. Schizophrenia is probably a variety of illnesses, which respond symptomatically to antidopaminergic agents much of the time. New research may provide "cures", but for now we are limited to the clinical use of DA receptor blocks with which to treat the spectrum of illnesses called schizophrenia.

C. Pharmacokinetics

Antipsychotic drugs are generally well absorbed after oral administration and may begin to produce clinical effects in 30 to 60 min.[24] Variation in bioavailability from one preparation to another may drastically alter antipsychotic blood levels and may alter the effective dosage a patient receives after switching from one brand to another, especially for chlorpromazine.

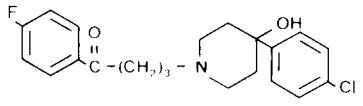
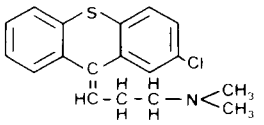
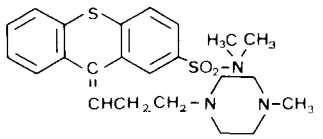
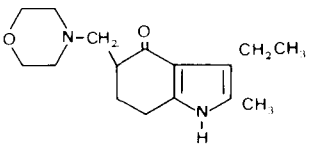
CHEMICAL STRUCTURE	GENERIC NAME	TRADE NAME
BUTYROPHENONES		
	Haloperidol	Haldol
THIOXANTHENES		
	Chlorprothixene	Taractan
	Thiothixene	Navane
DIHYDROINDOLONES		
	Molindone	Moban

FIGURE 3. Chemical structure of butyrophenone, thioxanthene, and dehydroindolone antipsychotics.

Various agents can interfere with intestinal absorption of antipsychotics. Antacids may interfere with absorption when given simultaneously with antipsychotic medication. Anticholinergic agents such as gastric antispasmodic agents (belladona alkaloids), highly anticholinergic tricyclic antidepressants (amitriptyline, imipramine and others), anticholinergic antiparkinson agents such as benztropine (Cogentin®) or trihexyphenidyl (Artane®) can slow intestinal motility and allow gut wall or bacterial metabolism of the drug. Liquid forms are more completely absorbed than tablets or capsules. After intramuscular injection, absorption is much more rapid and is often nearly complete (except for long-lasting depot forms) within 30 min.[25]

Once in the bloodstream, these drugs are 90 to 95% bound to plasma protein, and only the small proportion of unbound drug is pharmacologically active. All antipsychotic drugs are highly lipid soluble, pass the blood-brain barrier easily, and accumulate in brain and other lipid stores, where they may persist for months. After discontinuation of drug, they continue to be slowly released into the bloodstream. Phenothiazines seem to have an affinity for keratin-containing tissues (skin, lens, and cornea) and may accumulate in these tissues after prolonged, high-dose exposure.[26]

Metabolism of antipsychotics occurs primarily via hepatic microsomal oxidation to sulfoxides, glucuronide formation, or hydroxylation.[27] Small amounts are excreted unchanged.

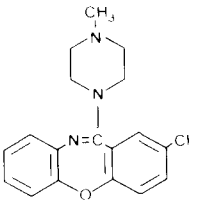
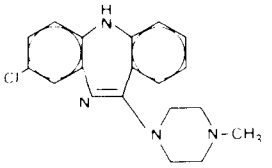
CHEMICAL STRUCTURE	GENERIC NAME	TRADE NAME
DIBENZOXAZEPINES		
	Loxapine	Loxitane
DIBENZODIAZEPINES		
	Clozapine	Not currently marketed for routine clinical use.

FIGURE 4. Chemical structure of dibenzoxazepine and dibenzodiazepine antipsychotics.

Table 1
MAJOR DOPAMINE SYSTEMS IN THE BRAIN

DA System	DA-related Functions	Effects of DA Receptor Blockade
Nigrostriatal	Mediates function of extrapyramidal motor system	Reversible: acute dystonia, pseudoparkinsonism, akathisia Irreversible: tardive dyskinesia (may be reversible if detected early) (except clozapine and thioridazine?)
Hypothalamic-pituitary	Regulates prolactin secretion, temperature, appetite, emesis	Increased prolactin levels → galactorrhea, amenorrhea, decreased libido (and fertility?) Loss of temperature regulation, increased appetite, antiemetic effect (except clozapine and thioridazine?)
Mesolimbic	Regulates stereotypic and ? other behaviors	?Antipsychotic
Mesocortical	Regulates behavior	?Antipsychotic

Excretion of the more polar conversion products is primarily renal, although some are excreted in bile. There is tremendous variability in the degree to which antipsychotics are metabolized. Chlorpromazine has over 100 possible metabolites;[28] in contrast, haloperidol has no important metabolites.[29] Any substance or condition capable of altering hepatic metabolism can alter antipsychotic blood levels. Barbiturates, for example, will induce hepatic metabolism of antipsychotics and lower blood levels. Impaired hepatic function (cirrhosis, hepatitis, aging) will diminish the rate of inactivation, cause decreased metabolism of drug, and increase levels. Agents such as tricyclic antidepressants, which compete with antipsychotics for hepatic metabolism, can raise antipsychotic levels.

IV. EFFICACY OF ANTIPSYCHOTIC DRUGS

A. Acute Treatment

The overall efficacy of antipsychotic drugs for treating the symptoms of acute schizophrenia is well established. One of the most important studies defining antipsychotic efficacy was a large placebo-controlled collaborative study conducted in the mid-1960s by the National Institute of Mental Health.[33-35] In a large group of patients, 75% were much improved after 6 weeks of medication treatment, and only a few drug-treated patients worsened. In the group receiving placebo, 20% improved, but an impressive 50% worsened. Davis[36] noted that these results are comparable to the effectiveness of medication treatment in other medical subspecialties (for example, streptomycin in treating tuberculosis). There is still controversy about the use of psychotherapy vs. medication for acute schizophrenia. May and colleagues[37,38] conducted an interesting series of studies in acute schizophrenic patients for whom various types of therapies were compared. They reported that antipsychotic medication alone was definitely superior to psychotherapy alone in treating acute schizophrenic illness, and that the combination was just slightly better than medication alone. These data support the contention that antipsychotic medication treatment is of utmost importance for treating serious illness like schizophrenia and that psychotherapy may be a helpful adjunct but is clearly not the first-line treatment choice.

B. Maintenance Treatment

Placebo-controlled drug maintenance studies have been conducted in a variety of schizophrenic patient populations in several countries. There is no doubt whatsoever that maintenance treatment prevents relapse in the majority of schizophrenic patients. Davis'[36] classic review summarized the findings of such studies prior to 1976 and found a dramatic, statistically significant difference between drug and placebo treatment. Hogarty and colleagues[39-42] compared active vs. placebo maintenance treatment in schizophrenic outpatients. Of patients receiving placebo, 63% experienced a relapse within 1 year as opposed to 26% of patients receiving active treatment. In fact, half of the drug-treated patients may have been noncompliant, which would probably reduce the 26% figure significantly. Thus, maintenance treatment is clearly beneficial for the majority of schizophrenic patients.

V. PREDICTION OF RESPONSE TO ANTIPSYCHOTIC MEDICATION

A. General Comments

Predicting and monitoring a response to medication requires specifying what the expected response will be. The literature contains studies measuring "response" to treatment which range from reduction of specific symptoms (e.g., hallucinations or assaultiveness) to reestablishment of social and occupational competence. The extent to which improvement can be expected, then, is quite dependent on the variable in question. This is particularly important for the treatment of schizophrenic patients. "Positive" symptoms of psychosis such as hallucinations or delusions, which are often reduced by antipsychotic medication, occur in schizophrenic, affective, and other psychoses.[43] These nonspecific symptoms may be associated with the "active" (possibly hyperdopaminergic) states in many psychotic patients. Other symptoms which may be related to the core process of schizophrenia are called "negative" symptoms, such as blunted affect and withdrawal.[44] These have been observed most often in those patients with poor premorbid adjustment and early and insidious onset of illness; these symptoms are sometimes accompanied by early neuroanatomic changes.[43,45] The "negative" symptoms tend to be less affected by antipsychotic medication[46] and are postulated by Crow to be possibly unrelated to dopaminergic transmission.[47] Accordingly, these "DA insensitive" symptoms are less responsive to antidopamine drugs. It is important,

then, to *define* the particular target symptoms and to have a reasonable expectation of outcome for that symptom. While "active" symptoms of psychosis in a chronic schizophrenic patient may respond to treatment, the chronic course and ultimately poor prognosis will likely not be altered significantly by medication treatment.

In general, patients who have responded to medication in the past are likely to respond favorably again. There is also good evidence that most patients will respond to medication, although, as noted above, there will be a broad range in the degree of the response. Finally, there are patients who actually do as well or better without medication or respond at a much lower dosage than is usually required for most patients.[22] The following sections in this chapter will explore possible ways to facilitate prediction of response, optimize treatment in drug-responders, and identify patients for whom medication is less likely to be helpful.

B. Diagnosis as a Predictor

The response of a psychotic patient receiving antipsychotic drugs is probably a combination of the nature of the underlying illness, expectations and definition of response, environmental and social factors, and medication effects. Also, the majority of studies on prediction of response to antipsychotic medication have been conducted in groups diagnosed as schizophrenic, but which probably contained nonschizophrenic patients with affective or other (e.g., organic or drug-induced) types of psychosis. Most patients with affective psychoses, for example, are likely to return to their previous level of functioning following treatment with antipsychotic drugs and other appropriate treatment.[49] For schizophrenic illnesses, even as narrowly defined by current DSM-III criteria, it is less easy to make prognostic statements. The concept of good prognosis and poor prognosis in schizophrenia has regained attention in recent years as an important way to subdivide this heterogenous group of illnesses. Considerable nosologic debate continues as to whether good prognosis schizophrenics have misdiagnosed affective disorders.[50] In any case, at the current level of diagnostic sophistication, there is clear variability in the acute response and ultimate outcome of patients meeting DSM-III criteria for schizophrenia. Variables which have been reported to be associated with good and poor prognosis subtypes are shown in Table 2.[50-68] There is more recent evidence that patients in the poor prognosis group also have demonstrable neuroanatomic abnormalities, neurophysiologic changes, and deficits in intellectual functioning.[45,47] As pointed out by May and Goldberg,[51] these variables are probably more general prognostic indicators of outcome regardless of the type of treatment given, than specific predictors of response to pharmacotherapy. These general points should be kept in mind as the following predictors of response to antipsychotic medication are reviewed.

C. Clinical Predictors of Antipsychotic Response

1. Symptoms at Presentation

Some symptoms seem to be more responsive in general to drug therapy than others. Thought disorder, hallucinations, delusions, insomnia, verbal aggression, agitation, anxiety, and confusional states are generally noted to be the most responsive to acute treatment with antipsychotic medication.[46,51,52,55,56] Negative symptoms such as self-neglect, poverty of speech, loss of drive, and flattening of affect seem to be less responsive.[46,47,51]

During early investigations of different phenothiazines, there appeared to be different constellations of psychotic symptoms which were preferentially reduced by one phenothiazine more than by another.[69-72] However, this did not prove to be the case when cross-validation was attempted.[73,74]

2. Demographic Predictors

There are conflicting opinions on whether sex plays a role in response to antipsychotic drugs. There have been reports that females respond better, but questions as to difference

Table 2
CLINICAL FEATURES ASSOCIATED WITH GOOD AND POOR OUTCOME IN SCHIZOPHRENIA

Poor outcome	Good outcome
Early age at onset	Later age at onset
Long duration of illness	Short duration of illness
Insidious onset	Acute onset
Poor premorbid functioning, asocial, schizoid personality	Good, premorbid functioning and social competence
Emotional blunting	Anxiety, tension, or other affective symptoms
Clear sensorium	Confusional state
No precipitating factors	Precipitating factors
Single	Married
Family history of schizophrenia	Family history of affective disorder, no family history of schizophrenia

in admission rates to hospitals, rater biases, and differences in body weight preclude any definitive statements at this time.[51] Married vs. single status has been associated with a good response to treatment for both males and females.[51,59,60] A later age of onset of illness also carries good prognostic value.[56] Low socioeconomic status carries a negative prognostic value for response to treatment.[61] Race has been extensively studied with respect to general prognostic variables and overall outcome, and does not by itself differ between schizophrenic patient groups.[62,63] Some of these demographic variables are highly likely to be associated wih premorbid level of function, particularly socioeconomic and marital status, and cannot easily be considered out of context.

3. Historical Predictors

Poor premorbid adjustment (also called asocial or poor social competence) is a factor associated with a generally poor prognosis. These patients often progress to a chronic or "process" schizophrenic clinical picture. Poor premorbid adjustment refers to patients with impaired interpersonal functioning which often begins very early in life. These patients are often single, have a low employment level, and schizoidal personality type.[64] Some studies have shown that patients with a good premorbid history respond better to antipsychotic medication than those with poor premorbid histories, both with acute treatment[65,66] and for maintenance.[67] Others have concluded the opposite — that drug therapy is associated with a greater improvement in poor prognosis patients.[68] Cole et al. studied the drug response association with the "process-reactive" dichotomy and could discern no predictive value.[75] Thus, the poor premorbid picture seems to have significance of overall prognosis, but seems to carry no identifiable predictive value for the individual patient response to pharmacotherapy.

Paranoid symptoms have been reported to be associated more often with good premorbid adjustment.[76,77] Poor premorbid patients exhibiting paranoid symptoms may have a better overall outcome than their nonparanoid counterparts.[78,79] Goldberg's group[80,81] found no difference between drug and placebo treatment on paranoid symptoms. Others have found that paranoid symptoms associated with a good response,[82] particularly within the good premorbid subgroup of patients.[83-85]

Other historical features associated with the positive outcome are an illness of sudden onset and short duration, the presence of a family history of affective illness, and the absence of a family history of schizophrenic illness.[51,52,55-57]

D. Biologic Predictors of Antipsychotic Response

1. Neurological Variables

a. Central Nervous System (CNS)

Within the spectrum of schizophrenic illness, there are several neurological variables which have been associated with either poor premorbid adjustment and/or poor response to antipsychotic drug treatment. There seems to be an unexpectedly high prevalence of neurologic "soft signs" (impaired hand-eye coordination, mild speech difficulty, impaired right-left discrimination, and others) in poor premorbid schizophrenic patients. Neuropsychological deficits have also been described in this poor premorbid group of patients using rating scales such as Halsted-Reitan, Wechsler Adult Intelligence, Luria-Nebraska, and Withers and Hinton Batteries.[46,89-92] Neuroanatomic studies have demonstrated structural abnormalities in the brains of schizophrenic patients. Computerized axial tomography and echoencephalographic studies have shown an enlargement of the cerebral ventricles of some schizophrenics.[46,89-96] If this finding is present early in the course of the illness, a poor outcome is more likely.[96] These findings are also associated with a poor response to antipsychotic treatment.[95,97] However, Carman et al. (personal communication) failed to replicate this finding in a series of 70 schizophrenic inpatients. Although enlargement of the cerebral ventricles is not specific for schizophrenic illness, the association of the anatomic changes with intellectual impairment and poor premorbid adjustment carry negative prognostic significance, and predict a relatively poor antipsychotic drug response. Taken together, these neurologic abnormalities and the downhill course of schizophrenia are suggestive of brain disease of unknown etiology. Whether this represents a true subgroup of schizophrenics or unrecognized organic illness resembling schizophrenia merits further research and clarification. Electroencephalographic (EEG) patterns have been studied in schizophrenic patients and may have some value in predicting treatment resistance, but data on this parameter are limited.[98-101] Several investigators have attempted to correlate behavioral effects of neuroleptics with baseline somatosensory-evoked potential response and auditory-evoked potential response in schizophrenia. Patterns consistent with impaired selective attention to stimuli were found, and the degree of reduction of late wave amplitude appeared related to the level of psychopathology. However, to date, no predictive value for these parameters has been demonstrated.

b. Autonomic Nervous System (ANS)

ANS parameters have also been studied in schizophrenics, both as biologic markers and as possible predictors of response to medication treatment.[102-108] Some schizophrenic patients exhibit higher resting heart rates and abnormal palmar skin conductance. These variables tend to show a relative lack of attenuation to sensory input in schizophrenic patients with a poor prognosis[106,108] and have been associated with the poor response to medication treatment.[103,107]

c. Other Variables

Other variables[109-112] such as smooth pursuit eye movements have been studied in schizophrenic patients. They are present more frequently in schizophrenics and in unaffected relatives of schizophrenics than in normals,[110] suggesting a genetic component. These may be of some diagnostic value, but do not appear to be affected by or predict response to antipsychotic medication.

Serum creatinine phosphokinase (CPK) has been reportedly elevated in acute schizophrenia[113] as well as in other psychotic stages,[113,114] and it has been suggested that this may reflect an increase in dopaminergic activity in the CNS. Twin studies indicate that the elevated CPK levels in schizophrenics are genetically influenced.[115] Unfortunately, CPK elevations are not specific to schizophrenic psychosis and are probably of limited predictive value, although they are said to be more highly elevated in some treatment-resistant patients.[113,114] Mono-

amine oxidase (MAO) levels in the platelets of schizophrenics have also been studied for predictive value as well as diagnostic significance.[116] There have been reports that platelet MAO levels are lower in paranoid schizophrenics than in other subtypes,[117] but this variable does not seem to be predictive of drug response.[116] Furthermore, there is evidence to suggest that low-platelet MAO may be a nonspecific marker for psychopathology[118] and, like CPK, is not specific for schizophrenic illness. Phenylethylamine (PEA) has potential stimulant and psychotomimetic properties in an organism spontaneously or iatrogenically deprived of normal monoamine oxidase function. Significantly greater urinary excretion of PEA has been reported among paranoid schizophrenic patients than either nonparanoid schizophrenic patients or nonpsychiatric control groups. However, no correlation to drug response has been found as yet. Despite attempts to relate HLA antigen patterns to response or lack thereof to neuroleptic agents, the most consistent correlations have merely been between the diagnosis schizophrenia and the antigen HLA B27, whereas subtype paranoid schizophrenia coincides with HLA-A9.

E. Pharmacologic Predictors of Antipsychotic Response

The DA hypothesis postulates that there is excessive DA activity in the brains of psychotic patients.[9] By observing the effects of various pharmacologic probes on DA-associated neuroendocrine, clinical, and subjective responses, there have been attempts to characterize potential drug responders.

1. Neuroendocrine Studies

Neuroendocrine studies have utilized growth hormone (GH) and prolactin (Pr), both of which are under partial control of DA. Preliminary data suggest that the degree of rise of GH following apomorphine, a DA agonist, may weakly predict short-term antipsychotic response.[119] The degree of rise in Pr following antipsychotic administration has been reported to correlate with clinical improvement.[120,121] However this is not a consistent finding and has limited clinical utility both because of variability in the Pr response[120] and the finding that the Pr response peaks before therapeutic effects are seen in some patients.[122]

2. Amphetamine Challenge

High dosages of drugs such as amphetamine,[15,16,123,125] L-dopa,[126] and methylphenidate,[125,127] which cause an increase in brain DA activity, can produce psychotic symptomatology reminiscent of schizophrenia in nonpsychotic, normal subjects. Even low dosages may occasionally cause psychotic symptoms.[128] Schizophrenic patients given low dosages of these agents often experience an exacerbation of psychosis.[19,125] *d*-Amphetamine has been employed as a pharmacologic probe in various groups of schizophrenic patients in an attempt to find drug-responsive subgroups.[18,19,125,129-133] It would be expected that patients who worsened (i.e., became more psychotic) after *d*-amphetamine would be expected to respond positively to antipsychotic medication treatment. Interestingly, it has been found that patients who are in a stable remission or in a stable, chronic psychotic state are less likely to experience an amphetamine-induced exacerbation of psychosis than other schizophrenic patients. Patients with no clinical change after amphetamine are less likely to improve after antipsychotic administration.[18,19,129-133] Van Kammen et al. have recently reported a series of studies indicating a heterogenous response to amphetamine in schizophrenic patients.[19,130-133] They found, paradoxically, that approximately one-third of the drug-free schizophrenic patients they tested actually improved clinically after receiving *d*-amphetamine.[19-132] Those patients who improved after amphetamine benefited more from subsequent antipsychotic treatment than those who remained unchanged or worsened.[19,130] Exacerbation of psychosis by amphetamine in patients who were receiving antipsychotic drugs predicted an early relapse after discontinuation of the antipsychotic drug.[133] Inconsistent responses to amphetamine

over time were also reported by this group. When some patients were rechallenged with amphetamine 4 months later, they did not necessarily respond in the same fashion as they had previously responded.[19] These variable responses were felt to be a reflection of the underlying neurochemical state of the patient (which apparently changed over time) rather than representing a consistent trait variable. Although the amphetamine challenge model provides an interesting pharmacologic probe with which to predict possible medication responsiveness, nonresponsiveness, and relapse upon withdrawal, it deserves further study before being used in routine clinical practice. Similar to amphetamine-induced improvement, paradoxical improvement in some schizophrenic patients after the administration of L-dopa has been reported.[20,21] Responses to neuroleptic drugs have been shown to be variable, and some schizophrenic patients actually improve after antipsychotic medications are withdrawn.[23] J. Strauss, M.D.[256] noted that the clinical state of schizophrenic patients is similarly quite variable if patients are evaluated at frequent intervals. This clinical variability may possibly parallel the above-mentioned variation in pharmacologic responsivity in schizophrenic patients and reflect changing brain DA transmission over time.

3. Methionine and Histamine

Two old and enduring findings in schizophrenia are the exacerbation of symptoms in approximately 50% of schizophrenics following oral methionine loading and the failure to develop a normal wheal and flare response to intradermal histamine injection. Neither finding has been successfully correlated with neuroleptic response in these patients to date.

4. Initial Response to Treatment

May et al.[134] assessed the degree of clinical improvement after 48 hr of drug treatment as a predictor of treatment outcome. An early positive response (within 48 hr) carried some predictive value for outcome after a 1-month course of antipsychotic drug treatment. Similar findings have been reported for haloperidol.[135] Subjective response to treatment has also been an area of interest as a potential predictor of response to treatment.[136-140] Patients who experience an initially dysphoric response to medication treatment have been shown to have a poor outcome of treatment with chlorpromazine[138] and thiothixine.[138,139] In some studies it was felt that the dysphoria was related to extrapyramidal effects and that this may have caused noncompliance and ultimately poor outcome.[138] Others did not find a relationship between side effects, blood levels of antipsychotics, and dysphoric response.[139] Singh et al.[136] suggested that the dysphoric responders were more often those with the poor prognosis or "process" characteristics and thus may have been fundamentally different from the nondysphoric patients.

5. Pharmacokinetic Predictors

Plasma concentrations may vary 20–fold or more in patients receiving similar dosages of antipsychotic medications.[141,142] Speculating that nonresponding patients may metabolize drugs rapidly to inactive compounds, Sakalis et al.[143] and Mackay et al.[144] have reported that patients who are considered drug responders have relatively higher levels of chlorpromazine or its pharmacologically active metabolite, 7-OH-chlorpromazine. Patients who were less responsive had higher levels of relatively inactive metabolites of chlorpromazine such as chlorpromazine sulfoxide. In a group of patients receiving chronic thioridazine treatment, those with higher levels of an active metabolite, sulphoridazine, were reported to show a greater clinical benefit than did those with lower levels of this active metabolite.[145]

Sakurai et al.[146] attempted to predict clinical outcome by examining the profile of chlorpromazine metabolites 3 hr after administering a 50-mg oral test dose to schizophrenic patients. While they found that a high ratio of chlorpromazine to its inactive metabolites in the blood after 3 hr was correlated with better eventual outcome in a substantial number of

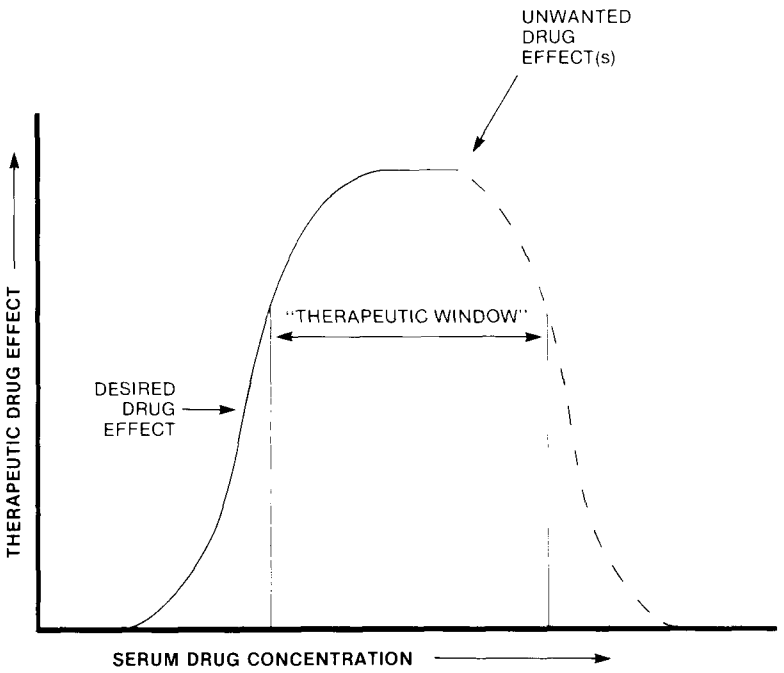


FIGURE 5. The range of drug concentrations within which the highest likelihood of producing a maximum therapeutic response is called the "therapeutic window".

patients, nearly a third of patients had outcomes opposite the chemical prediction.[147] Other pharmacokinetic approaches to predicting response are suggested by the finding that some apparent nonresponders have very low (or in a few cases, extremely high) blood levels of drug despite being given dosages that are usually therapeutic. Smith et al.[148] showed that patients who are apparently nonresponders may have exceedingly low plasma and red blood cell levels of butaperazine, and that this may explain the apparent resistance to drug treatment. They also presented some similar (although preliminary) data for haloperidol and thiothixine. They did not find evidence for more rapid metabolism of drug in patients with lower blood levels and suggested that absorption may be an important pharmacologic variable in apparent nonresponse in some patients. These data suggest that a low blood level of drug may be used as a "predictor" of nonresponse in patients receiving usually adequate doses of antipsychotic medication.

VI. BLOOD LEVELS AND CLINICAL RESPONSE

A common method used to relate drug concentration to clinical response is the construction of a dose-response curve (see Figure 5). As can be seen, no effect occurs at very low drug concentrations. As drug levels rise, the drug effect increases to a maximum and plateaus, after which no further drug effect occurs. However, as concentration of drug continues to rise beyond this point, other pharmacologic effects, side effects, and toxicity may occur with a resulting decrease in the desired drug effect. The range of drug concentrations within which desired effects are most likely to occur in the absence of confounding or toxic drug effects is called the "therapeutic window".

For some psychotropic drugs (anticonvulsants, some antidepressants, and lithium), there is more than a rough idea of the therapeutic range of blood levels. Unfortunately, there is

very limited information on such ranges for most of the antipsychotic drugs. Possible reasons for this may be the use of treatment-resistant, chronically psychotic patients in research trials, the lack of appropriate methodologic (i.e., fixed-dosage trial) design, and failure to account for active metabolites of the drugs administered. Even with drugs which are highly metabolized, such as chlorpromazine, there are studies showing a correlation between blood levels and clinical response. Some indicate that a therapeutic range may exist for chlorpromazine and other phenothiazines. Curry et al.[149,150] and Rivera-Calimlin et al.[151,152] and Wode-Helgodt et al.[153] noted that patients with extremely low (around 30 to 40 ng/mℓ) chlorpromazine levels had a poor response. Patients with excessively high levels were poor responders also and improved with a lowering of the dosage. These data indicate a possible curvilinear response (or therapeutic window) for chlorpromazine. Dysken et al.[154] have recently shown a similar "inverted U"-shaped response curve for fluphenazine, another phenothiazine antipsychotic drug. Garver et al.[155] similarly reported a curvilinear relationship between butaperazine levels and clinical response. In contrast to the above studies, however, there are a number of studies failing to show any correlation between blood levels and clinical response.[156,157] The lack of uniformity in findings is not surprising in light of the variability with which drugs like chlorpromazine are converted to active metabolites. Failing to account for active metabolite can at least partially explain the difficulty in relating blood levels in clinical response for the highly metabolized antipsychotic drugs. Haloperidol, a drug with no important metabolites,[29] has allowed for more consistent correlations between blood levels in clinical response to be ascertained. Magliozzi et al.[158] reported that patients with haloperidol levels between 8 and 18 ng/mℓ improved to a greater extent than did patients whose blood levels fell outside of this range. Similar findings were reported by Smith et al.,[159] who showed a trend toward better response with patients with haloperidol levels between 5 and 14 ng/mℓ compared with those falling outside this range.

Our own studies[160] suggest that a high proportion of acutely psychotic schizophrenic inpatients who respond to treatment with haloperidol have plasma levels in the range of 5 to 15 ng/mℓ. This is in basic agreement with the studies mentioned above. Our studies and others apparently identify a range of plasma levels within which most acute schizophrenic patients who respond to haloperidol will fall. There is certainly no linear relationship between haloperidol levels and clinical response. This encouraging agreement between different groups of investigators strongly suggests that haloperidol may have a therapeutic window. Hollister and Kim[161] recently assessed blood levels and clinical response relationship in a group of treatment-resistant schizophrenics. In this study, they observed that treatment-resistant patients may require somewhat higher haloperidol blood levels for response — in the range of 20 to 50 ng/mℓ. These studies with haloperidol indicate that, when all of the active drug can be measured, reproducible correlations between blood levels and clinical response can be obtained. If a haloperidol "window" exists, it may also be possible to develop a single dose prediction test similar to those currently used for lithium and nortriptyline.

Some investigators have measured red blood cell (RBC) concentrations of antipsychotic drugs, postulating that this measure may better reflect the amount of drug reaching critical sites in the CNS. Both butaperazine[155] and haloperidol[159] RBC levels of drug were found to be more highly correlated with clinical response than were plasma drug levels. This interesting approach deserves further attention as a way to optimize studies of the relationship between blood levels and clinical response.

A number of studies have correlated plasma concentrations of chlorpramazine and autonomic side effects, such as orthostatic hypotension, sedation, pupillary size, and increased pulse rate and extrapyramidal symptoms.[162–164] Whether these effects are due to the parent compound, psychoactive metabolites, or nonantipsychotic metabolites, requires further clarification.

VII. NEUROLEPTIC RADIORECEPTOR ASSAY

As was mentioned in the previous section, consistent correlation of blood levels and clinical response has been lacking, at least in part, because of the inability to account for all of the active metabolites of the more highly metabolized drugs. In the recent past, a new assay technique has been developed which may provide a method for standardization of antipsychotic medication treatments. Creese and Snyder[165] reported a method by which the total amount of DA-blocking activity in the serum of patients receiving antipsychotic medications may be measured. The neuroleptic radioreceptor assay (NRRA) consists of incubating tissue rich in DA receptors (calf caudate) with radiolabeled spiroperidol, a butyrophenone. When patient serum is added, the labeled drug is displaced from the DA receptors in proportion to the amount of DA-blocking activity present in the added serum, and is expressed as units of neuroleptic activity. This ingenious technique allows for all active (even unknown) metabolites to be measured. Very good correlation seems to exist between neuroleptic activity in blood and clinical response. Calil et al.,[166] Tune et al.,[167,168] and Dunlop et al.[169] have demonstrated a relationship between neuroleptic blood levels as measured by the NRRA and clinical response. No correlation between the dosage of medication administered, drug levels, and clinical response was discernible. Cohen et al. measured steady-state serum neuroleptic activity in patients receiving thioridazine.[170] In this study, clinical response was correlated highly with the serum neuroleptic activity, whereas dosage of drug and severity of psychosis at entry into the study, as measured by clinical rating scales, did not correlate with clinical improvement. The patients with the highest levels of neuroleptic activity improved the most rapidly, while those with lower neuroleptic activity levels responded more slowly or not at all. The investigators did not find an upper limit to the therapeutic neuroleptic activity levels in this study, but were employing only moderate dosages. They did discern a minimum level of effective neuroleptic activity, suggesting a threshold below which an antipsychotic effect was not obtained. The same group has recently measured neuroleptic levels in a number of patients taking various antipsychotic medications.[171] In contrast to the expectation that measurable neuroleptic activity would be approximately at the same level for clinically effective dosages of different drugs in various patients, they found that the high-potency antipsychotics in clinically effective dosages produced much lower serum neuroleptic activity than the clinically comparable dosages of low potency antipsychotics. For example, fluphenazine (mean dosage of 10 mg/day) in four patients produced neuroleptic activity in the range of 12 to 43 units while, in six patients, thioridazine (mean dose 300 mg/day) yielded a range of 430 to 1200 units. Others have found similar difference in serum neuroleptic activity between clinically comparable dosages of high and low potency neuroleptics.[172,173] Various explanations have been advanced for this apparent discrepancy, including the presence of metabolites in the blood which may be active but are unevenly distributed between plasma and brain, possible variations in protein binding of various metabolites, and artifacts unique to the assay. Because of this variability, the therapeutic range of serum neuroleptic activity must be determined independently for each individual antipsychotic agent.

Relapse may also relate to blood levels. Maintenance neuroleptic treatment has been clearly demonstrated to reduce the incidence of schizophrenic relapse. Nevertheless, relapse is common and occurs in over 25% of schizophrenic patients who are treated with neuroleptics. Although some patients who have relapses have discontinued or reduced their doses of medication, compliance failure alone does not in itself account for the high rate of relapse. The NRRA has recently been used to study the maintenance treatment of outpatient schizophrenics. Brown et al.[174] reported findings from a study of 61 patients. After determination of serum neuroleptic activity, patients were followed for a 6-month period. The ten patients who relapsed during this time had relatively low serum neuroleptic levels at the outset of

the study when compared to the nonrelapsing patients. Six of these patients were in remission; of these, five had the lowest serum neuroleptic levels in their treatment group and the sixth had the second lowest in his group. This report suggests that very low serum neuroleptic levels may identify those patients at the risk for early relapse. These investigators also noted that some patients with residual psychotic symptoms had neuroleptic activity levels which were in the same range as patients in complete remission. It would be of interest to know if a further increase in neuroleptic activity in patients with residual symptoms could result in increased clinical improvement.

Although there are not yet enough data for determination of the therapeutic range of neuroleptic activity for every one of the various antipsychotic agents, the NRRA is useful in current practice. For example, a patient who is receiving a standard dose of antipsychotic medication and is not responding may have extremely low levels of neuroleptic activity and could be identified in this fashion. The dosage could then be adjusted accordingly upward. Likewise, patients who have very high levels of neuroleptic activity and are responding poorly may benefit from lowering the dosage. Overtreatment of patients who are responding well could also be avoided, so as to minimize the potential risk associated with excessive neuroleptic treatment. There are already some data suggesting that patients with tardive dyskinesia may have extremely high neuroleptic levels for their neuroleptic dose in their serum. Finally, nonresponsive or poorly responsive patients who have received adequate medication trials could be identified by this method and spared the discomfort and risk of ineffective treatment.

VIII. PRETREATMENT CONSIDERATIONS

A. History

A complete medical and psychiatric history should be obtained prior to initiating antipsychotic drug therapy. The patient may on occasion be unwilling or unable to give a meaningful history, and information should be sought from the family, significant others, persons accompanying the patient, hospital records, or other sources. Recent medical illness, head trauma, infection, prior medical illnesses, and prior history of substance abuse should be elicited and recorded.

Establishing an accurate diagnosis will allow the clinician to better predict response to treatment and prognosis. Additionally, a prior antipsychotic drug treatment history should be elicited. If a patient has had a good response to a particular agent in the past, this can be helpful in choosing an effective agent and prescribing the dosage to which the patient responded previously. Similarly, if a family member has responded well to a particular medication, this pharmacogenetic information may guide the clinician's choice for treatment. Previous adverse experiences to antipsychotic drugs should also be assessed. This includes both physical effects (extrapyramidal effects, impaired sexual function, orthostatic hypotension, etc.) and subjective adverse effects. A more acceptable medication may then be used so as to avoid noncompliance. A list of other medications the patient has been taking should be recorded. These include antacids, prescription drugs, over-the-counter hypnotics, recreational drugs (alcohol, cigarettes, sedative-hypnotics, etc.). A survey of recently discontinued drugs should also be included, since patients will often fail to report these unless specifically asked.

An attempt to elicit symptoms which could later be mistaken for drug effects should be made, including dizziness, motor disturbances, gastrointestinal complaints (constipation, dry mouth), cardiovascular complaints (palpitations, chest pain), and neurologic complaints (restlessness, tremor, headache, visual disturbances). Such symptoms may be mistaken later for adverse drug effects and prompt discontinuation of potentially effective treatment.

B. Physical and Laboratory Examination

It is important to vigorously eliminate from serious considerations all possible reversible syndromes and other known illnesses which can present as schizophreniform psychosis. A complete physical examination, including vital signs, and a thorough neurologic examination is imperative. Blood pressure (baseline and orthostatic changes) provides a necessary baseline which may facilitate the initial treatment choice and be a useful reference point. An excited patient may have an elevated blood pressure on initial exam, so repeating this measure can help avoid inaccurately attributing a drop in blood pressure to medication effects. Observation and recording of the gait, evidence for any dyskinetic movements, or other neurologic abnormalities provide an accurate baseline to which to refer as necessary. Since many patients have been exposed to antipsychotic drugs in the past, it also provides an important medicolegal reference point. The presence of other physical signs such as needle marks, nystagmus, enlarged liver, jaundice, or other symptoms (e.g., visual hallucinations) can provide important diagnostic clues for a possible organic etiology of the presenting symptoms.

Laboratory testing (see Chapter 2, Psychiatric Misdiagnosis) should be as extensive as the differential diagnosis, and at a minimum should include serum electrolytes, BUN, creatinine, fasting blood glucose, complete blood count, urinalysis, vitamin testing, thyroid testing, and a sophisticated GC or GC/MS blood tests for drugs of abuse. A cardiogram (ECG) and chest X-ray (if not obtained in the prior 6 months) should be ordered. Additional diagnostic laboratory testing (CT scan, EEG, neuroendocrine studies, blood cultures, etc.) should be obtained as indicated by the history, physical, neurological examination, and initial laboratory findings.

1. Observation of the Patient

Although in emergency situations immediate treatment is sometimes necessary, a medication and drug-free observation period is important in completing the initial diagnostic evaluation and choosing the agent best suited for the patient. In addition to improving diagnosis and optimizing the pharmacotherapeutic choice, it may allow identification of the individual patient who will improve spontaneously without chemotherapy.

2. Target Symptoms

The goals of treatment should be specified at the onset of therapy by defining the various target symptom(s) to be treated. These should be documented in the medical record and used as a baseline against which to assess response to treatment. Any change or lack of change with drug therapy should be documented. Examples of possible target symptoms appear in Table 3.

3. The Alliance

Prior to administering any medication to a patient, the reasons for treatment and the expected therapeutic and adverse effects should be explained simply and as completely as possible. This will enhance patient cooperation and avoid unnecessary refusal of medication by a frightened patient who has experienced an unexpected adverse effect. Any thorough workup and treatment plan includes taking the time to explain treatment to a patient in order to maximize compliance.

4. Choosing the Drug

If the patient has previously had a good response to a particular agent and there are no contraindications to using this agent, this may be the antipsychotic of choice. If an adverse effect has been experienced, the choice should also be guided by these data. There are no antipsychotic drugs which are superior in efficacy to others, nor are any drugs more specific for certain symptoms. Accordingly, there is no reason to prescribe more than one antipsy-

Table 3
TARGET SYMPTOMS FOR ANTIPSYCHOTIC DRUG THERAPY

Anorexia	Delusional thinking
Agitation	Hallucinations
Assaultive behavior	Hostile behavior
Blunting of affect	Insomnia
Bizarre thinking	Manic symptoms
Catatonic behavior	Paranoid thinking
Confusion or disorientation	Psychomotor excitation
	Social withdrawal
	Thought disorder

chotic at a time for any patient. If there are no compelling historical factors in guiding drug choice, the decision about which drug to use is based on tailoring the side effects of the drug to the individual patient. Table 4 shows the commonly used antipsychotic drugs grouped according to chemical class, with equivalence to chlorpromazine, and a profile of the side effects. There are a variety of antipsychotic medications currently available for use.

Since these medications are similar in action, it seems most prudent for the clinician to become familiar with a few agents in both the high and low potency range and which are also available in parenteral forms. This can help the clinician avoid confusion and optimize the psychopharmacological use of these agents, especially for the beginning psychiatric practitioner or nonpsychiatrist physician. The primary side effects associated with drug choice considered here will be sedation, anticholinergic, antiadrenergic, and extrapyramidal effects.

1. *Sedation* is produced by all of the antipsychotic drugs to some extent, probably through antihistaminic CNS effects.[175,176] It is understandably the greatest in the older phenothiazines, which were originally developed as antihistamines. As a rule of thumb, the low-potency agents, such as chlorpromazine and thioridazine produce the most sedation (up to 80% of patients early in treatment). The high-potency phenothiazines (fluphenazine and trifluoperazine) and the butyrophenone class (haloperidol) are relatively less sedating. A common misconception is that some antipsychotic drugs are activating (e.g., thiothixine or haloperidol), and that only agents like chlorpromazine are sedating. The contention that apathetic patients will respond better to so-called "activating" agents while the excited psychotic patient will improve more with a sedating drug is incorrect. Psychomotor activation is calmed by all antipsychotics and this action is independent of sedating effects; these effects seem to be a result of antipsychotic effects as opposed to nonspecific sedation. Likewise, apathetic patients are similarly activated by all types of antipsychotic drugs.
2. *Anticholinergic* effects differ in degree among the various antipsychotics. Those most commonly experienced are dry mouth, blurred vision, tachycardia, constipation, and urinary hesitancy or retention. These result from the inherent antimuscarinic (atropine-like) effects of the drug. Chlorpromazine and thioridazine are the most anticholinergic, and high-potency agents such as thiothixine, trifluoperazine, and haloperidol produce less anticholinergic effects.[175] Sensitivity to these effects varies widely on an individual patient basis. Elderly patients or patients with minimal cerebral reserve on the basis of organic disease may experience anticholinergic delirium even at relatively low dosages of the low-potency, high-anticholinergic antipsychotics. At very high dosages of these agents (e.g., over 1000 mg/day), even younger patients may experience adverse effects on the sensorium. Cardiac patients may experience excessive heart rate increases from these medications, and this should be kept in mind when choosing a drug treatment.

Table 4
COMPARATIVE PROPERTIES OF COMMONLY USED ANTIPSYCHOTIC DRUGS

Chemical name (trade name)	Antipsychotic potency	Usual adult oral dosage (mg/day)[a]	Dose in mg equal to 100 mg. chlorpromazine	Ratio to chlorpromazine in mg:mg	Sedation	Anticholinergic	Autonomic effects (hypotension)	Extrapyramidal effects	Parenteral[b] form available
Phenothiazines									
Aliphatic									
Chlorpromazine (Thorazine, others)	Low	100—1500	100	1:1	High	High	High	Low	Yes
Piperidine									
Mesoridazine (Serentil)	Low	50—400	50	1:2	High	High	High	Low	Yes
Thioridazine (Mellaril)	Low	100—800[c]	100	1:1	High	High	High	Low	Yes
Piperazine									
Fluphenazine (Permitil, Prolixin)	High	2—10	2—5	1:50	Low	Low	Low	High	Yes
Perphenazine (Trilafon)	High	8—64	4—8	1:15	Low	Low	Low to I.m.	High	Yes
Trifluoperazine (Stelazine)	High	5—80	2—5	1:20	Low	Low	Low	High	Yes
Thioxanthines									
Aliphatic									
Chlorprothixine (Taractan)	Low	100—600	100	1:2	High	High	High	Low	Yes
Piperazine									
Thiothixine (Navane)	High	5—60	2—4	1:50	Low	Low	Low	High	Yes

Butyrophenones									
Haloperidol (Haldol)	High	2—100	2—4	1:50	Low	Low	Low	High	Yes
Dihydroindolones									
Molindone (Lidone®, Moban)	I.m.	50—200	10	1:100	I.m.	I.m.	I.m.	I.m.	No
Dibenzoxazepines									
Loxapine (Danolin, Loxitane)	I.m.	50—250	10	1:10	I.m.	I.m.	I.m.	High	Yes
Depot forms									
Fluphenazine enanthate (Prolixin® enanthate)	High	1mg[d]	0.5	1:200	Low	Low	Low	High	Depot
Fluphenazine decanoate (Prolixin decanoate)	High	1mg[e]	0.5	1:200	Low	Low	Low	High	Depot

Note: I.M., intermediate.

[a] These are only approximate dosage ranges. Lower doses may suffice, or high doses may be required for antipsychotic effect. Elderly patients or patients with impaired hepatic function may require less.
[b] Use approximately 1/2 the oral dose shown for equivalence.
[c] Do not prescribe over 800 mg/day, since retinopathy may occur.
[d] 1 mg (0.5 to 4/cc) every 10 to 14 days. (Not a daily dosage)
[e] 1 mg (0.5 to 4/cc) every 14 to 21 days. (Not a daily dosage)

3. *Autonomic effects*, primarily orthostatic hypotension, may result from peripheral alpha-adrenergic blockade by antipsychotic drugs.[175] These are most prominent with the lower potency agents. Autonomic effects are most likely to be most prominent when patients sit up or stand from a recumbent position. Elderly patients are the most sensitive to orthostatic hypotension, and these can be significant. Also, patients receiving other medications such as tricyclic antidepressants (which also block alpha adrenergic receptors) or beta receptor antagonists may experience synergistic or additive autonomic effects and are thus more susceptible to significant hypotension.
4. *Extrapyramidal effects* develop in 15 to 90% of patients, depending on the age, sex, and agent in question.[177-179] They include acute dystonia (sudden involuntary contraction of the neck, mouth, tongue, extraocular, or postural muscles), Parkinsonian effects (bradykinesia, rigidity, tremor), and akathisia (restlessness, pacing). To a significant degree, the extrapyramidal effects occur in proportion to the potency of the antipsychotic medication used. Haloperidol and the other more potent agents seem to cause significantly more extrapyramidal effects than do the lower potency agents. This is in part because the lower potency agents are more anticholinergic and have "built-in" antiparkinson effects. For thioridazine, it may also be due to more selective DA receptor blockade.[12] Acute dystonic reactions tend to occur very early in treatment, often within a few hours or during the first few days, and are more common in younger patients, especially younger male patients.[177,179] Akathisia and drug-induced or pseudoparkinsonian side effects usually emerge later (after 1-3 weeks of treatment). Pseudoparkinsonian symptoms occur more frequently in elderly females than other patient groups.[179]

C. Choosing the Dosage

The effective dosage for acute antipsychotic therapy is in large part an empirical decision. It is probably better to err initially on the side of overmedication to bring the psychosis under control than to allow the psychotic illness to be undertreated for an unnecessarily long period of time. It is comforting to know that there is a wide margin of safety for antipsychotic drugs, i.e., the ratio of the effective dose to the lethal or toxic dose for antipsychotic drugs is generally high. The initial dosage used may be suggested by the prior drug history. If not, the generally effective daily dosage for acute psychosis ranges from 300 to 1500 mg of chlorpromazine per day or the equivalent dosage of another agent. This figure varies according to several factors. Larger patients may require more drug and small, frail patients often require less. However, unlike most other drugs, there is no straightforward relationship between body size and dosage requirement. Elderly patients may often respond to a lower dosage. Smokers will often require larger dosages because of enhanced hepatic metabolism of drug, as will patients taking other drugs which enhance hepatic metabolism (for example, anticonvulsants or sedative-hypnotics). Conversely, patients with decreased hepatic function may require less drug. Activated, acutely psychotic patients often require higher dosages early in treatment. The bioavailability of drugs varies between different manufacturers and dosage preparations. Elixirs are often more completely absorbed than are tablets. Intramuscular injection forms are more completely absorbed than other preparations. If sedation seems indicated, a lower potency agent may be used. However, many clinicians prefer the high-potency agents because of the lower incidence of cardiovascular toxicity[181] as well as avoiding oversedation of the patient.

IX. TREATING THE PATIENT

A. Initiating Treatment (See Figure 6)

For nonemergencies, an acutely psychotic patient may be initially given oral doses of a high-potency antipsychotic such as haloperidol, 5 to 10 mg tid. Haloperidol has the advan-

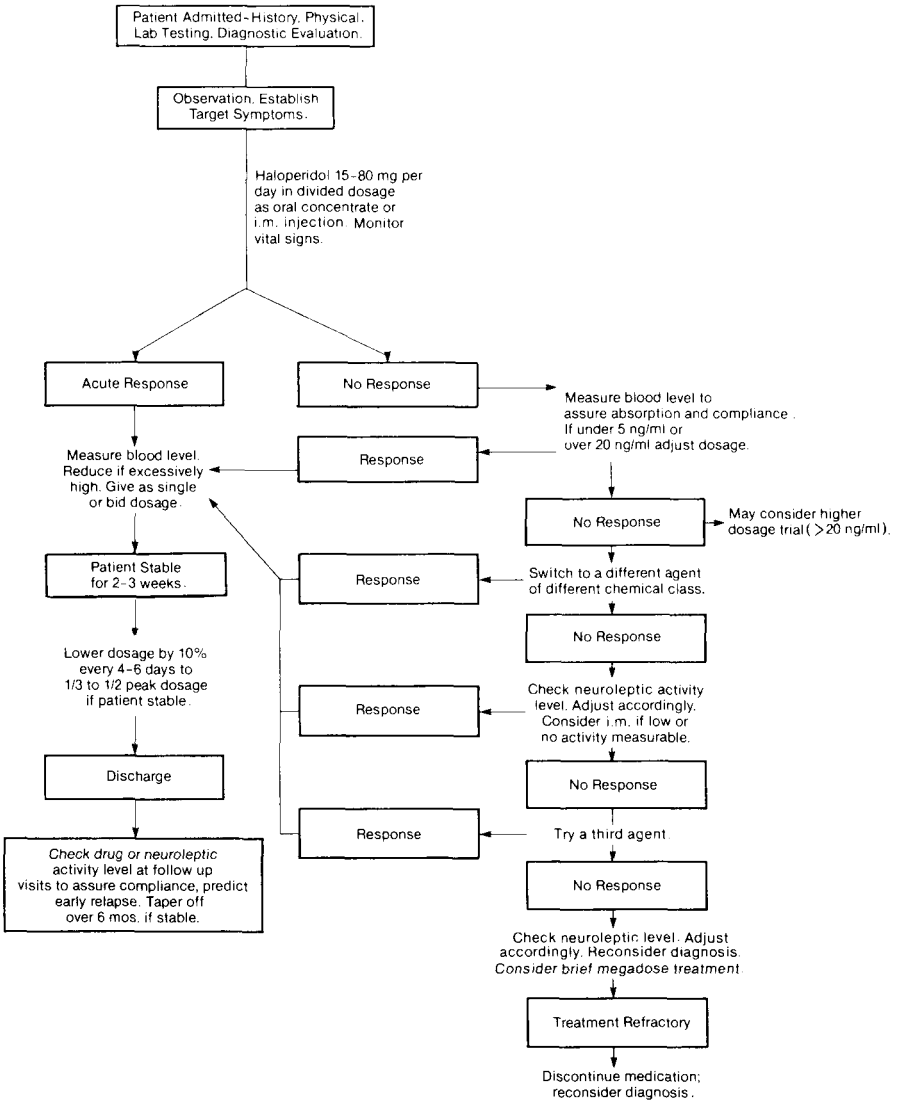


FIGURE 6. Flow diagram for treating acute psychosis using haloperidol.

tages of minimal sedation and cardiovascular toxicity[181] and is an extremely useful agent for treating acute psychosis. It has the distinct advantage of having no active metabolites,[29] and there is an emerging literature suggesting a relationship between clinical response and plasma levels. As noted above, there seems to be a maximal therapeutic effect in approximately the 5 to 15 mg/mℓ steady-state serum level range with response being less frequent at higher or lower serum levels.[158-161]

As-needed (prn) orders for additional antipsychotic medication up to every hour (5 to 10 mg. p.o. or 5 mg i.m.) for emergency use. Similarly, a prn order for antiparkinson medication (1 to 2 mg benztropine or 25 to 50 mg diphenhydramine i.m.) in case of acute dystonia should be written. If minimal antipsychotic effects occur after 24 hr, the dosage may be increased by 50% daily or 2 to 3 days until an effective maintenance dosage is reached. Usually the required dosage will be 20 to 60 mg of haloperidol per day, but may range as high as 100 mg/day in some patients. Compliance may be maximized by using elixirs or

liquid concentrations for initial oral administration, since some patients may sequester tablets in their mouths and later discard them. If, at higher dosages (80 to 100 mg of haloperidol) no antipsychotic effects are apparent, and no extrapyramidal side effects have emerged, a blood level should be obtained to assure that adequate intestinal absorption has occurred.

B. Rapid Neuroleptization

A number of reports of "rapid psychotolysis" have appeared. Some investigators suggest that psychotic symptoms may be controlled more quickly by initially giving high dosages (e.g., 5 to 10 mg of haloperidol i.m. every 30 to 60 min).[181] The rationale behind this is similar to giving a loading dose of digitalis ("digitizing dose") to rapidly achieve a therapeutic blood level.[182] However, controlled studies comparing low-dose vs. high-dose initial treatment do not bear out this hypothesis.[183-185] It may, however, be preferable to achieve rapid control of belligerent, agitated, and potentially dangerous patients in some instances. Some suggest that, if sedation is the goal, then sedatives should be co-administered with antipsychotics early in treatment. The controversial point must be left to the judgement of the individual clinician. In those who opt for initially using frequent dosage of antipsychotics for controlling potentially dangerous patients, high-potency agents such as haloperidol have been shown to be relatively safe agents;[181] low-potency agents with more anticholinergic effects should be avoided. When converting the dosage from i.m. injection to the oral form, the dosage required will increase by 50 to 100% due to decreased bioavailability.

C. Onset of Action

Lehman[185] has described an approximate schedule of the expected therapeutic effects when the sufficient dosage has been reached. These may vary between individual patients, but can be a helpful guide in judging whether an adequate dosage level has been obtained. It is imperative that the clinician allow adequate time to elapse before considering either extreme dosages or switching drugs.

A decrease in arousal (irritability, excitation, insomnia, assaultiveness) should occur within 2 to 3 weeks, although cooperation may occur earlier (1 to 5 days). Affective symptoms (anxiety, apathy, withdrawal) should begin to respond in 2 to 5 weeks. Thought disorder and perceptual disturbances (hallucinations and delusions) often require the longest period of time to subside (6 to 8 weeks). These are very general guidelines — some patients may respond very quickly while others will require even longer. The most important point is to give an *adequate* trial of medication prior to switching drugs or raising the dosage to unusually high levels. For haloperidol-treated patients, a blood level at the time the therapeutic response occurs can be a useful guide to future treatment. For other, more highly metabolized drugs, a serum neuroleptic level may serve a similar purpose.

Even when prescribing an antipsychotic in a plasma range where maximum efficacy and minimum of toxic effects exists, the patients maximal response frequently takes 4 to 8 weeks. Slow response is typical; no response suggests metabolic or compliance problems. If blood levels exist for 30 consecutive days changing to another antipsychotic is advised.

D. Stabilization

After a therapeutic effect has begun to appear, the dosage schedule may be simplified by using a bid or single hs dosage schedule. Since the half-life of all the antipsychotics is long, the therapeutic effect of medication is not diminished during a once-a-day schedule. In addition to a slow excretion rate, the high liquid solubility of these drugs allows for an accumulation in lipid stores which can act as a depot for continued release as blood levels decline. The bid schedule commonly recommended consists of giving 1/3 of the total dose in the a.m. and 2/3 in the evening. The hs dosage schedule allows for peak anticholinergic and sedating effects to occur during the hours of sleep and minimizes the need for hypnotics

and antiparkinson medication. The patient can also benefit from reduced daytime sedation and participate more fully in the ward activities. An exception to the single dosage schedule may be the elderly patient or patients with decreased metabolic capacity who may experience high blood levels for excessive periods. For these patients, lower, more frequent dosages may be more desirable.

E. The Nonresponder

Several important factors should be considered prior to deciding that a patient has not responded to medication. Poor oral absorption or noncompliance can be checked by measuring a serum blood level or neuroleptic activity level of the agent. If levels are very high, the patient may benefit from a reduction in dosage, since there is evidence that some antipsychotic drugs have curvilinear dose-response curves. If the level is very low, it may be wise to raise the dosage to assure that an adequate trial has been completed. If there has been no clinical response at a moderate blood level for an adequate period of time, one should choose an antipsychotic medication of a different chemical class. If a patient has had an adequate trial of two or three types of antipsychotic medication with no response, a trial of extremely high doses may be considered. Whether "megadose" treatment is more beneficial than moderate-dose treatment remains controversial.[186-188] If appropriate medical supervision of a trial of high-dose therapy is assured, however, the potential benefits may outweigh the risks of a chronic debilitating psychosis. As an example of the extremes which have been explored safely, Rifkin et al. used dosages of up to 1200 mg of fluphenazine in a group of treatment-resistant acute and chronic schizophrenics with beneficial results in a few patients.[189] However, when the same group restudied the very high (1200 mg/day) vs. standard (30 mg/day), they found no marked differences in therapeutic effect.[190] Additionally, some patients worsened and experienced significant akinisia. Prien, Cole, and Levine[191,192] studied moderately high dosages of chlorpromazine (2000 vs. 300 mg) and trifluoperazine (80 mg vs. 15 mg) and found that the higher dosages were more beneficial than lower dosages in chronic schizophrenics. Gardos et al. reported that 40 mg/day thiothixine was superior to 10 mg/day.[193] Very recently Hollister and Kim[161] used 50 mg/day haloperidol in treatment-refractory schizophrenic patients and achieved some therapeutic benefit[6] of 11 previously resistant patients. Compared to the 1200 mg trifluoperazine dosage, these above-mentioned studies used more moderate dosage. It may be that ultra-high dosages help an occasional treatment-refractory patient, but this area requires further clarification. Since this is a controversial area, and there are no adequate guidelines, the rationale for the use of megadose therapy should be discussed with the patient and family if possible, and careful documentation in the medical record is advised.

F. Stabilization

As the acute psychotic symptoms begin to subside, the dosage of antipsychotic drug is gradually lowered while keeping symptoms under control. The dosage can usually be reduced by 10% every 4 to 6 days to about 1/3 to 1/2 the peak treatment dose. Remember that about five times the half-life of the drug is required before steady-state blood concentrations are reached, so lowering the dosage too rapidly should be avoided.

G. After Discharge

For patients who have had their first psychotic episode, medication should be gradually tapered after discharge over a period of about 6 months and discontinued if no recurrence of psychotic symptoms emerges. The patient should be followed at least monthly for the next 6 months to assure that remission is maintained. The decision to continue medication on a maintenance basis is difficult and there are no simple guidelines. Drug maintenance clearly reduces the rate of relapse by at least 50% as was discussed earlier, but it is also

apparent that some patients will relapse despite drug maintenance while others may do well for years with no drug treatment.[61] Additionally, there is a definite risk of tardive dyskinesia associated with antipsychotic medication treatment and the risk of unnecessary exposure to medication must be minimized. There is no effective predictor of which patients will require maintenance. Garfinkel[194] suggests that drug treatment should continue for 6 months following the first psychotic episode. Following the second episode, he suggests lengthening treatment to a 1-year period. Following a third episode, long-term maintenance should be considered.

During maintenance treatment, the dosage should be lowered gradually to achieve the lowest effective level. This must be assessed on an individual basis. Despite optimal family support and patient education, an estimated 40 to 70% of outpatients fail to take their medication properly.[195] Regular blood level measurement may improve compliance. Unfortunately, some patients become uncooperative and violent when they relapse and refuse medication at the time they most need it. For this type of extremely noncompliant patient, long-acting phenothiazines are indicated.[195] Two forms, fluphenazine decanoate and fluphenazine enanthate, are available. The enanthate form is slightly shorter acting (10 to 14 days) than is the decanoate form (2 to 4 weeks). After i.m. injection of these highly lipid soluble agents, they redistribute to the fatty tissues and are slowly released into the bloodstream. For conversion purposes, 25 mg of the depot form is approximately equal to 5 mg of oral fluphenazine. To taper depot medications, the dosage may be reduced at each injection or, alternatively, the interval between injections can be increased.

During maintenance treatment, blood levels may be taken at various times to serve the purpose of identifying noncompliant patients. The practice of obtaining levels on a routine basis (biweekly or monthly) initially for 6 months, and at least every 3 to 6 months thereafter, with occasional "surprise" levels will maximize cooperation. Additionally, blood levels may allow for early recognition of those patients at risk for early relapse.[174]

H. Antiparkinson Medication

EPS may result from striatal DA blockade in a substantial number of patients receiving antipsychotic medication. Various antiparkinson medications are used to treat these adverse effects, and are shown in Table 5 with the usual daily dosage ranges. All are anticholinergic except amantadine, which is a DA agonist that can be useful for patients who cannot tolerate anticholinergic effects.[196]

When they occur, acute dystonias can be dramatic, painful, and frightening to the patient. In a hospital setting, intravenous injection of 1 to 2 mg (2 mg i.m.) benztropine or 25 to 50 mg (50 mg i.m.) diphenhydramine will readily reverse dystonia. There is considerable disagreement about whether to use antiparkinson medication prophylactically to prevent the emergence of EPS. Proponents suggest that they enhance compliance in patients who are distressed by undertreated EPS, especially akathisia and akinesia.[197,198] Others, however, suggest that symptoms should be treated only as they emerge.[199] Anticholinergic drugs lower blood levels and may slow GI motility and decrease intestinal absorption.[200] There is some concern that they may antagonize the therapeutic effects of antipsychotic agents within the CNS[201] and may also interfere with memory.[202] Additionally, there is evidence that anticholinergic drugs have abuse liability.[203] It seems prudent to avoid routine prophylaxis for hospitalized patients being treated with antipsychotic medication and to provide an as-needed (prn) order for treating any acute dystonia which occurs. Subsequently, treatment may be continued for a few weeks and the antiparkinson medication can usually be tapered as tolerance to extrapyramidal effects develops. There are some instances where initial prophylaxis may be advisable. For extremely paranoid hospitalized patients or outpatients with whom a good therapeutic alliance is essential, initial prophylaxis may be warranted. In any case, antiparkinson medication should be thoughtfully prescribed on an individualized basis.

Table 5
COMPARATIVE DOSAGES OF ANTIPARKINSON DRUGS[a]

Generic name (trade name)	Usual daily dosage range (mg/day)	Schedule of administration (times per day)
Amantadine[b] (Symmetrel®)	100—300	1—3
Benztropine (Cogentin®)	1—6	1—3
Biperiden (Akineton®)	2—4	1—4
Diphenhydramine[c] (Benadryl®)	25—100	1—4
Orphenadrine[c] (Disipal®)	100—300	1—3
Procyclidine (Kemadrin®)	5—15	1—4
Trihexyphenidyl (Artane®)	5—15	1—4

[a] Most are available as injectable hydrochloride solutions. Diphenhydramine (25 or 50 mg) and benztropine (1 to 2 mg) are most often used i.v. or i.m., respectively, for acute dystonias.
[b] Amantadine is nonanticholinergic and may be used to avoid this effect.
[c] Both antihistaminic (sedating) and anticholinergic.

Some patients who have persistent, bothersome extrapyramidal effects will require maintenance treatment with antiparkinson medication. This should be provided at the lowest effective dosage level. At each medication review, the use of these adjunctive agents should be reconsidered and lowered or discontinued if possible.

X. ADVERSE EFFECTS OF ANTIPSYCHOTIC AGENTS

A. Central Nervous System Effects

1. Reversible Extrapyramidal Effects

Various extrapyramidal effects are shown in Table 6. Acute dystonias occur most often during the first few hours or days of treatment. These should be recognized and treated promptly. As was noted earlier, nursing staff should have a prn order of antiparkinson medication for emergency use. The usual treatment consists of 1 or 2 mg benztropine i.m. or i.v. or 25 to 50 mg of diphenhydramine i.v. or i.m. Antiparkinson medication should be subsequently continued for the next few weeks after which it can usually be tapered and discontinued. Younger male patients appear to be the most susceptible to acute dystonia.[177] Pseudoparkinsonism commonly emerges after the first few weeks of treatment. It can usually be treated adequately with antiparkinson agents. Amantadine can be used as a second-line treatment for patients (especially elderly patients) who cannot tolerate anticholinergic antiparkinson drugs (Table 5). Remember that amantadine has DA stimulating properties, and can occasionally exacerbate psychosis. Prior to altering the antipsychotic medication regimen, it should be discontinued in any patient whose psychosis worsens. Two extrapyramidal symptoms are occasionally mistaken for psychopathology. *Akinesia* induced by antipsychotic drugs can be mistaken for catatonic states sometimes associated with schizophrenic symptoms.[203] It should be considered in the differential diagnosis of a mute, motorically retarded, or catatonic patient, and may respond to a lowering of the antipsychotic drug dosage. *Akathisia,* a syndrome of restlessness, pacing, and fidgeting often appears after a few weeks

Table 6
EXTRAPYRAMIDAL EFFECTS OF ANTIPSYCHOTIC DRUGS

Reversible	Symptom	Onset	Treatment
Acute dystonia	Involuntary contraction of face, tongue, neck, back, oculogyric crisis, laryngospasm	Early (1—5 days)	Reduce dosage or use antiparkinson agent i.m. or i.v. for acute symptoms. Brief prophylaxis till tolerance develops (1—4 weeks usually.) See Table 5.
Akathisia	Motor restlessness, feeling the need to move, pacing, moving legs or feet while sitting or standing Sometimes mistaken for psychotic agitation and treated inappropriately with increase of antipsychotics	1—2 weeks	Reduce dosage or use antiparkinson agent. Diazepam may be helpful
Parkinsonism	Bradykinesia, rigidity, cogwheeling, resting (6—8 cps) tremor, loss of postural reflexes. Also seborrhea, sialorrhea, masked facial expression	1—4 weeks	Reduce dosage or use antiparkinson agent
Rabbit syndrome	Perioral parkinsonian tremor mistaken for tardive dyskinesia	1—4 weeks	Reduce dose or use antiparkinson agent
Akinesia (Akinetic mutism)	Waxy flexibility, poverty of speech and movement, posturing. Sometimes mistaken for true catatonia and treated inappropriately with increase of antipsychotics	1—4 weeks	Reduce dosage or use antiparkinson agent
Irreversible			
Tardive dyskinesia	Dyskinetic tongue, face, perioral movement, choreic movements of fingers, limbs or trunk	Variable	Prevention or early detection (see text).

of treatment. The patient may complain of inner restlessness and stress. This is sometimes mistaken for acute psychotic excitement and is inappropriately treated with an increase in antipsychotic medication. Akathisia will often respond to a reduction in antipsychotic dosage, antiparkinson medication, or a benzodiazepine such as diazepam. It seems to be more resistant than other EPS to antiparkinson treatment.

2. Irreversible Extrapyramidal Effects — Tardive Dyskinesia

Practicing clinicians are painfully aware that long-term administration of antipsychotics can cause tardive dyskinesia (TD). It is believed to be a result of DA receptor supersensitivity produced by prolonged receptor blockade by antipsychotics.[7] The syndrome consists of abnormal, involuntary movements of the tongue, mouth, jaw, and face. In severe cases, postural muscles are also affected. The movements can range in severity from barely discernible tongue or lip movements to dramatic and incapacitating choreoathetoid movements. More unusual cases can involve involuntary muscle controlling respiration and occasionally result in respiratory alkalosis.[204] Chewing and swallowing difficulties may increase the risk of aspiration for some patients.

The estimated prevalence in patients receiving antipsychotic medication treatment range from 0.5 to 56%.[205] Variation in these estimates probably arises from a combination of variation in sophistication in measurement, masking of TD by medication treatment, and spontaneous fluctuation of TD movements. Another complicating factor is the spontaneous

appearance of TD-like movements with schizophrenic illness. One study recently reported that a substantial proportion of schizophrenic patients who have never received antipsychotic medication manifested symptoms indistinguishable from TD.[206]

Various risk factors for TD have been suggested, but few have been uniformly verified. Elderly patients have been reported to be more susceptible to TD than younger patients.[207] Whether increased age is also related to a longer duration of treatment with medication as a possible contribution to age as a risk factor is unclear. Women may develop TD more often than men[209] and elderly females seem to be especially at risk.[208,209] Brain-damaged patients have been reported to be more susceptible to TD than other patients.[209,210] but organic pathology is certainly not a prerequisite for the development of TD.[210] A few reports have suggested that patients with affective disorders may be at greater risk than others.[211,212]

The role of medication in inducing TD has been examined by many investigators. While it is true that most patients developing serious TD have probably received high doses of antipsychotic medications over long periods of time, the literature does not support the contention that a linear relationship between duration of treatment and incidence of TD exists. Some reports suggest that low-potency agents are more frequently associated with TD,[213] while others support exactly the opposite.[214] High-potency depot forms of antipsychotics may carry a higher risk of producing TD than lower potency agents.[209,214] In two studies, patients with extremely high serum neuroleptic activity levels were shown to have a higher prevalence of TD than those with lower levels.[215,216] Periodic drug holidays are advisable for many patients to reassess the continued need for medication. Some authors recommend that they can be used to uncover covert dyskinesia otherwise masked by medication. However, there is some evidence that a higher frequency of drug-free periods may be associated with an increased rate of irreversible TD,[217] and some recent animal data support this possibility.[13] Crane has suggested that agents which produce Parkinsonian symptoms increase the risk of development of TD.[218] Although all the currently available antipsychotic agents are known to produce TD, clozapine, an atypical antipsychotic agent, does not seem to produce EPS.[10,11] It has been reported not to produce TD,[219] but, interestingly, seems to be able to suppress dyskinetic movements in some TD patients.[220] There has been limited clinical experience with clozapine in this country because of reports of fatal agranulocytosis associated with its use in humans.[221] However, it is currently being reevaluated for clinical use and merits further evaluation as a possible agent with a lower risk for TD. Thioridazine, like clozapine, seems to have selective DA blocking properties and produces less EPS than other antipsychotics.[12,24,25] Animal[13] and human[14] studies suggest that it might produce less TD than high-potency agents such as haloperidol, but thioridazine is reportedly capable of inducing TD in humans.[222] The administration of high-potency anticholinergic agents may exacerbate TD and may possibly predispose patients receiving antipsychotics to TD.[209,210]

The reversibility of TD seems to be a function of how early it is detected. Dyskinetic movements usually emerge upon lowering or discontinuing medication. Reversible or withdrawal TD and irreversible TD are indistinguishable initially. There is good evidence that, for younger patients, TD is reversible if medication is stopped and, even in severe TD, the improvement rate seems to increase with the duration of follow-up. Dyskinesia that remains present for over 6 months is unlikely to disappear completely.[223] Early detection, then, is the most important method for reducing irreversibility of TD. Patients should be examined periodically for TD, especially after medication dosage is decreased when the chances of detection are greatest. General observation of the patient may reveal subtle postural, arm, hand, or finger movements. While conversing with the patient, one should watch for abnormal mouth or tongue movements. To more formally examine a patient, one should ask the patient about any dental problems to assure that irritation in the mouth will not be mistaken for early TD. Observe the patient's tongue with the mouth open for small writhing movements

Table 7
DIFFERENTIAL DIAGNOSIS OF TARDIVE DYSKINESIA

Idiopathic	Drug-related
Associated with psychosis (schizophrenic mannerisms and movements	Antipsychotics
Senile (senile, orofacial, dyskinesia, Meige's syndrome)	Phenytoin
Tics	Antimalarials
Tourette's syndrome	Antihistamines
Dental problems	Tricyclics
	Amphetamine
	Methylyphenidate
	Intoxication
	L-Dopa
	Methyldopa
	Heavy metals (mg^{++}) and others

Genetic
Huntington's chorea
Wilson's disease
Torsion dystonia
Familial chorea

Associated with metabolic/systemic disease	Other tremor
Uremia	Lithium tremor (9—12 cps) — an accentuated action tremor.
Hyperthyroidism	Parkinsonian tremor (6—8 cps) — occurs at rest, decreased by anticholinergics. Both are regular
Hepatic failure	Rabbit syndrome is an oral parkinsonian tremor sometimes associated with antipsychotic treatment
Lupus and other vasculitis	
Hypoparathyroidism	
CNS neoplasm	
Chorea gravidarium	

Postinfectious
Sydenham's chorea
Postencephalitic

or larger tongue movements for about 30 sec. The patient can then be asked to protrude the tongue and similar observation can be made. Asking the patient to raise one hand and touch each finger to the thumb may activate subtle movements. Record the presence or absence of dyskinetic movements at each evaluation. Some investigators advocate using a pharmacologic probe such as brief administration of a high-potency anticholinergic medication such as benztropine to unmask occult TD.

If TD-like movements are found, it is important to be sure of the diagnosis. The differential diagnosis (see Table 7) includes numerous other etiologies.[224,225] Neurologic consultation may be advisable to confirm a questionable diagnosis. If other causes are ruled out, the need for further antipsychotic medication treatment must be reassessed. Tapering or discontinuing the medication is advised, especially for patients with no recent drug holidays, and alternate forms of treatment (e.g., antidepressants or lithium for mood disorders) should be considered. Anticholinergics should be discontinued. If the psychotic symptoms are not exacerbated, the patient should be followed and reevaluated periodically. For patients who experience a recurrence of psychotic symptoms, reserpine may suppress TD and control psychosis.[226] Other antipsychotics such as thioridazine or mesoridazine may be helpful in

Table 8
STRATEGY FOR MANAGEMENT OF PERSISTENT TARDIVE DYSKINESIA

1. Rule out other causes (Table 7)
2. Document abnormal involuntary movements by area (i.e., mouth, tongue, fingers, etc.)
3. Reduce or discontinue antipsychotic medication
4. Discontinue anticholinergic medication. Observe drug free
5. If patient worsens (movements or exacerbation of psychosis), add reserpine in low doses (0.25 mg/day), monitor blood pressure, and increase slowly to maximum of 3—4 mg/day. Watch for signs of depression. Discontinue if no improvement or if adverse effects appear
6. Add low potency agent such as thioridazine or mesoridazine in lowest effective dosage
7. Consider a trial of lithium carbonate for 1 to 2 months
8. Obtain informed consent by discussing with patient and family. Document need for continued antipsychotic medication

Table 9
TREATMENTS FOR PERSISTENT TARDIVE DYSKINESIA

Treatment	Mechanism
Antipsychotic (neuroleptic)	Suppress by blocking DA receptors
Depleting agents (e.g., reserpine)	Deplete DA
Synthesis inhibitors (alpha methylparathyrosine)	Inhibit DA synthesis
Realease blockers (lithium)	Inhibit DA release
Cholinergic agents (lecithin, choline, deanol)	Increase acetylcholine activity in basal ganglia
GABA-ergic agents (baclofen, valproic acid, chlonazepam, diazepam, others)	Increase GABA concentration and inhibit DA activity in basal ganglia

controlling TD and psychosis, and may possibly present less risk to the patient due to the relative sparing of the extrapyramidal DA system.[205] Avoid high-potency antipsychotics if at all possible. Adding lithium carbonate may be helpful in some cases, but there is limited data on this.[227] The patient and family should be advised about the risks and benefits of further treatment and should participate in any decision to continue antipsychotic medication treatment. This should be documented carefully in the medical record. (See Table 8 for an outline of the treatment strategy.)

Aside from the offending agents themselves, there are a variety of symptomatic treatments for TD which have been studied, all of which have had limited success.[227,228] Various strategies have been employed and the usual enthusiasm and initial success associated with new drug treatments have been reported. However, the success rates decrease under double-blind, placebo-controlled scrutiny. Table 9 shows the various agents reported to improve TD movements. The question of informed consent is becoming an increasingly important feature of treating patients with antipsychotic medication. Although there is a risk of TD involved in treating any patient with antipsychotics, the relative benefits often outweigh the risks. For acutely psychotic patients, the benefits (more often than not) definitely outweigh the risks. After the patient has recovered and stabilized, the future risks of TD should be presented and discussed with the patient and family. For a chronic schizophrenic, drug treatment may make a difference between living with a painful, debilitating chronic psychosis or remaining in relative remission in the community. There are no easy answers, and each patient's treatment program should be individualized and reevaluated at regular intervals. The lowest possible effective dosage of antipsychotic medication should be sought and should be used for as short a time as possible with periodic evaluation for TD.

Table 10
OTHER CNS EFFECTS

Effect	Mechanism	Comments
Sedation	Antihistaminic	Low potency agents > others, usually improves
Delirium	Anticholinergic	Low potency agents > others. Caution in elderly and organically impaired. Physostigmine test helpful in diagnosis
Lowered seizure threshold	?Anticholinergic	Low potency agents > others, especially at high or rapidly rising dosage
Neuroleptic malignant syndrome	?Hypothalamic mechanism (unknown)	Rare. EPS with hyperthermia appear first. 20% fatal. Early recognition essential

B. Other CNS Effects (See Table 10)

Antipsychotic medication treatment can increase the risk of seizures, especially for patients with preexisting seizure disorders.[229-231] This effect is rare and is more often associated with lower potency agents, especially with very high dosages or after a rapid increase in dosage. Caution is therefore advised for patients with a known history of seizure disorder. Sedation, as was discussed earlier, can be a problem for some patients. It occurs more frequently with the lower-potency agents with antihistaminic properties, and often improves after a few weeks of treatment. Confusion or delirium as a result of the anticholinergic effects of antipsychotics occurs more frequently with lower-potency agents. It is more likely to occur in the elderly or organically impaired patient, or in patients taking more than one agent with anticholinergic properties. Occasionally mistaken for a worsening of psychosis, anticholinergic delirium can be properly diagnosed by examination of the patient (dilated pupils, dry, flushed skin, rapid pulse, elevated temperature, mild hypertension) and more definitively by the physostigmine test (1 to 2 mg physostigmine salicylate i.v., repeat in 30 min) with proper medical supervision and monitoring. Neuroleptic malignant syndrome (NMS) is a poorly understood, rare, adverse effect of antipsychotic treatment consisting of pronounced extrapyramidal symptoms (rigidity and involuntary movements); severe hyperthermia, tachypnea, autonomic signs (diaphoresis, increased salivation, blood pressure fluctuation, tachycardia); and a fluctuating level of consciousness.[232-234] Laboratory abnormalities include leukocytosis, elevated muscle (CPK) and liver enzymes. It usually begins soon after treatment is initiated or after an increase in the dose of medication. Haloperidol seems to be most frequently associated with this syndrome.[234] The etiology of this hypothalamic crisis is unknown,[232] but fatality from aspiration, hypoventilation from decreased chest wall compliance, cardiovascular collapse, and renal failure occur in up to 20% of patients.[233] Early recognition is imperative and NMS should be suspected in any patient exhibiting pronounced EPS and hyperthermia in the absence of infection. After stopping the offending agent, the syndrome usually resolves in several days (longer for depot forms). Further treatment consists of supportive medical care (antipyretics, cooling blankets, fluid replacement) and treatment of secondary complications.

Reports of permanent CNS damage resulting from combined haloperidol and lithium have appeared in the literature.[235] While a rare, synergistic effect cannot be ruled out, it is likely that at least some of these cases were due to an unrecognized combination of NMS and lithium toxicity.[234]

Table 11
CARDIOVASCULAR EFFECTS

Effect	Mechanism	Comment
Orthostatic hypotension, syncope, dizziness	Alpha-adrenergic blockade	Low potency agents > others. Caution in elderly, cardiac patients. Elastic stockings may help.
ECG effects: ST-segment depression, T-wave flattening, notching, inversion. ↑ P-R interval ↑ QRS duration ↑ Q-T interval	Quinidine-like effect	Low potency agents > others, especially thioridazine. Avoid in patients with cardiac disease.
Sinus tachycardia	Anticholinergic	Low potency agents > others. Caution for patients with cardiac disease.

C. Cardiovascular Effects

Orthostatic hypotension, as discussed earlier, is probably the most serious cardiovascular effect of antipsychotics. Serious orthostasis or frank syncope can result. It is especially common in elderly or cardiac patients who may be taking several different drugs simultaneously (especially beta-adrenergic blockers or vasodilators). Early detection of possible orthostatic hypotension by careful monitoring is the best preventive measure. For mildly symptomatic patients, elastic stockings may be helpful. Should a patient require acute medical treatment for severe, acute hypotension, general medical support is advised. If the usual techniques (recumbent position, fluid replacement, oxygen) fail and pressor agents are indicated, alpha-adrenergic agents such as Levophed® (*l*-norepinephrine) should be used. Beta-agonists such as isoproterenol or epinephrine may worsen hypotension in combination with antipsychotic-induced alpha-blockade and should be avoided. Congestive heart failure has been associated with antipsychotics,[235] possibly by decreasing cardiac contractility. It is unlikely that a healthy individual will experience any serious difficulty, but elderly or cardiac patients may be at increased risk, and high-potency agents may be safer in these patients. Agents with strong anticholinergic properties which could cause an elevated heart rate similarly should be avoided. The ECG changes most commonly seen are shown in Table 11, and seem to be associated more with low-potency agents. Dosages over 200 mg of thioridazine per day may cause some effects, while dosages several times this amount are probably required to produce significant conduction and repolarization effects. Antipsychotics, especially phenothiazines, have quinidine-like effects and may be arrhythmogenic. Sinus tachycardia, atrial fibrillation and flutter, premature ventricular contractions, ventricular tachycardia, and A-V conduction disturbances have all been reported.[237] These are most often seen with high dosages of low-potency antipsychotics. High-potency antipsychotic agents such as haloperidol provide a wider margin of safety and should be considered in treating cardiac patients or patients with preexisting cardiac conduction defects.

D. Gastrointestinal Effects (See Table 12)

These are primarily anticholinergic and include dry mouth and constipation as the most frequent effects. Urecholine® (10 to 25 mg t.i.d.) may help dry mouth. Stool softeners can usually help constipation. Paralytic ilius occurs rarely, most often in the elderly patient. Dysphagia, a rarely recognized Parkinsonian side effect, can predispose patients to aspiration and its complications.[238] A small percentage (0.5 to 2%) of patients may experience cholestatic jaundice, usually during the first few weeks of treatment.[239] This is more often

Table 12
GASTROINTESTINAL EFFECTS

Effect	Mechanism	Comment
Dry mouth, constipation, fecal impaction, paralytic ileus	Anticholinergic	Low potency agents > others. Caution in elderly.
Dysphagia	Parkinsonian effect	Increased risk for aspiration. Antiparkinson agents may be useful.
Hepatotoxicity (jaundice, elevated liver enzymes)	Allergic or idiosyncratic	Chlorpromazine and other phenothiazines > other agents. Switch to another class if continued treatment urgent.

associated with chlorpromazine treatment than with other antipsychotics. Treatment consists of stopping the drug. If a patient must be treated, switching to a chemically dissimilar class of antipsychotics is usually safe. Liver enzymes and bilirubin usually return to normal within a month. Patients who have symptoms or laboratory abnormalities for a longer period of time should be further evaluated medically.

E. Genitourinary Effects

Distressing but rarely serious genitourinary effects can occur with antipsychotic treatment (Table 13). Urinary hesitancy is common in the elderly, and especially in males with enlarged prostates. Urinary retention may rarely occur. Using low-anticholinergic agents may be helpful in minimizing this effect. Urecholine® (10 to 25 mg t.i.d.) may help counteract the peripheral anticholinergic effects. Impaired erection or ejaculatory dysfunction (impaired, delayed, or retrograde ejaculation) in males can be an extremely distressing problem and is most often associated with thioridazine.[240,241] Priapism may also be a rare side effect of the phenothiazines.[242] Since patients are often embarrassed to volunteer information about sexual difficulties, they should be questioned specifically about this. These are often ameliorated by switching to another agent and reassuring the patient.

F. Endocrine and Metabolic Effects (Table 14)

Hyperprolactinemia from antipsychotic treatment may cause breast enlargement with or without galactorrhea in either sex. This can be especially distressing for extremely psychotic male patients. Amenorrhea or irregular menses due to increased prolactin levels often occur in females receiving antipsychotic agents. For females of child-bearing age with breast enlargement and amenorrhea, pregnancy should be ruled out by appropriate consultation. Antipsychotic drugs can cause false positive pregnancy tests.[243] The use of the beta-subunit of human chorionic gonadotropin has been suggested to be a helpful laboratory aid in diagnosing pregnancy in the presence of antipsychotics.[244] Decreased libido and fertility are occasionally observed and may relate to alterations in pituitary-gonadal hormones, although some experts feel that these are of doubtful clinical significance.[245] Thioridazine may suppress testosterone production in males more than other antipsychotics.[246]

Other hypothalamic effects may occur. Increased appetite is commonly seen in patients receiving antipsychotics and weight gain is frequent. Inappropriate secretion of antidiuretic hormone (SIADH) may be mistaken for psychogenic polydipsia and should not be overlooked in patients with water craving.[247] Temperature regulation can be impaired by antipsychotic drugs (both hypo- and hyperthermia) and patients should be warned to use extra caution when being exposed to temperature extremes in either direction.

Antipsychotic medications may interfere with regulation of blood glucose. This is rarely of clinical significance, and there is no contraindication to using antipsychotic medication in patients with diabetes.

Table 13
GENITOURINARY EFFECTS

Effect	Mechanism	Comment
Urinary hesitancy, urinary retention	Anticholinergic	Low potency agents > others. Caution in elderly, especially males with enlarged prostate
Impaired erection, ejaculatory disturbance (absent, delayed, retrograde), priapism	Multiple autonomic effects	Thioridazine > others; switching agents may help

Table 14
METABOLIC AND ENDOCRINE EFFECTS

Effect	Mechanism	Comment
Galactorrhea, irregular menses or amenorrhea	Prolactin elevation	Rule out pregnancy in females
Decreased libido	Hypothalamic	Thioridazine may be > others in men
Increased appetite	Hypothalamic	Caloric restriction to control weight gain
Polydipsia (nonpsychogenic)	Inappropriate ADH secretion	Rule out SIADH[a]
Impaired temperature regulation (hypothermia or hyperthermia)	Hypothalamic	Advise patient

Table 15
DERMATOLOGIC EFFECTS

Effect	Mechanism	Comment
Photosensitivity, hyperpigmentation	Drug-protein complexes formed in skin	Chlorpromazine > other agents. Prevent with sunscreen. Switch to agent of another class
Rash, urticaria, pruritis, exfoliative dermatitis (rare)	Allergic	Switch to agent of another class

G. Dermatologic Effects (Table 15)

Photosensitivity can occur with antipsychotic drugs, most notably with chlorpromazine and thiothixine, but can occur with most agents.[248] It may be avoided by using a sunscreen preparation on sun-exposed skin areas. Patients who experience this effect should avoid sunlight and switch to a different antipsychotic medication. A related effect which occurs later is hyperpigmentation. Sun-exposed areas become a blue-gray color. This occurs more often with chlorpromazine than with other agents, and often occurs in conjunction with lens and cornea changes (see next section) after long-term exposure to high dosages of chlorpromazine. High-potency agents of a different class should be used in patients with a history of hyperpigmentation. As with any drug, allergic rashes may occur. Rarely, progression to severe exfoliative dermatitis results.

Table 16
OPHTHALMOLOGIC EFFECTS

Effect	Mechanism	Comment
Blurred vision	Anticholinergic	Tolerance usually develops, can use less anticholinergic agent Pilocarpine eyedrops
Precipitation of narrow-angle glaucoma	Anticholinergic	Immediate medical treatment
Pigmentary retinopathy	Drug-melanin interaction in retina	Thioridazine > other phenothiazines. Avoid > 800 mg thioridazine per day. Switch to high potency nonphenothiazine
Lens and corneal opacities	Drug-protein interaction	Chlorpromazine in high dosages. Switch to high potency nonphenothiazine

H. Ophthalmologic Effects (Table 16)

Agents with high anticholinergic properties can cause blurred vision in some patients, which is more bothersome than serious. This usually improves within a few weeks of treatment, but, if it persists, switching to a high-potency agent or adding pilocarpine eyedrops usually suffices. Precipitating narrow-angle glaucoma can be a serious adverse effect which requires immediate medical attention. Patients with open-angle glaucoma can usually be treated safely with agents with low anticholinergic properties, but ocular pressure should be checked periodically to ensure safety. Irreversible retinal pigmentation and degeneration can result from high doses (over 1200 mg per day) of thioridazine.[249] For this reason, dosages under 800 mg are recommended. If a patient should develop retinal pigmentation, switching to a nonphenothiazine is indicated. Corneal and lenticular opacities may result from long-term, high-dose treatment with phenothiazines.[250] It is usually reversible if the offending agent is stopped and another agent is substituted.

I. Hematologic Effects (Table 17)

Transient leukopenia is encountered in about 1% of the patients taking phenothiazine antipsychotics.[251] Rarely, it may herald the onset of agranulocytosis, a potentially lethal problem. It usually occurs during the second month of treatment. Routine blood counts during early treatment might be useful, but astute clinical observation is more important. This effect is not dose-related and may occur after the initiation of treatment of any new agent.[252] Patients developing suspicious symptoms — fever, malaise, sore throat, or other manifestations of infection should be immediately evaluated for leukopenia.

J. Developmental Effects

Despite the lack of evidence for serious risk of fetal malformation due to phenothiazine treatment, the safety of using drugs during pregnancy cannot be assumed. Antipsychotic drugs cross the placental barrier. Subtle, possibly long-term behavioral effects (behavioral teratogenesis) may be possible, and long-term learning disabilities have been demonstrated in the offspring of female rats given antipsychotics during development.[253] As a general rule, it is best to avoid the use of any drugs during pregnancy, particularly during the first trimester. For pregnant females with serious psychiatric illness, however, the risks of not taking medicine must also be considered to balance the clinical decision. Informed consent should be obtained under these circumstances. Antipsychotics are secreted in breast milk to

Table 17
HEMATOLOGIC EFFECTS

Effect	Mechanism	Comment
Leukopenia	(Unknown)	Benign, usually transient
Agranulocytosis	Probably allergic	Discontinue agent. Immediate medical attention required

Table 18
IMPORTANT DRUG INTERACTIONS WITH ANTIPSYCHOTIC MEDICATION

Agent	Effect
Antacids	Decrease absorption of antipsychotic
Anesthetics	Potentiate hypotension
Anticholinergics	Decrease absorption
Anticoagulants	Increase bleeding time
Antidepressants	Increase tricyclic levels, additive hypotensive effects
Antihypertensives	
Beta blockers (propranalol)	Potentiate hypotension
Diuretics and smooth muscle blockers	May potentiate hypotension
Alpha methyldopa	May potentiate hypotension
Guanethidine	Antagonizes antihypertensive effect
Clonidine	Variable
Anticonvulsants	May decrease antiseizure effectiveness
Barbiturates (chronic use)	Decrease antipsychotic level
(acute use)	Increase CNS depressant effect
Estrogens	May increase antipsychotic blood level
Oral hypoglycemics	Variable
L-Dopa	Mutual antagonism
Lithium	Possible toxic synergism with haloperidol
Narcotics	Potentiate analgesia
Pressor agents	
Alpha agonists (norepinephrine)	Antagonize pressor effect
Beta agonists (isoproterenol)	Marked hypotension
Quinidine	May potentiate cardiac effects
Sedative-hypnotics	Additive CNS depressant effects

some extent, and lactating mothers should be advised to avoid breast feeding while taking antipsychotic medication.

K. Drug Interactions

Medical and psychiatric disorders often coexist. Some patients may be taking any of a variety of medications simultaneously with antipsychotics, and clinicians should be aware of the most common interactions. The more important antipsychotic drug interactions appear in Table 18.

L. Sudden Death

Occasional reports of sudden death in previously healthy patients receiving antipsychotic medication have appeared in the literature. Numerous causes including asphyxiation, cardiac arrhythmias, aspiration from impaired swallowing, and dystonic strangulation have been advanced. Leber[254] recently reviewed this phenomenon and raised serious questions as to whether there is any evidence indicating that there is a greater risk of sudden death in patients

receiving antipsychotic medication. He cited one study showing that the risk of death in unmedicated, hospitalized schizophrenic patients was not different than it was in in the era prior to the introduction to antipsychotic medication.[255] Only well-controlled, epidemiologic studies will answer this question. All medication treatments carry some risk. At the present time there does not seem to be a need for undue concern over possible sudden death in patients receiving antipsychotic medications.

XI. SUMMARY

Antipsychotic medication treatment is an important pharmacologic tool for the general psychiatrist. The need for careful identification of drug responders by careful neurodiagnostic evaluation and establishing reasonable treatment outcome expectations has been stressed. A logical approach to antipsychotic treatment with the routine use of blood levels can help optimize treatment response and compliance. It is our hope that the basic pharmacologic principles stressed in this chapter will provide helpful guidelines for the front-line practitioner for improving antipsychotic treatment in a general psychiatric practice.

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Chapter 9

ANXIOLYTICS: PREDICTING RESPONSE/MAXIMIZING EFFICACY

Cary Hamlin and Mark S. Gold

TABLE OF CONTENTS

I. INTRODUCTION

In this chapter we will discuss the nature and clinical scope of the symptom of anxiety, its differential diagnosis and how to treat it using drugs and behavior therapy. The recent distinction between endogenous and exogenous anxiety is developed from the data which support it. The occurrence of these is placed within the natural histories of anxiety syndromes, and both the DSM III and Sheehan's classification of these syndromes[24] are discussed. The differential diagnosis of anxiety, including history, physical examination, and laboratory examination points of difference are discussed optimizing treatment response by marking the correct diagnosis is emphasized. Treatment approaches using the expanding group of available anxiolytics in specific syndromes are based upon data from the molecular biology of receptor binding in various neurotransmitter systems, observed efficacy, toxicity, comparative efficacy, pharmacokinetics, and efficacy of drug combinations. The increasing role of measurements of plasma drug concentrations in deciding upon dosage schemes is discussed. Some comparative efficacy studies between the behavioral approaches to specific anxiety syndromes are discussed, and the role of drug therapy-behavior therapy combinations is emphasized. Finally, sample case treatment protocols in selected anxiety syndromes are discussed to simulate real case management, and the use of target symptoms and the laboratory as a guide to therapy is discussed. The material in this chapter will provide the reader with an extensive data base for the practical management of anxiety disorders.

II. CONCEPTS OF ANXIETY AND FEAR

The term anxiety is derived from the German "angst" meaning fear, and has been defined in the literature differently by different authors. May defined anxiety as diffuse apprehension which differs from fear in its vagueness and objectlessness.[1] Freud states the following: "... the conclusion we have come to then, is this. Anxiety is a reaction to a situation of danger."[2] Wolpe and Lazarus defined anxiety as an emotional habit associated with autonomic arousal involving a primitive level of neural organization.[3] Izard defined anxiety as a combination of two or more of seven "fundamental emotions" (e.g., fear, guilt, interest, surprise, shame, anger, and joy), one of which is fear.[4] Each of these definitions merits consideration as a summary of professional experience related to anxiety, and for drawing attention to the features of anxiety. These features are as follows.

Anxiety is a fear-like emotion associated with a subjective sense of impending doom which motivates escape. It is a response to situations perceived as dangerous. It can be associated with new situations by conditioned response learning. The emotional response is disproportionate to the objective threat. Anxiety is associated with characteristic posture,

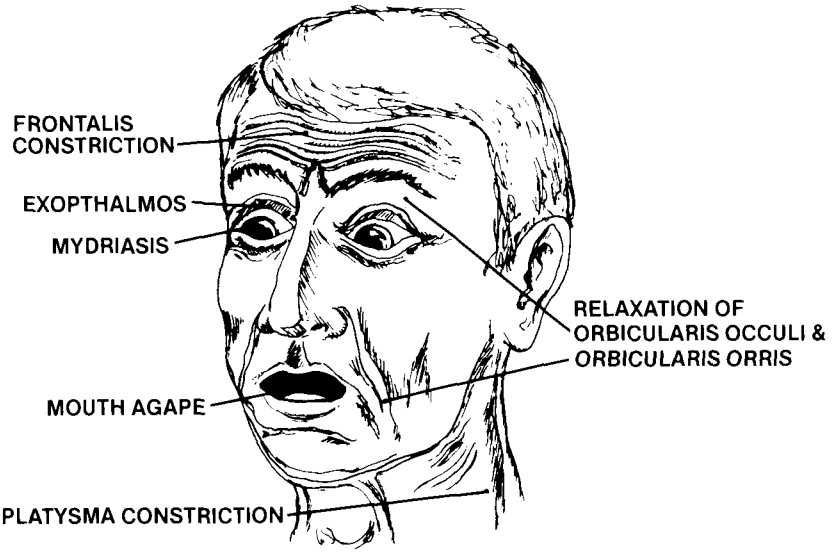

FIGURE 1. Facial expression of anxiety.

muscle tone, and neuroendocrine changes. Anxiety is an epiphenomenon of nervous system physiology. Anxiety problems usually present as fear complexed with other emotions. Universal agreement upon any specific definition of anxiety is unlikely, but an integration of the preceding features approximates the truth. Anxiety is defined here simply to mean morbid fear.

The mood of fear is part of a complex nervous system mechanism which normally provides for homeostasis of the external milieu and thus for survival of the individual. Noxious exposure, i.e., negative deviations from physiological optimums of internal regulation (e.g., glucose concentration, oxygen pressure, fluid volume, tissue damage, body temperature, etc.), serves as an unconditioned stimulus to fear and a timely signal of a threat to survival.

One develops the subjective sense that something awful is about to happen. One's affect takes on a characteristic expression, as Charles Darwin noted in 1872 (see Figure 1).[5] One's muscle tonus[6,7] is increased in certain groups as a result of increased gamma motor neuron activity; however, very acute fear can be associated with decreased muscle tonus. Tension-type headache and fatigue are common. The peripheral sympathetic nervous system is activated resulting in elevations of epinephrine and norepinephrine with resulting symptoms and signs (e.g., dry mouth, sweaty cold hands and feet, paresthesias, sinus tachycardia, elevated blood pressure, shortness of breath, hyperventilation, light headedness, sighing, urinary hesitancy, and constipation).[6-9] Chronically anxious women may have irregular menstruation or amenorrhea. Very acute fear is often associated with parasympathetic activation and gaps of cardiac action (rarely cardiac arrest), syncope, decreased BP, diarrhea, nausea, urinary frequency, and even incontinence of urine or stool. Fear is associated with the alarm reaction of Selye's general adaptation syndrome, and ACTH and cortisol plasma levels increase.[10] There are a variety of other neuroendocrine changes including elevations of TSH, ADH, GH; and depression of prolactin, FSH, and LH.[11-17]

Mental status examination of an extremely fearful person will reveal beta-adrenergic tremor, increased locomotor drive and pacing, hand wringing, fidgeting, fearful mood and affect, inhibition of euphoric responses and libido, increased vigilance and scanning, disaster avoidance planning, inhibition of drowsiness, difficulty falling asleep, and concretization of thinking.

One's fear motivates behavior to avoid the impending noxious exposure.[18] If the avoidance behavior is successful, one feels a euphoric burst, heaves a sigh of relief, and survives.

The relationship between task performance, fear, and task complexity is given by the Yerkes-Dodson Law.[19] For tasks of a given complexity, the relationship of performance to fear is an "inverted U shaped curve!" The performance optimum approaches zero fear as task complexity becomes great. For complex tasks then, fear disrupts performance.

The picture of fear in the monkey is quite similar to that in man. Darwin was the first to note the similarity of muscle contractions in the face and affective expression.[5] There is also hand wringing, hair pulling, pacing, potentiated startle, clutching, and a tendency to flee.[20] The fact that fear-like states exist in all mammals, reptiles, birds, and amphibians is a testimony to the success of fear as an evolutionary tool to promote survival.[21]

III. CLINICAL OCCURRENCE OF FEAR AND ANXIETY

A. Normal Fear

Fear is an emotion which is commonly and universally experienced in human life. A random study of adults in a Western population found that 40% were significantly afraid at the time of interview.[22] Normal people worry a lot. Everyday life is full of situations which could lead to doom. Most do not, and this fact is in no small part due to the avoidance behaviors which fears motivate. Threats are foreseen, and dangers are averted. Unfamiliar threats provoke nervousness and avoidance, but with practice threats become familiar, avoidance becomes automatic, and nervousness only arises again if avoidance is unsuccessful. The mood of fear can be a realistic reaction to dangerous circumstances. Such fear is normal and appropriate, and treatment of such fear might harm the patient by compromising his defenses.

B. Differential Diagnosis of Anxiety

Having ruled out normal fear in the differential diagnosis of anxiety, one is left with the mental or physical disorders which have anxiety as a prominent symptom.

The diagnosis of mental disorders in general and anxiety-phobic disorders in particular has been a nosological nightmare, with few workers having complete confidence that what they described as being an anxiety neurotic was quite the same as someone else's description. The presence of many unconscious dynamic mechanisms made objective assessment difficult. The presence of heterogeneity within experimental groups made conclusions about treatment effects tentative. However, recent advances in understanding of the natural history of anxiety disorders have resolved much of this muddle.

A considerable improvement in nosology has resulted from the implementation of Diagnostic and Statistical Manual III (DSM III) and multiaxial assessment.[23] This method utilizes good syndromal classification system, which permits a description of stressors, symptoms, and signs, character structure, concomitant physical illness, and coping success. Adult anxiety and fear disorders, according to DSM III, (Axis I) are as follows:

Adjustment Reaction with Anxious Mood, Simple Phobia, Post Traumatic Stress Disorder, Panic Disorder, Panic Attacks with Agoraphobia, Agoraphobia (only), Social Phobia, Hypochondriasis, Obsessive-Compulsive Disorder, and Generalized Anxiety Disorder.

Sheehan and Sheehan, who have subjected anxiety-phobic diorders to Kraeplinian analysis of changes in symptoms over time, believe that the DSM III syndromal classification system is seriously inadequate in a number of ways.[24] It is difficult to make distinctions between symptom configurations because a single patient may pass from one configuration to another during the course of illness. The categories are not mutually exclusive. The Sheehans have proposed an alternative syndromal classification which asserts that many of these disorders are simply different responses to endogenous anxiety at various times after its onset. Dis-

tinctions between somatization disorder, hypochondriasis, panic disorder, agoraphobia with panic attacks, agoraphobia, generalized anxiety disorder, social phobia, and depersonalization disorder lose relevance to diagnosis and become relevant only in terms of understanding coping strategy or for understanding secondary conditioning of panic. The Sheehans have incorporated the above disorders into four endogenous anxiety conditions: minor endogenous anxiety, major endogenous anxiety, minor endogenous phobic anxiety, and major endogenous phobic anxiety. Simple phobia, post traumatic stress disorder, and adjustment anxiety are renamed exogenous phobic anxiety, chronic exogenous anxiety, and acute exogenous anxiety. This classification system properly notes that some anxiety is an understandable (albeit excessive) response to external stress, and some anxiety reflects neuropathology of the stress response mechanism. Sheehan's new classification system will be presented and criticized within sections on the "old" DSM III system.

Depressive and Schizophrenic Disorders (DSM III Axis I) which have anxiety as a prominent symptom are as follows:

Dysthymic Disorder, Major Depression, Bipolar Depression, Schizophreniform Disorder, Paranoid Schizophrenia, Paranoid Disorder.

C. Anxiety in Adjustment Disorder

Adjustment Reaction with Anxious Mood (DSM III) is a condition in which anxiety (excessive fear) follows within three months of identified stress. This anxiety may significantly impair social or vocational functioning. The diagnosis is not made if the overreaction is part of a general pattern of such reactions. The gamut of possible stressors can cause this reaction, including physical illness. Sheehan calls this disorder Acute Exogenous Anxiety.

D. Anxiety in Simple Phobia

Simple Phobia (DSM III) is a persistent and irrational fear of an object or situation which is known to be reasonably safe. The feared objects are commonly animals like snakes or spiders, or dead people, but they may be almost anything. The feared situations are commonly falling, flying, heights, closed spaces, thunderstorms, darkness, but also may be almost anything. The anxiety is anticipatory of the occurrence of the specific object or situation, and it is associated with avoidance of that object or situation.

The onset of simple phobia can occur at any time of life, and it is often associated with some traumatic experience the patient relates to the object or situation. Some simple phobias, such as of snakes or falling, can be instinctual. Anxiety can generalize and result in generalized anxiety disorder.

Simple phobia is not diagnosed if the situation is being alone or trapped (agoraphobia), a social setting (social phobia), or if it occurs in the presence of another mental disorder. Sheehan calls this disorder Exogenous Phobic Anxiety.

E. Anxiety in Post Traumatic Stress Disorder

Post Traumatic Stress Disorder (DSM III) consists of anxiety associated with reexperience of a prior traumatic event. The traumatic event must be objectively extremely stressful such as experiencing murder, rape, accidents, natural disasters, war, etc. It is stress which is "outside the range of usual human experience" (DSM III). The later anxiety reaction may occur years after the event. Reexperience is indicated by the belief that it is about to happen again, anxiety and avoidance behaviors, intrusive recollection, difficulty falling asleep, nightmares, potentiated startle, and sympathetic arousal. Friedman, who has studied the syndome in veterans, emphasizes that anxiety is associated with guilt about having survived, and that patients may feel responsible somehow for the event.[25] They are preoccupied with it and withdraw from friends and hobbies. Intense guilt may be associated with frank paranoia. Friedman has called attention to these patients' use of compulsive personality defenses (e.g.,

isolation of affect, "over controlled") as a coping strategy; but he notes that it is the severity of the stress and not personality characteristics which predicts the magnitude of psychopathology.[25] Sheehan calls this disorder Chronic Exogenous Anxiety.

F. Anxiety in Panic Disorder

Panic Disorder (DSM III) patients report spontaneous acute anxiety attacks, and they must have three attacks within 3 weeks. Sheehan has pointed out that patients having less frequent panic attacks of the same type probably have the same disorder, and notes that three panic attacks in 3 months qualifies for Major Endogenous Anxiety. In DSM III terms, such patients are diagnosed Atypical Anxiety Disorder.

The typical story of the onset of the anxiety attacks is remarkably the same in different patients.

The majority of these patients have a Compulsive Personality Disorder or at least prominent Compulsive Personality defenses. There is a history of anxiety when out of control, a tendency to experience being out of control as not being good enough, and the use of compulsive rituals, like writing lists of things to do, to attempt to reestablish control. These patients have a lot of overly negative thinking and usually expect the worst.

Prior to the onset of the panic attacks, there is usually a history of increased stress and striving compared to other times in the patient's life. Going to college or graduate school, getting married, having children, moving, starting a new job, getting separated or divorced or breaking up with a steady date, having the flu, etc., or some combination of stresses are often seen in the few months prior to onset. Often there has been the feeling that one was behind and having to work hard just to keep up. Furthermore, in the hour or so prior to onset there also is commonly a history of a stressful activity; domestic discord; exercise, rush hour traffic, being late for an appointment, etc. Occasionally there is no unusual stress at all at the time of onset.

Usually the onset is acute, without warning, and experienced as a bolt from the blue. Sheehan has noted that the anxiety is maximal within seconds, in contrast to anticipatory anxiety which requires several minutes to reach maximum intensity, if it ever does.[24] Sometimes a combination of vertigo, nausea, and tension headache occur fleetingly beforehand. The patient is gripped by an apprehension that death is imminent. The heart is felt pounding rapidly or skipping, and this may be experienced as painful. The patient commonly fears that he is having a heart attack. Breathing is fast and shallow. The patient is short of breath, light headed, and may be afraid "my lungs were filling up." The patients often have observable palor, sweating, mydriasis, and diffuse tremor. Diarrhea is occasionally seen and nausea is common. Feelings of unsteady legs often lead the patient to fear falling down, and stories of patients obliged to sit down on the sidewalk are not rare. The patient's experience of her surroundings and herself is altered, and depersonalization and/or derealization is seen in the majority. Attention is decreased and patients note that things don't sink in. One patient noted being so scared she couldn't move or think. And then after about 5 or 10 min the extreme anxiety goes away as suddenly as it came. The patient is breathless, weak, fatigued, and wondering "what was that?"

Histories from many panic disorder patients reveal that full-fledged spontaneous attacks are only the tip of the iceberg of endogenous anxiety which these patients experience. Commonly, they also experience partial spontaneous panic attacks, and these may also reinforce secondary apprehension and avoidance. The "minor endogenous anxiety" attacks consist of one or two symptoms of a complete panic attack, such as tachycardia, shortness of breath, hyperventilation, paresthesias, hot flashes, nausea, tremor, depersonalization, sweating, alterations of sensory perception of sound, light, apprehension, etc. These minor attacks can be confused with cardiac, respiratory, gastrointestinal, or other neuroendocrine diseases as well as exogenous anticipatory anxiety which panic patients also experience.

Proper identification of them as endogenous anxiety attacks can be assured by noting that they occur spontaneously and have an instantaneous onset. The patient is surprised by the event. If patients have only minor attacks, three in 3 months, Sheehan classifies this as Minor Endogenous Anxiety.[24] If patients have three major attacks in 3 months, and have minor attacks also, the patients have Major Endogenous Anxiety. It is important to note that panic disorder often presents with minor endogenous attacks years before major attacks or phobic avoidance occurs.

These patients usually don't have to experience anxiety attacks more than once or twice before consulting their physician. Typically, the physician takes a history, does a physical and laboratory tests and tells them he can find nothing wrong except that they are nervous. This uniformly fails to reassure the patient who correctly surmises there is something awfully wrong. Patients "doctor shop" and frequently end up at the cardiologist (10 to 14% of cardiology patients), the neurologist ("I must have a brain tumor"), and the psychiatrist ("I must be going crazy"). Commonly, they are misdiagnosed and placed on a benzodiazepane hypoglycemic diet, psychotherapy, a neuroleptic; and they continue to have panic attacks. They become preoccupied by symptoms and they lose hope.

Sheehan has outlined seven stages in the natural history of panic disorder.[26] Stage one consists of sub-panic anxiety attacks. Stage two consists of panic attacks as previously described. Stage three consists of hypochondriasis symptoms. Stage four consists of single phobia. Stage five consists of social phobia. Stage six is agoraphobia. Stage seven is depression. Sheehan notes that the frequency of panic attacks determines the rate of progression through the stages, and those with infrequent attacks may not develop all the stages. The usual endogenous anxiety attack rate is about two to four per week. Sub-panic attacks with less than three symptoms also occur, usually mixed with full panic attacks.

Isaac Marks et al. were the first to report that some patients with panic disorder and agoraphobia turned to the abuse of alcohol and other sedatives to cope with anxiety.[27] He estimated the incidence of such abuse in this population to be 10%. These findings were repeated by Donald Klein's group, and they comment, "We believe one should suspect this syndrome in all sedative and alcohol abusing patients who have histories of anxiety attacks in the past, or evidence of phobias, of both."[28] A careful clinical history of some alcohol and sedative abusers will reveal the "closet" panic disorder, and will suggest a most effective course of treatment.

Sheehan's attempt to unify a number of anxiety states as successive phenomenological phases in the natural history of "endogenous anxiety" deserves careful consideration. If he is correct, then he has added significantly to the problem of understanding the pathophysiology of anxiety. Does real life conform to this model? Is it really true that hypochondriasis, social phobia, depersonalization disorder, somatization disorder, generalized anxiety disorder, and agoraphobia only exist associated with and in response to anxiety attacks?

Several social phobic patients, whom we have interviewed since the dichotomy between endogenous anxiety and exogenous anxiety has been clearly defined, have said that they never experienced endogenous anxiety. Further, the premorbid personalities of panic disorder patients who become socially phobic vs. other socially phobic patients seem different. Those who have anxiety attacks are seldom shy or avoidant premorbidly, and they develop social phobia in embarrassment of their tremulousness and lack of self-control. This is part of a pattern of anxiety and guilt in respect to loss of control. Our nonendogenous social phobic patients experienced anxiety of embarrassing themselves as part of a pattern of easily feeling embarrassed. Thus, anxiety is primary to shame in panic disorder, but shame is primary to anxiety in the other social phobics. Neither depends upon exogenous factors.

In the case of social phobias, it isn't true that they are *only* secondary to endogenous anxiety attacks; thus Sheehan's classification system leaves some anxiety patients without

Table 1
STIMULI TO ANTICIPATORY ANXIETY IN AGORAPHOBIA[34]

	(%)
Joining line in store	96
A definite appointment	91
Feeling trapped at the hairdresser	89
Increasing distance from home	87
Domestic quarrels	82

Table 2
STIMULI TO ANTICIPATORY ANXIETY RELIEF IN AGORAPHOBIA[34]

	(%)
Spouse's arrival	85
Sitting near the door in hall or restaurant	76
Being accompanied by a friend	60

a diagnosis. What the situation is for hypochondriasis, depersonalization, somatization, and generalized anxiety awaits further study. The mental disorders which produce anxiety are less murky than they used to be, particularly by Sheehan's accounts of panic disorders; but they have yet to be totally and clearly accounted for by anyone.

G. Anxiety in Agoraphobia with Panic Attacks

The patient's reaction to the panic attacks can take several forms, as previously noted, and one of these is development of agoraphobic symptomatology. The patient tries to anticipate situations where having a panic attack would be particularly disastrous, a process proceeding by "what ifs?" For example, "what if I were driving on the expressway and I had a panic attack?" What if I were on a bridge ...?" "What if I were in an elevator...?" Places perceived as difficult to escape from are the first to be associated with anticipatory phobic anxiety and the first to be avoided (see Table 1). Other people, sometimes significant others but often casual acquaintances, come to be seen as escape routes, and the patients develop anticipatory anxiety if alone (see Table 2). Sometimes patients are so adept at getting other people to stay with them that they are not territorially restricted at all, but this is not the rule. Usually, there is a progressive restriction of mobility until the patient is housebound with a sequence of friends and relatives providing constant companionship.

It is asserted by some clinicians that the development of agoraphobic symptoms occurs because of patients having had panic attacks in supermarkets, on bridges and elsewhere outside the home, and that secondary anticipatory anxiety in those situations is conditioned by those events. Patients thus retreat to home because they don't get panic attacks there. While there is no doubt that classical conditioning can produce housebound patients, this assertion has not been supported by data from most of them. Patients invariably do experience high anxiety in check out lines, on bridges, etc., but careful questioning will reveal that it is not panic anxiety but anticipatory anxiety. Histories of spontaneous panic occurring first are rare. Also, several patients have reported a few panic attacks in succession, then much rumination about what if, then being housebound. There were no intermediate conditioning experiences at all. Finally, some patients report panic attacks first occurred at home, yet

they became housebound. Thus, classical conditioning to panic experiences is neither necessary nor sufficient to the development of secondary anticipatory anxiety and agoraphobic situation type avoidance. Progression of agoraphobic situation avoidance can proceed by anticipatory hypothetical thinking about having panic attacks.

Panic disorder does not always progress to agoraphobia. Sometimes the patients obsess about the palpitation of their hearts and develop hypochondriasis. Some obsess about how ridiculous they look trembling or flushed and develop social phobia. Sometimes the patients progress to a generalized anxiety without agoraphobia. Sometimes the patients develop agoraphobia and generalized anxiety. Sheehan's stages are reported to progress by the frequency and severity of panic attacks, but these assertions are unconfirmed.[24] The parameters which determine one outcome of panic disorder vs. another hopefully will be clarified by future research.

In Table 3, the frequency symptoms other than phobias in agoraphobics and controls are listed.

H. Endogenous Anxiety Hypothesis

Donald Klein first advanced the hypothesis that spontaneous anxiety attacks were endogenous biological events unlike the anticipatory anxiety of psychoanalytic or learning theory.[287] An increasing body of knowledge supports this view. Already cited data from phenomenology and natural history of panic disorders support it. Data from phamacology will be presented in the sections on treatment. Data from physiology and genetics supporting the endogenous anxiety hypothesis are presented here.

Physiological data which suggest that spontaneous anxiety is associated with cellular pathology comes from two sources: different responses to standard stressors, and the association of panic attacks with nonnervous dysfunction. The first observation of a panic response to epinephrine infusion in anxiety disorder patients was probably made by Tompkins et al. in 1919.[31] They noted that soldiers with "irritable heart syndrome," but not control soldiers, developed anxiety attacks when given epinephrine (i.v.). This observation was repeated by Hunt et al. in 1932.[32,33] Unfortunately, these studies were marred by poor selection criteria caused by psychiatric naivete; the experimental groups were probably diagnostically diverse. This weakness was overcome by Lindemann and Finesinger's 1938 article confirming panic response in the panic disordered.[34,35] Others repeated the observations.[36-38]

Vlachakis and DeGuia found that norepinephrine infusion does not cause panic, which suggests that the panic response is specific to epinephrine.[39] Panic can be provoked by infusion of isoproterenol and this is blocked by propranolol, which suggests that beta adrenergic stimulation may underlie the epinephrine effect.[40,41]

The panic disordered are hypersensitive to a variety of physiologic challenges. They are more sensitive than normal to exercise, noise, bright light, and heat stresses.[42-44] We have observed that they perceive a standard painful stimulus more intensely and develop more anxiety in response to it than do normals.[45] They are more sensitive to separation stress than normal.[46] They have more spontaneous fluctuations of skin conductance measured by galvanic skin response, and are slower to habituate than normals.[47] They, but not normals, respond to sodium lactate infusion with a panic attack; this response is blocked by pretreatment with monoamine oxidase inhibitors or tricyclic antidepressants, which also stop their spontaneous panic attacks.[48-54]

The fact that panic disorder patients are hypersensitive to physiologic challenges has begun to be used as a diagnostic tool to determine homogeneity of nosologic groups, and to assess the adequacy of anti-panic medication.

Klein and Liebowitz, who pioneered in lactate infusion testing, report that 72% of patients with spontaneous panic attacks, but 0% of controls, respond to sodium lactate with panic.[55]

Table 3
SYMPTOMS OTHER THAN PHOBIAS IN AGORAPHOBICS AND CONTROLS[36]

	Agoraphobics (%)	Controls (%)
Generalized anxiety	80	17
Depression	30	3
Obsessional signs	10	3
Depersonalization	40	13
Decreased libido	53	3
Significant sedative abuse	10	—

Re-infusion of responders after 6 months of imipramine which stopped the spontaneous attacks resulted in 0% panic attacks. One month after the discontinuation of imipramine, lactate infusion testing still did not produce panic. Lactate-induced panic was associated with significant elevations of epinephrine and diastolic blood pressure. Thus examination of subjective mood changes, blood pressure, and catacholamine responses to lactate infusion can assist the diagnosis and medication management of patients with panic disorder.

Nonnervous abnormalities, specifically mitral valve prolapse and "straight back syndrome," may be associated with spontaneous panic attacks. Venkatesh et al., Kantor et al., Gorman et al., Brown et al., Udoshi et al., Davis et al., Crocoe et al., have observed associations of these three factors.[56-62] However, Sheehan has examined the relationship of panic attacks and mitral valve prolapse in a large series of patients using two-dimensional echocardiography, and he doubts that panic disorder is associated with mitral valve prolapse with more than random frequency. Further research is needed to resolve the question of nonnervous pathology and panic disorder.

Panic disorder is a genetic illness. The high familial prevalence was first noted by White over 30 years ago.[63] Early findings of 5% prevalence in the general population, but almost 50% in the children of one affected parent and 62% in the children of two affected parents, suggested an autosomal dominant trait having incomplete penitrance. This mechanism has been confirmed by a number of recent investigations.[64-66]

The endogenous anxiety hypothesis of panic disorder is therefore supported by data from a number of sources: from natural history, that there is a uniform age of onset of panic attacks which occur spontaneously; from physiology, that patients' anxiety is hyper-responsive to a variety of stressors; from pharmacology, that specific catacholamine manipulations eliminate panic; and from genetics, that spontaneous panic attacks are in an inherited trait. What neuropathological changes are responsible for endogenous anxiety is under investigation, but that there are such changes is difficult to dispute.

I. Anxiety in Agoraphobia without Panic Attacks

Agoraphobia without panic attacks (DSM III) has also been called "nonspecific insecurity syndrome." This disorder is chronic and insidious and its origin can be traced into childhood. Patients have an anticipatory fear of leaving safe places such as the home or the company of others upon whom they are dependent. Patients often have little experience of independence and considerable anxiety is provoked by the need to be self-reliant. Although their anticipatory anxiety can be intense, they do not experience anxiety attacks as agoraphobics with panic attacks do. Sheehan questions the existence of agoraphobia without panic attacks and notes that such a history is rare. The development of agoraphobia in the absence of even minor endogenous attacks is rare in our experience also.

J. Anxiety in Social Phobia

The social phobic fears the scrutiny of others. Situations in which such scrutiny occurs include lavatories, restaurants, public speaking, etc. Almost always there is a history of chronically low self-esteem and shyness, and a tendency to perceive reasonable behavior as inadequate and embarrassing. The social phobic expects to embarrass himself, fears embarrassing himself, develops anticipatory anxiety of social situations in spite of an awareness that the fear is excessive but often goes to the event anyway because "he should." Often there is fear that trembling in a social gathering will make one appear foolish. Note is taken of the tendency for people having an Avoidant Personality to develop social phobia.

K. Anxiety in Hypochondriasis

The hyponchrondriac is convinced that a symptom he has indicates serious disease. He is preoccupied by worry about the illness he anticipates having. His preoccupation with his health causes withdrawal from social and vocational commitment. He is not reassured by medical evaluation because of a phenomenal capacity to see the limitations in the evaluation procedures.

The anxiety is anticipatory and the diagnosis should not be made in the presence of panic, depression, or other mental disorders. Note is taken of the frequency with which these patients have preexisting compulsive personality and excessive guilt.

L. Anxiety in Generalized Anxiety Disorder

Generalized Anxiety Disorder (DSM III) patients have continuous presence for a month of (1) intense anxiety which is loosely attached to bad things that might happen, (2) tremulousness, fidgeting, increased tonus, potentiated startle, inability to relax, fatigue; (3) sympathetic hyperactivity, and (4) hypervigilance and decreased concentration, impatience, and difficulty falling asleep.

Generalized anxiety can be found associated with many different prior anxiety problems, and for the diagnosis it cannot be secondary to these.

M. Anxiety in Obsessive-Compulsive Disorder

In adolescence or adult life one sees the development of symptoms of obsessive-compulsive disorder in 0.05% of the general population, usually in people with premorbid features of Compulsive Personality.[67-68]

DSM III criteria for diagnosis are

1. The presence of either obsessions or compulsions. Obsessions are recurrent, persistent ideas that are ego-dystonic. Compulsions are repetitive and seemingly purposeful behaviors performed according to certain rules or in a stereotyped fashion. Compulsions are designed to produce or prevent some future situation. The acts are performed with a sense of compulsion and accomplish some reduction in anxiety, but the individual recognizes they are senseless.
2. Symptoms distress the patient and interfere with daily functioning.
3. Symptoms are not part of Tourette's Disorder, Schizophrenia, Major Depression, or Organic Mental Disorder.

Classical histories include patients with fear of contamination by germs who wash compulsively until their hands and forearms are erthymatous, patients with aggressive impulses who check themselves or write compulsively, and patients with obsessive slowness who must deliberate a long time to answer any question, even their names. These subtypes are not dichotomous, and the same patient may shift from one type to another during the typically chronic course.[69-72] There can be mixed states. Moods of guilt and anxiety are prominent.

Specific fears that objects have germs may lead patients to classify the house in terms of safe and unsafe places, and the perceived spread of germs by conditioned association may leave the patient with a generalized anxiety disorder and no place safe to hide. Disassociative symptoms of depersonalization are very common.[73] Obsessional phobias and anxiety symptoms have a compulsive quality and are associated with ritualized and other obsessional phenomena. People with Compulsive Personality frequently become depressed (33% of all Major Depression) and during depression may develop obsessional symptoms.[74] People with obsessive compulsive disorder may also become depressed, and their obsessional symptoms may increase. Obsessionals who become depressed attempt suicide less frequently than others with major depression.

Obsessional symptoms can occur in paranoid schizophrenia, after encephalitis, after concussion, in atherosclerotic dementia, and in hypothyroidism.[75] Of all patients who develop obsessive-compulsive disorder, 85% do so by age 35 years. Patients sick enough to require hospitalization seldom recover completely.[76]

N. Anxiety in Physical Illness

Pain produces anxiety if it is suficiently intense, independent of its implications vis-a-vis survival.[77] Thus trauma of many kinds (i.e., burns, fractures, arthritis, etc.), renal or biliary colic, headache, etc. are associated with anxiety symptoms. When the meaning of the pain is ominous or ambiguous, the amount of anxiety seen can be considerable.

The physical causes of anxiety-like symptoms include the following:[78]

1. Cardiovascular: Angina pectoris, arrhythmias, congestive heart failure, hypertension, hypovolemia, myocardial infarction, syncope (of multiple causes), valvular disease, vascular collapse (shock)
2. Dietary: Caffeinism, monosodium glutamate (Chinese-restaurant syndrome), vitamin-deficiency disease
3. Drug-related: Akathisia — secondary to antipsychotic drugs, anticholinergic toxicity, digitalis toxicity, hallucinogens, hypotensive agents, stimulants (amphetamines, cocaine, and related drugs), withdrawal syndromes (alcohol or sedative-hypnotics)
4. Hematologic: Anemias
5. Immunologic: Anaphylaxis, systemic lupus erythematosus
6. Metabolic: Hyperadrenalism (Cushing's disease), hyperkalemia, hyperthermia, hyperthyroidism, hypocalcemia, hypoglycemia, hyponatremia, hypothyroidism, menopause, porphyria (acute intermittent)
7. Neurologic: Encephalopathies (infectious, metabolic, and toxic), essential tremor, intracranial mass lesions, postconcussion syndrome, seizure disorders (especially of the temporal lobe), vertigo, catastrophic anxiety in dementia
8. Respiratory: Asthma, chronic obstructive pulmonary disease, pneumonia, pneumothorax, pulmonary edema, pulmonary embolism
9. Secreting tumors: carcinoid, insulinoma, pheochromocytoma

O. Differential Diagnostic Paradigm

The differential diagnosis of the symptom of anxiety consists of eliciting information about the patient with anxiety which permits classification of the patient as having one or more of the preceding conditions.

The first question which must be answered by data from the anxious patient is does the patient have a "physical" illness which explains the anxiety? In many of these conditions, (e.g., advanced COPD) the diagnosis will be made by "augenblink," and later it will be confirmed by laboratory and physical exam studies. In others, a careful history physical exam and routine laboratory may not be definitive, and only specific, highly specialized

tests done at the right time will reveal the cause, (e.g., pheochromocytoma). Clinical judgement from a broad based assessment of all the historical and physical exam data will usually suggest which patients need 24 hr urines for vanillylmandelic acid and which need a chest X-ray for pulmonary edema. Physical illness produces anxiety by several mechanisms, and these are useful to keep in mind to structure the differential diagnosis. One mechanism is by disruption of the internal milieu, such as occurs in pain, hypoxia, hypoglycemia, etc. This mechanism includes most of the cardiovascular, hematologic, and respiratory causes. Many metabolic and secreting tumor diseases also produce anxiety by this mechanism. A second mechanism is by disruption of avoidance mechanisms which renders them frequently unsuccessful. This mechanism operates in all conditions which produce diffuse cognitive or recent memory impairment, such as the deliria, dementias, etc., which occur by degenerative, infectious, traumatic, neoplastic, vascular, metabolic, or toxic causes. A third mechanism is direct selective physical activation of brain systems involved in fear or nociceptive response. This mechanism operates in some focal brain disease, such as third ventricle epidemoma or limbic epilipsy, in sedative or opiate withdrawal, in stimulant intoxication or caffeinism, in some endocrinopathy, etc. Some physical diseases, e.g., delirium tremens, produce anxiety by several mechanisms operating together.

The second question which must be answered, if the answer to the first question about physical causes is negative, is does the patient have a schizophrenic or depressive condition which explains the anxiety? Historical differential points which would result in a positive answer to question two are, respectively; the presence of voices, delusional reference, delusional paranoia, or formal thought disorder; or the presence of continuous anhedonia, continuous anergia, delusional guilt, or biological signs of depression. Biologic markers of depression are important in ruling it in or out. Primary anxiety disorders are not associated with a positive dexamethasone suppression test or an abnormality thyroid stimulating hormone (TSH) response to thyrotropin release hormone (TRH) in our experience or Sheehan's.[79,80] A composite of historical, mental status examination, psychologic tests, and psychiatric laboratory tests will permit the second question to be answered either positively or negatively. If the answer to both the physical anxiety and the psychotic anxiety questions is negative, then one is dealing with a primary anxiety disorder. Keep in mind that one often sees Major Depression or Atypical Depression in the course of panic disorders and that antidepressants will mask the spontaneous panic attacks, perhaps leading to incomplete diagnostic assessment.

The third question which one must answer in the differential diagnosis of the symptom of anxiety if the first two answers are negative is what anxiety disorder does patient have? The recent differentiation between endogenous and exogenous anxiety reduces this complicated question to a series of simple ones.

If the patient has a sufficient number of spontaneous, surprising anxiety attacks with instantaneous onset, then the patient has a panic disorder. Further questioning can elucidate what secondary symptomatology might also be present, such as hypochondriasis, social phobia, agoraphobia, or depression. This historical assessment can be backed up by objective laboratory assessment of the response to sodium lactate infusion. The presence of a panic response to lactate confirms the diagnosis of endogenous anxiety, and this information is particularly important if the type of anxiety the patient experiences is difficult to establish from the patient's history. Lactate infusion testing may also be helpful to differentiate the agitated depressive with panic disorder from the agitated depressive without it; however, more systematic data are needed upon this point. Biologic markers of endogenous anxiety can be expected to play an increasing role in psychiatric differential diagnosis in the coming years.

If the patient has only exogenous anticipatory anxiety, then one can decide from history whether it is adjustment anxiety, simple phobia, post-traumatic stress disorder, obsessive-

compulsive disorder, dissociative disorder, hypochondriasis, social phobia, etc. by using the differential points previously discussed.

The end result of a careful differential diagnosis of anxiety is a label which has important implications for treatment.

IV. TREATMENT OF ANXIETY

The complete differential diagnosis of anxiety requires considerable time and painstaking effort, and the psychiatry skeptic might ask "why bother? Psychiatric treatments are non-specific and don't do much for patients anyway." The answer to this skeptic is in part provided by Donald Klein, M.D., who has been a leader in the advance of biological methods into anxiety disorders.

"The development of effective psychopharmacological agents confronted the psychiatric profession with the inadequacy of its diagnostic system for the provision of rational indications and contraindications for drug therapy ... (studies) emphasize the utility of psychiatric diagnosis ... for prediction of treatment outcome."[81]

The treatment of anxiety rests upon the diagnosis of the anxiety-causing illness. This statement will not surprise physicians familiar with the treatment of any other symptom; it is a basic principle of medical practice. It also holds for psychiatry. For example, one would not treat generalized anxiety associated with hyperthyroidism with progressive relaxation, one would use propilthio uracil. One would not treat panic attacks associated with the aura of post-traumatic limbic epilepsy with phenylzine, one would use carbamazpine. One would not treat anxiety associated with joint pain in degenerative arthritis of the hip with chronic barbiturates, one would use opiates, then surgery. One would not use benzodiazepines and psychotherapy for anxiety attacks in panic disorder, one would use (say) desipramine. Why not? Because they don't work.

Correct diagnosis of the anxiety-producing illness and selection of a specific course of action which is directed at that illness offer the best chance of successful treatment.

A. Anxiolytics and Anxiety

A decade ago, a discussion of the drug treatment of anxiety would have been entitled "Anxiolytics" and would have consisted primarily of the sedative-hypnotic class. Today, although the subject matter includes that class of drugs, so many drugs of other classes have been proved to be valuable in certain anxiety states that to entitle this section "Anxiolytics" is almost misleading. The so-called tricyclic antidepressants and their second-generation descendants are effective anxiolytics.[26,82-84] So are the monoamine oxidase inhibitors.[85,86] Neuroleptics, including the new anxiolytic, buproprion, can be anxiolytic as well as antipsychotic.[87-91] Beta adrenergic blockers are anxiolytics.[92-93] So is the amino acid l-tryptophan.[94] Clonidine is anxiolytic.[95-97] Opiate drugs, as clinicians have known for generations, are anxiolytic.[98] This anxiolytic pharmacopedia has expanded considerably in a relatively short period of time, and this trend is expected to continue as the biological revolution which has transformed medicine catches fire in psychiatry too. The prognosis for the treatment of anxiety is good.

B. Molecular Biology of Anxiolytics

1. Receptor Binding

It is important to know how anxiolytics work to improve psychopharmacological responses. If one could establish the mechanism by which a given drug diminishes anxiety, then one could select the most specific drug which accomplishes that and one would minimize therapeutic concentrations and lessen the possibility of undesirable side effects. If one could establish the mechanism by which drugs diminish anxiety, and if one found a number of

different mechanisms and different neurotransmitter systems were involved, then possibilities to increase therapeutic effect by drug combinations might be revealed. It is clearly important to know how a given effective drug works.

How might a relationship between therapeutic effects and molecular mechanisms be established? Any nerve drug has a set of receptors to which it binds. Such binding may be effective by directly simulating the receptor or blocking the action of the endogenous ligand on the receptor. The net effect of the drug depends upon its action upon the receptor and upon the role of the receptor in the regulation of its neurotransmitter system. Changes in the regulation of the neurotransmitter system occasioned by the drug usually produce compensatory regulatory changes in other receptors which may in fact be the basis of the therapeutic action of the drug. How can one discover which action of a number of receptor actions is responsible for an observed therapeutic effect?

For each drug and each receptor there exists a range of concentration of drug beneath which and above which no specific receptor binding occurs. This range of concentration is marked by a physical constant, the K_I, which is the concentration of drug at which half the receptors are occupied.[99] The K_I is a function of the affinity of the drug for the receptor.[99] A rank ordering of the K_Is a drug has for its set of receptors reveals that at any concentration of drug some receptors will be occupied and some will not be occupied. An unoccupied receptor cannot be associated with a therapeutic action.

Another way to establish a relationship between molecular mechanisms and therapeutic effects is to consider the concentrations at which a variety of drugs which bind to a given receptor exhibit therapeutic effects. If the correlation of minimum effective concentrations for therapeutic effects of a set of drugs and the K_Is of those drugs for binding to a receptor is high, then that result is consistent with the conclusion that the therapeutic effect of the drug is by binding to that receptor. This sort of information has been elicited, and it demonstrates the neuronal mechanisms of action of a number of psychotropic drugs: barbiturates bind to the chloride channel of the GABA receptor, benzodiazepines bind to the benzodiazepine receptor, opiates bind to encephalin or endorphin receptors, neuroleptics bind to dopamine receptors, tricyclics and their descendants bind to the serotonin transporter receptor and/or to the norepinephrine transporter receptor and/or to the histamine receptor, clonidine binds to alpha-2 receptors on adrenergic or noradrenergic neurons, propranolol and similar drugs bind to beta adrenergic receptors.[100-108]

2. Benzodiazepines — Molecular Mechanisms

Benzodiazepines are not general neuronol depressants as are barbiturates, ethanol, and other sedatives.[109] Autoradiographic and synaptosomal studies reveal that benzodiazepines bind to specific proteins (200,000 dalton Mol wt tetramer) on presynaptic neuronal membranes.[110-113] The binding is specific because the (+) enantiomers of benzodiazepines are highly anxiolytic and highly potent to displace bound radiolabeled diazepam, while the (−) enantiomers are weak on both these actions.[114-115] Inhibitory constants (K_I) range from lorazepam (3 n*M*) to chlordiazepoxide (570 n*M*)[116-120] (see Table 4).

There is a strong correlation between the usual anxiolytic dose of benzodiazepine and their K_Is, which suggests benzodiazepine receptor binding is related to anxiolysis.[121,122] Benzodiazepine receptors are distributed primarily in the diencephalon, telecephalon, and cerebellar cortex; and they are very dense in the cerebral cortex, basal ganglia (see autoradiograph, Figure 2), and hypothalamus.[102,123,124] Benzodiazepine receptors are functionally interrelated with gamma amino butyric acid (Gaba) receptors everywhere there are benzodiazepine receptors (see Figure 3), however not all gaba receptors are so related. Gaba or barbiturate binding causes allosteric changes in the benzodiazepine receptor which facilitates the binding of benzodiazepine and vice-versa.[125-127] Gaba system differentiation causes benzodiazepine receptor supersensitivity (increased receptor), while chronic benzodiazepine

Table 4
DISPLACING POTENCY OF ^{3}H-DIAZEPAM BINDING, K_i

	(n*M*)		(n*M*)
Clonazepam	3	Diazepam	7
Flunitrazepam	3	Flurazepam	13
Lorazepam	3	Oxazepam	15
Nitrazepam	6	Chlorazepate	60
		Chloriazepoxide	570

administration is associated with benzodiazepine receptor subsensitivity (decreased receptors).[128,129] Intravenous administration of benzodiazepines is associated with decreased neuronal firing in the noradrenergic locus coeruleus and decreases noradrenergic turnover in the thalamus and cerebral cortex.[130,131]

The search for endogenous benzodiazepines goes on in many research laboratories, and current candidates include the beta carbolines and hypoxanthine.[132]

3. Monoaminergic Drugs — Molecular Mechanisms

Monoaminergic drugs affect the catecholaminergic or serotonergic neurotransmitter systems of the brain directly. Adrenergic, noradrenergic, dopaminergic, or serotonergic receptors are blocked or stimulated alone or in combination with other receptors to produce overall changes in neurotransmission and frequently to induce compensatory changes in other receptors. Each of these neurotransmitter systems has been implicated in anxiety and the stress response in animal studies and each of these has been implicated in the pathophysiology of human anxiety disorders by the effects of monoaminergic drugs upon them and those disorders.

Ungerstedt, building upon the work of Dahlstrom and Fuxe with Falk-Hillarp Fluorescence Histochemistry, provided in 1971 the first "stereotaxic mapping of the monoamine pathways" in the rat, and pointed to a role of dopamine pathways in attention to multi-modal sensory inputs.[133-136]

His anatomical work has been confirmed and extended. Currently the anatomy of the monoaminergic pathways of the brain is known in some detail.

4. Noradrenergic/Adrenergic Systems

Numerous experiments have suggested that there is a relationship between adrenergic/noradrenergic neurotransmission and anxiety. Redmond has proposed that locus coeruleus noradrenergic hyperactivity is involved in monkey-primate anxiety.[20] Increased locus coeruleus activity, which is induced by chemical or electrical stimulation, results in an increase in threat-associated behaviors just like real pain or threat does. Decreased locus coeruleus activity results in decreased threat-associated behaviors and a decreased response to real threats.

This relationship of noradrenergic/adrenergic neurotransmission to anxiety may also be true for human primates. Consider that:

1. The noradrenergic inhibitory alpha 2 autoreceptor antagonist yohimbine causes anxiety[137,138]
2. The alpha 2 autoreceptor agonist clonidine blocks it[95,139-141]
3. The beta receptor down regulating tricyclics and MAOIs block it[84]
4. The beta receptor blocker propranolol blocks it[93]

and state anxiety has been related to noradrenergic/adrenergic turnover.[142,143] These obser-

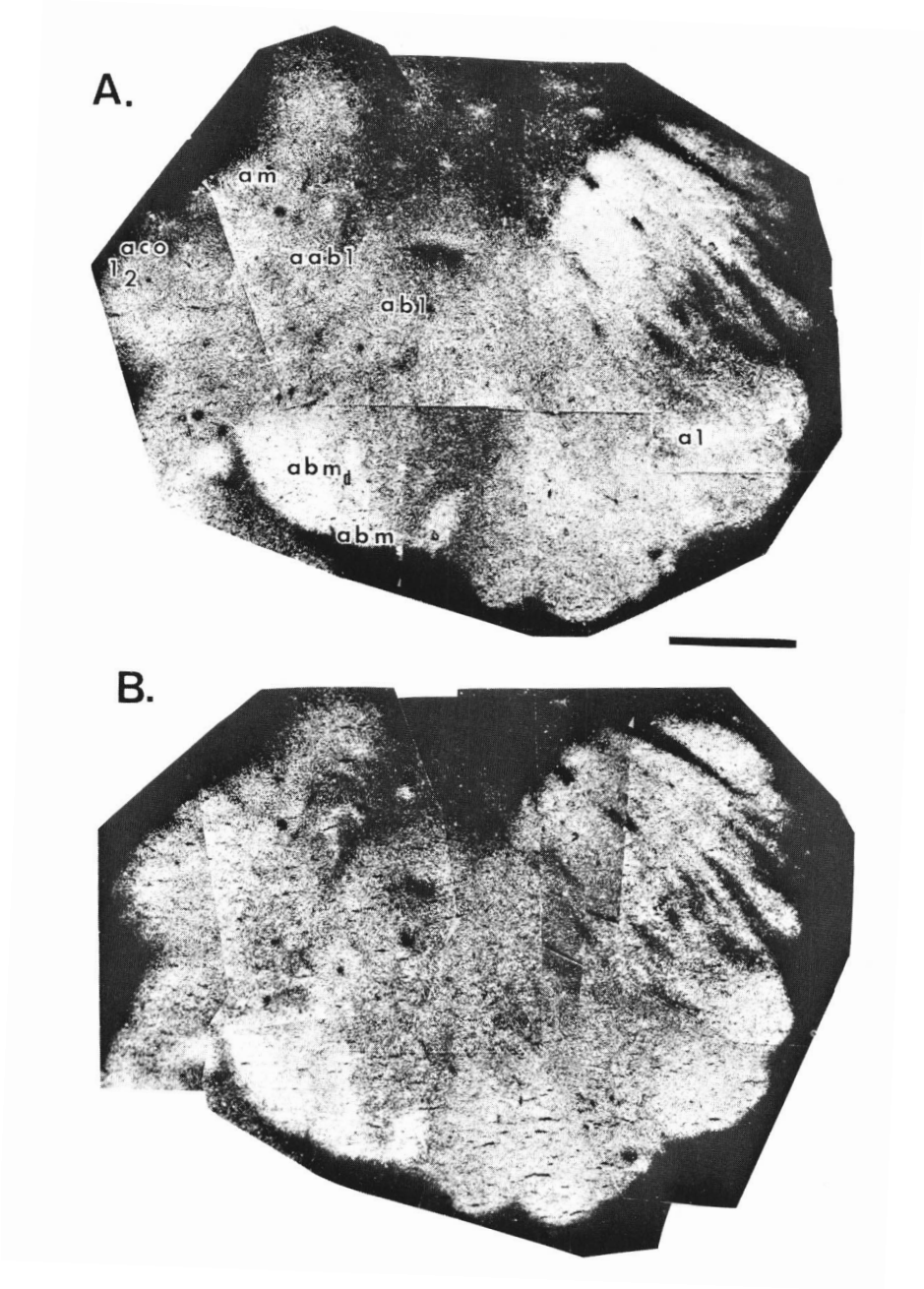

FIGURE 2. Benzodiazepine autoradiography of the human amygdala. (A) Total binding of [^{3}H]-flunitrazepam (type 1 and 2 receptors); (B) binding of [^{3}H]-flunitrazepam after CL 218, 872 (type 2 receptors). am = medial nucleus; aco = central nucleus; aabl = accessory basal nucleus; abl = basal nucleus; abm = baso-medial nucleus; al = lateral nucleus. (Reprinted with permission of Peter Whitehouse, M. D. and Debra Niehoff, M. D.[329])

vations are a fairly convincing data base for a hyperadrenergic hypothesis of anxiety, and a careful evaluation of the function of adrenergic/noradrenergic systems in patients with various anxiety disorders is needed. A sketch of these systems and their molecular pharmacology will provide a basis to understand their clinical pharmacologic uses.

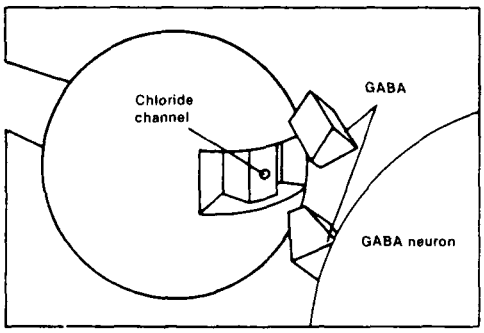

Fig. 3a. Hyperexcitability Feedback Signal Releases GABA.

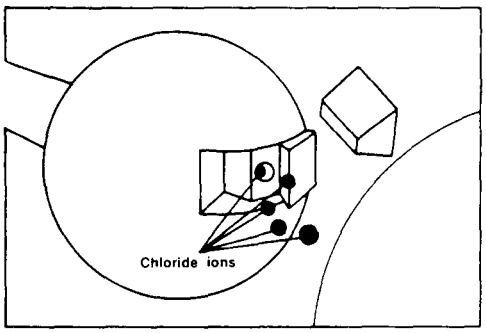

Fig. 3c Neuronal Membrane Becomes More Permeable to Chloride Ions.

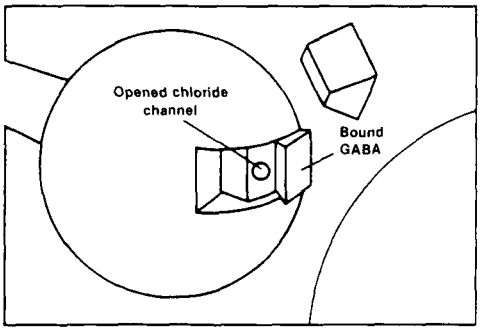

Fig. 3b. GABA Binds to its Recognition Site, Opening the Chloride Channel.

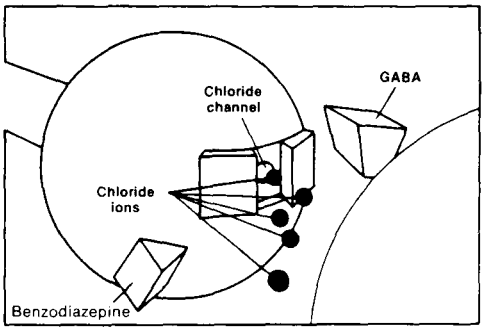

Fig. 3d. Binding of Benzodiazepine Enhances Effect of GABA; Chloride Permeability Increases Further.

FIGURE 3. GABA. (Reprinted from Snyder, S. H., *Psychiatric Ann.*, II (Suppl. II), 19, 1981. With permission.)

Norepinephrine and epinephrinergic pathways have cell bodies and dendrites in the brain stems reticular formation and project hundreds of thousands of varicosities (boutons) per cell posteriorly to the spinal cord, superiorly to the cerebellum, and anteriorly to the forebrain in "ventral bundle" and "dorsal bundle" axonal bundles (see Figure 4). Fibers in the ventral bundle from nuclei A5 and A7 project to the hypothalamus, amygdala, and stria terminalis. Fibers from the locus coeruleus (A6) project to the brain stem, cerebellum, amygdala, septum, cingulate gyrus, and neocortex (diffusely). Ungerstedt first noted that a single neuron may have synapses in the cerebellar cortex, cerebral cortex, and brain stem, which implicates these neurons in organization of widely different aspects of response (see Figure). The stimuli and receptor inputs to the noradrenergic neuron, and its output receptors, together with some agonists and antagonists of each receptor which could be used to manipulate its activity are listed Table 5.[134,144-149]

The receptors which provide input from the other systems include benzodiazepine and GABA receptors, endorphin receptors, alpha-2 adrenergic autoreceptors, and norepinephrine-epinephrine transporter. Intracellularly, on the outside of mitochondria, monoamine oxidase regulates catabolism of the catacholamines.

Stimulation of the afferent receptors depresses neuronal firing or removes active neurotransmitters.

Opiates stimulate the endorphin receptor.

Benzodiazepines stimulate the benzodiazepine receptor.

Clonidine stimulates the alpha-2 adrenergic receptor.

Blockade of the afferent receptors enhances neuronal firing and adds active neurotransmitter.

Naloxone blocks the endorphin receptor.[157]

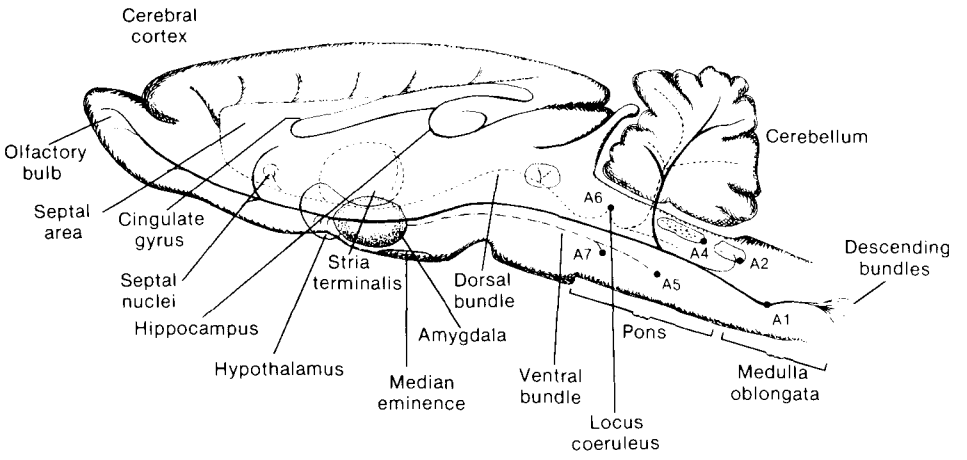

FIGURE 4. Distribution of norepinephrine-containing neurons in rat brain.

Table 5
NORADRENERGIC RECEPTORS

A. Input

Stimuli	Receptors	Agonists	Antagonists
Stress	Alpha[2] Adrenergic	Clonidine	Yohimbine
Pain	Endorphin	Morphine	Naloxone
Hypoglycemia	Benzoliazepine	Lorazepam	Beta-carboline-3-carboxylic ethyl ester
Dopamine	Gaba	Barbiturate	
		Apomorphine	Haloperidol
Serotonin		Trazodone	Ergotamine

B. Output

Alpha[1] Adrenergic	Ephedrine	Phenoxybenzamine
Alpha[2] Adrenergic	Clonidine	Yohimbine
Beta Adrenergic	Isoproterinol	Propranolol

Piperoxane or yohimbine block the alpha-2 adrenergic receptor.[161] Tricyclic drugs (see Figure 5), block intraneuronal transport of active neurotransmitter.[162-164] Monoamine oxidase inhibitors enhance neurotransmitter released per impulse by stopping intraneuronal catabolism.[165] Nociceptive inputs (e.g., pain, hypoglycemia, hypoxia, etc.) stimulate these neurons.

Adrenergic transmission is received by alpha-1, alpha-2, and beta receptors on next neurons in sympatic areas. Alpha-1 receptors are stimulated by ephedrine and blocked by phenoxbenzamine. Beta receptors are stimulated by isproterinol and blocked by propranolol and related drugs.

Acute potentiation of adrenergic transmission results in enhanced alpha-1 and beta effects;

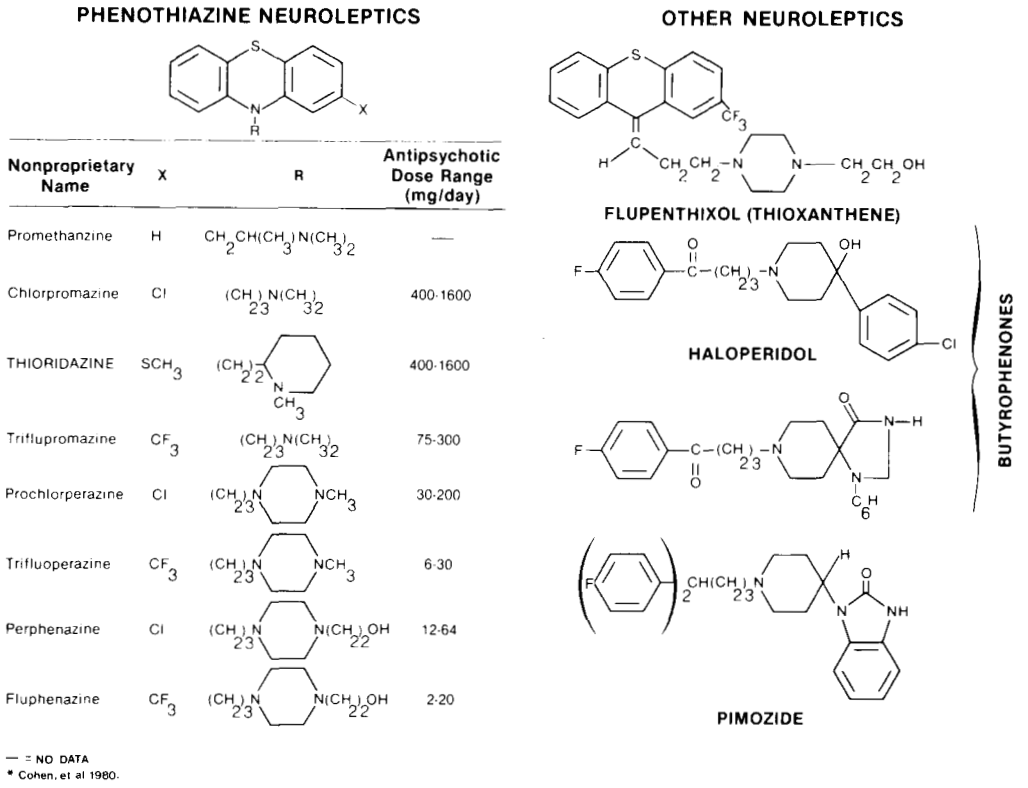

FIGURE 5. Chemical structures, antipsychotic doses, and plasma levels of neuroleptics.

however, chronic potentiation shifts the transmission towards alpha-1 because of a down regulation of beta receptor number and thus activity over about 3 weeks.[100,166] Some recently discovered pharmacological manipulations of the beta receptor may come to be important for the treatment of anxiety. Hyperthyroidism increases B receptor density.[167] Combination of antidepressant and alpha-2 blocker accelerates and increases the beta adrenergic and the alpha-2 receptor subsensitivity induced by either alone.[168-171] Acute and chronic administration of amphetamine or cocaine caused an increase beta adrenergic density in rat brain.[172] Chronic fluphenazine causes increased beta adrenergic receptor density without binding directly to the beta adrenergic receptor.[173] Chronic desmethylimipraminl doesn't change norepiniphrine transporter, alpha, adrenergic, serotonergic, enkephlinergic, cholinergic or histaminergic receptor density.[174] Chronic trazodone doesn't change beta adrenergic receptors, but results in increased numbers of 5HT receptors.[149] The K_i of trazodone on 5HT is 570 nm.[175]

5. Dopaminergic Systems

Brain dopaminergic pathways have been implicated in human anxiety. The pan-anxiety which is seen in schizophreniform disorder responds acutely to a variety of dopamine receptor blocking drugs. Furthermore, the average clinically effective dose of each of these neuroleptics correlates very closely with the K_i of that neuroleptic for dopamine receptor binding. Thus, in schizophreniform disorder at least, the mechanism of anxiolytics is probably dopamine receptor blockade.[176,177] The K_is of a number of commonly used neuroleptics are given in Table 6.

Table 6
NEUROLEPTICS

Neuroleptic	K_i(n*M*)
Fluphenazine	0.6
Haloperidol	1
Thiothixene	2
Trifluoperazine	4
Molindone	9
Thioridazine	15
Chlorpromazine	40

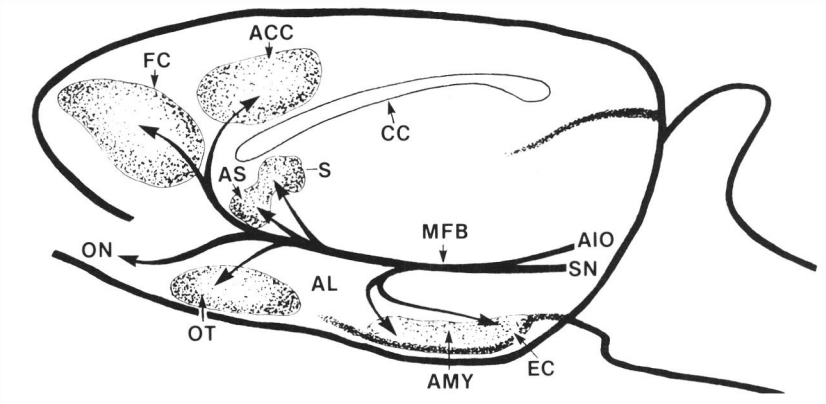

FIGURE 6. Diagrammatic representation of the distribution of dopamine neurons in rat brain. Fiber pathways (solid black lines) originate from dopamine neuron cell bodies in substantia nigra (SN) and ventro-medial tegmentum (A10) and project in medial forebrain bundle (MFB) to striatum (S), nucleus accumbens septii (AS), olfactory tubercle (OT), frontal cortex (FC), anterior cingulate cortex (ACC), entorhinal cortex (EC), and amygdala (AMY). (Data from Lindvall and Bjorklund.[284])

There has been a long history of physicians treating "neurotic" anxiety with small doses of neuroleptic[87,178-184] (see Figure 6). Interestingly, dopamine receptor agonists (e.g., apomorphine, benztropine) have been used clinically as anxiolytics.[185-187]

Dopaminergic pathways can be divided into three systems.[134] The mesolimbic system has all bodies in the ventral tegmental area and project to the accubens, amygdala, septum, olfactory tubercle, cingulum, and pre-frontal cortex. The nigrostriatal system has cell bodies in the substantia nigra and projects to the neostriatum and amygdala. The third dopaminergic system consists of intra hypothalamic projections of hypothalamic neurons (Figure 7).

There are dopamine autoreceptors upon nigrostriatal and mesolimbic dopamine neurons.[188] Low doses of dopamine agonist drugs like apomorphine reduce dopamine synthesis and transmission, and have been associated with anxiolytic effects in man.[185,186] Dopamine neurons contain benzodiazepine-gaba receptors, and benzodiazepines have been shown to decrease dopamine turnover.[189] Dopamine neurons contain a transporter receptor which removes active neurotransmitter, and this is blocked by benztropine. Dopamine neurons can be stimulated by stressful inputs, including pain and hypoglycemia.[190-193] Dopamine neurotransmission is potentiated by monoamineoxidase inhibitors, similarly to norepinephrenergic neurons. Dopamine stimulates next neuron receptors in its synaptic fields, and these can be stimulated by high-dose apomorphine to produce nausea and by neuroleptics to block

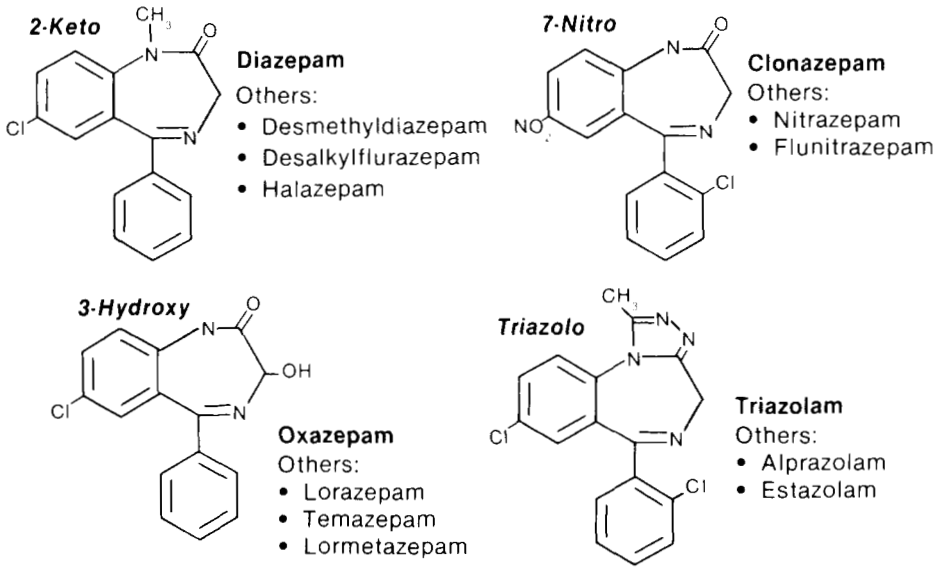

FIGURE 7. Classification of chemical structure of benzodiazepines.

that transmission.[194] Deafferentation results in synthesis of increased numbers of post synaptic dopamine receptors being synthesized.[195]

The usual explanation of the action of agonists upon anxiety is that presynaptic dopamine autoreceptors inhibit dopamine synthesis and thus decrease transmission without having much effect on postsynaptic dopamine receptors. Unfortunately for this theory, Bannon et al. have shown that the relevant meso-corticol dopamine systems lack autoreceptors.[188,196] Thus, both dopamine agonists and antagonists have been shown to be anxiolytic.

6. Serotonergic Systems

The serotonin (or 5-hydroxytryptamine) neurons are located in the midline of the dorsal brainstem, in the raphe nuclei para giganto cellular nucleus and the area postrema. Serotonergic neurons send axons in the medial forebrain bundle and elsewhere to terminate in the brainstem reticular formation, hypothalamus, lateral geniculate, amygdala, pallidum, hypocampus, anterior thalamus, and cerebral cortex. Descending fibers reach the spinal cord.

Serotonergic neurons are activated by nociception and contain serotonin transporter which removes active neurotransmitter. Serotonin transporter is blocked by certain tricyclic drugs, and chronic blockade is associated with increased sensitivity of post synaptic serotonin receptors. Potentiation of serotonergic transmission by monoamine oxidase inhibitors also causes post synaptic receptor supersensitivity. Serotonin neurotransmission is potentiated by enhanced biosynthesis secondary to increased extra cellular concentrations of L-tryptophan.

Two pieces of information suggest that improvement in obsessive-compulsive disorder is caused by the action of clomipramine to potentiate serotonergic systems. Thoren et al. compared improvement in obsessive-compulsive symptoms in patients treated with clomipramine, which blocks both serotonin and norepinephrine transporter in the steady state, and nortriptyline which blocks only norepinephrine transporter. Improvement was significantly better with clomipramine.[300] Thoren also reported that changes in CSF 5HIAA (metabolite of 5HT), but not MHPG (metabolite of NE) correlated with symptomatic improvement.[301] L-tryptophan potentiated the improvement observed with tricyclic. Thus a role for serotonin in the improvement is suggested.

Table 7
PLASMA LEVELS AND GLOBAL IMPROVEMENT AFTER 6 WEEKS OF DIAZEPAM TREATMENT (N = 54)[16]

	Global Improvement		
	Very much or much (N = 31)	Little (N = 10)	None or deterioration (N = 13)
Diazepam (D)	438 ± 203	470 ± 321	290 ± 160
Desmethyl-diazepam (DD)	714 ± 277	660 ± 601	443 ± 252
D + DD	1152 ± 446	1130 ± 905	733 ± 395
D + DD 750	10	14	
D ± DD 750	20	8	

Note: Numbers represent plasma levels (ng/mℓ).

C. Clinical Pharmacology of Benzodiazepines

The widespread use of benzodiazepines in the last 20 years has created alarm in some circles that a widespread problem of benzodiazepine abuse exists. Between 10 and 17% of adults in the Western World were taking benzodiazepines in 1971.[197] In 1972, there were 70 million prescriptions for chlordiazepoxide or diazepam in the U.S.[198] Estimates of the incidence of significant mental illness in Western populations approximate 30% of adults.[199] In a large general practice study, less than 1% of nonmentally ill patients received tranquilizers, but 50% of mentally ill patients did.[200] Benzodiazepine dependence has been demonstrated by Hollister et al., but its incidence is very low.[201] In the 17-year period starting in 1960, there were less than 200 cases of benzodiazepine dependence reported in the literature.[202] In western Europe, where systematic health data are collected routinely, in the last 20 years there have been about 400 cases of benzodiazepine dependence among greater than 400 million treated persons.[203] The conclusion can be reached that the large numbers treated do not constitute benzodiazepine abuse.

Numerous controlled clinical trials indicate that benzodiazepines are effective anxiolytics and superior to placebos in "neurotic" patients.[204-209] All of the benzodiazepines in clinical use exhibit this action. Most studies have examined efficacy over short periods of less than 6 weeks, but some studies show that the effect is maintained over 6 months of treatment.[210,211] The amount of anxiety reduction in a 6-week course of treatment is usually about 75%, compared to 35% improvement with placebo.[212] The amount of improvement at 6 weeks is similar to that seen at 6 months in patients treated with diazepam.[212] Patients with mild or moderate anxiety may become asymptomatic on benzodiazepines, but severely anxious patients usually remain somewhat anxious. If the patient's anxiety has not responded somewhat at 1 week, it is unlikely to respond later.[212]

Rickels has shown clearly that effective anxiolysis depends upon the presence of an adequate blood level of benzodiazepine.[212] Patients with plasma levels of diazepam and desmethyldiazepam below 750 ng/mℓ experience little or no reduction in anxiety, whereas patients whose levels were greater than 750 ng/mℓ were usually much improved (see Table 7). Other workers (e.g., Dasberg et al.) also find a minimal effective level of diazepam and desmethyldiazepam but at about 400 ng/mℓ.[213-215]

Anti-anxiety doses of benzodiazepines are given in Table 8. A classification of the chemical structures of benzodiazepines is given in Figure 8.

Table 8
ANXIOLYTIC DOSES OF BENZODIAZEPINES

Benzodiazepine	Anti-anxiety dose (mg q.d.)
Chlordiazepoxide	15—100
Diazepam	5—40
Oxazepam	30—120
Clorazepate	11.175—60
Lorazepam	1—4
Alprazolam	1—4
Halazepam	20—120
Pracepam	20—60

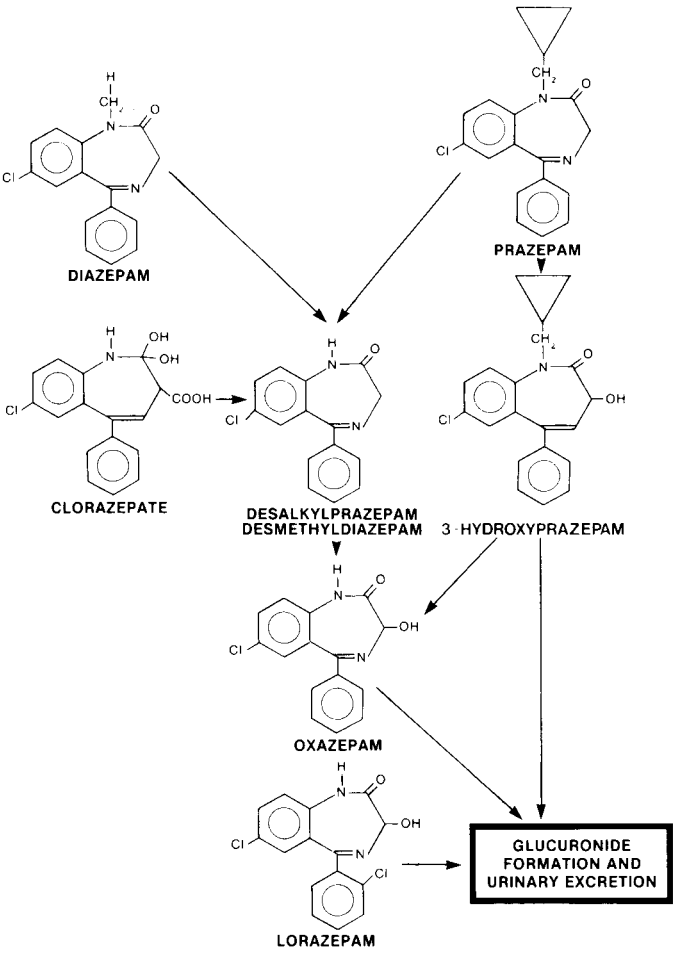

FIGURE 8. Pathways of benzodiazepine catabolism.

A weakness in many benzodiazepine studies is that the study population consists of mixed "neurotic" patients. Although the "average" neurotic patient clearly responds to benzodiazepines, some patients may respond well and some patients may respond poorly. The

response of patients with adjustment anxiety to benzodiazepines has been shown to be good, and a dose-dependent decrease in subjective and somatic anxiety symptoms has been reported.[209] Benzodiazepines have been shown to be superior to placebo in treating anxiety associated with physical illness, which as has been mentioned is a special case of adjustment anxiety. Benzodiazepines have been shown to be superior to placebo in the treatment of obsessive-compulsive disorder anxiety, and they result in about a 30% reduction in subjective and somatic symptoms but they are less effective than antidepressants.[216]

The spontaneous anxiety attacks which occur in panic disorder and agoraphobia with panic attacks do not in general respond to benzodiazepines.[217] An exception to this statement may be the triazolobenzodiazepine alprazolam. Sheehan et al. have reported high doses of alprazolam to have acute antipanic effects.[218] Whether the failure of other benzodiazepines to block panic is because they haven't been used in high enough doses, or whether the triazolo ring structure of alprazolam gives it new properties related to another receptor remains to be established.

A useful rule of thumb in deciding to treat anxious, neurotic patients with benzodiazepines is this: if the patient has exogenous anticipatory anxiety, as defined in the differential diagnosis section, then it will respond to benzodiazepine. If the patient has endogenous panic anxiety, then it will not.

The anxiolytic efficacy of benzodiazepines compared to other benzodiazepines has been examined in several controlled studies. The preponderance of studies find different benzodiazepines administered on a flexible dosage basis to be equally efficacious, however, some studies report lorazepam or alprazolam to be superior to diazepam on some measures.[219-221] Whether or not there are differences in anxiolytic efficacy, there are differences between benzodiazepines in terms of side effects. Studies report that lorazepam has fewer side effects than diazepam which has fewer side effects than chlordiazepoxide.[222,223] Use of high-affinity benzodiazepines would probably assure therapeutic effectiveness at minimum toxicity.

The anxiolytic efficacy of benzodiazepines compared to barbiturates and nonspecific sedatives has been examined in several controlled studies.[224,225] It is generally concluded that benzodiazepines are superior to barbiturates in the treatment of neurotic anxiety or in anxiety associated with physical illness. Furthermore, risks associated with the toxic sedative effects of barbiturates are not present with benzodiazepines. Respiratory suppression is seldom seen with even intravenous benzodiazepine, but it is a serious risk with barbiturates, particularly when taken after ethanol. Withdrawal reactions are more likely to be severe and associated with seizures when barbiturates are used. Benzodiazepines are more effective and less toxic than barbiturates, and they should be used in preference to barbiturates in the treatment of anxiety.

The anxiolytic efficacy of benzodiazepines has been compared to beta adrenergic blockers, and these studies will be presented in section IV. E., Clinical Pharmacology of Beta Adrenergic Receptor Blockers.

The anxiolytic efficacy of benzodiazepines has been compared to neuroleptics in controlled studies.[87-89,204,205,226] The majority of studies show anxiolytic equivalence for the two classes of drugs on neurotic anxiety. Chlorpromazine has been reported to produce deterioration in panic disorder, and benzodiazepines are not effective.[227-229] Neuroleptic is more effective than benzodiazepine in the treatment of anxiety in schizophrenia or psychotic depression; however, combinations of these drugs are sometimes more efficacious. Benzodiazepines do not produce the extrapyramidal side effects which are seen with neuroleptic and do not pose risks of tardive dyskinesia. Use of benzodiazepines in the elderly (e.g., for catastrophic anxiety in dementia) has been associated with deterioration of mental status.[230-231] Neuroleptics provide anxiolysis without provoking delirium.

The selection of benzodiazepines vs. neuroleptics in treatment of anxiety depends upon what disorder is being treated and the risk of undesired side effects.

At the time of the peak plasma concentration of benzodiazepines, symptoms of lassitude sedation, increased reaction time, motor incoordination, and psychomotor impairment can be seen.[232] Cognition is less affected than motor performance. Headache can be seen. Paradoxical excitement can be seen in the elderly and delirium has been reported. Disinhibition of aggressive impulses has been reported. Impaired ability to operate a motor vehicle has been demonstrated, particularly lateral position control; and driving while being treated with benzodiazepines is associated with a five- to ten-fold increase in accident rate.[233,234] Patients should be cautioned about motor performance impairment, which is most pronounced in the first few weeks of treatment. Cholestatic jaundice has been reported; however, it is uncommon.[235] Benzodiazepines cross the placental barrier and, because of possible teratogenic effects on the fetus, are not recommended in pregnant women.[236] Gynecomastia associated with benzodiazepines use has been reported.[237]

Withdrawal reactions have been reported from benzodiazepines. Hollister et al. reported withdrawal reactions from chlordiazepoxide.[201] In general, higher doses and longer times are required to produce significant benzodiazepine withdrawal. Abrupt discontinuation of usual anxiolytic doses of benzodiazepines is usually not associated with severe withdrawal symptoms. However, in about 5%, there may be significant rebound anxiety.[238,239] Withdrawal reactions which include seizure are rare, but withdrawal reactions including nausea, tremulousness, insomnia, and anxiety are seen.[239,240]

The pharmacokinetics of benzodiazepines have been studied. Benzodiazepines can be administered p.o., i.m., i.v.; however, intramuscular administration of chlordiazepoxide or diazepam is not recommended because drug precipitation at the injection site results in erratic systemic distribution.[241,242] Some benzodiazepines are absorbed rapidly from the gut, e.g., diazepam, chlorazepate, and may produce a euphoric "buzz."[243] Patients prone to drug abuse should probably not be given these agents.

Steady-state plasma levels are reached in about 3 days for short half-life and about 2 weeks for long half-life benzodiazepines.[244-246] Short half-life benzodiazepines, e.g., oxazepam, lorazepam, and alprazolam, are conjugated to form glucuronides and eliminated in the urine. Their elimination half-lives are in the 5- to 15-hr range, and they must be administered in divided doses. Long half-life benzodiazepines are metabolized to desmethyldiazepam by microsomal enzymes, e.g., diazepam, clorazepate, prazepam, and halazepam. Desmethyldiazepam is an active benzodiazepine with a 36- to 200-hr half-life (see Figure 9). These are effectively given in once-a-day dosing schedules, and are unlikely to produce rebound anxiety if doses are skipped.[246] The role of the liver in catabolism of benzodiazepines is clinically significant in patients with liver failure or in the elderly because half-lives are prolonged and doses must be adjusted downward.[247,248] Anti-acids are known to reduce clorazepate absorption from the gut by interfering with hydrolysis to desmethyldiazepam.[249,250] Drugs which compete for microsomal enzymes may similarly increase benzodiazepine half-life, e.g., ETOH, cimetadine, etc.[251,252] Care must be taken in the intravenous administration of benzodiazepines that the dose is given slowly (2 mg diazepam per minute) because respiratory arrest does sometimes occur.[253]

D. Clinical Pharmacology of Beta Adrenergic Receptor Blockers

Granville-Grossman and Turner, in their 1966 *Lancet* study, reported that beta blockers eliminate the somatic symptoms of anxiety, e.g., palpitations, nervous tremor, sweating, urinary hesitancy, etc., and they suggested propranolol could be used for those symptoms.[92] They demonstrated that 80 mg a day of propranolol in divided doses was superior to placebo in these reductions. Later evidence has confirmed their report. Numerous uncontrolled trials have found that 95% of patients with such symptoms given propranolol improve.[254] Controlled investigations have established the anxiolytic effectiveness of beta adrenergic receptor blockage; however, some debate has centered upon whether or not these are central nervous

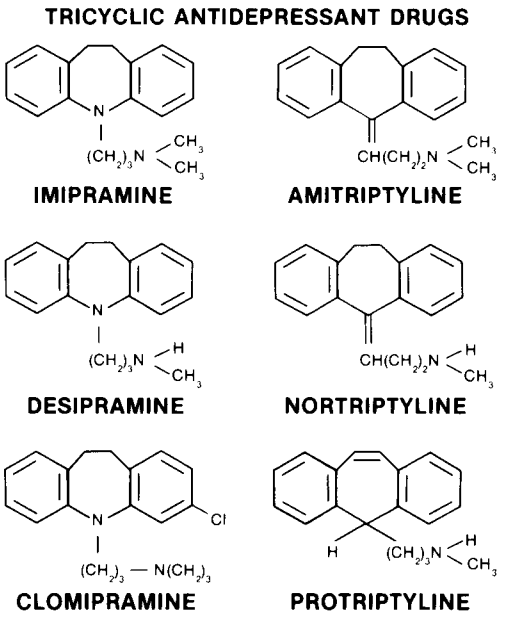

FIGURE 9. Chemical structure of tricyclic drugs.

system actions upon subjective symptoms of anxiety.[255-260] The study of Kathol et al. confirms that high doses of propranolol (160 mg qd) can reduce subjective anxiety symptoms in chronically anxious patients.[93] Controlled studies of high doses of other beta adrenergic blockers confirm that they too reduce subjective and somatic symptoms of anxiety.[261,262] These data are consistent with the conclusion that beta adrenergic blockade is anxiolytic for many anxious patients.

Bonn et al. examined the effect of practolol (400 mg qd), which doesn't cross the blood-brain barrier, upon anxiety and found that 100% of anxious patients improved.[263] The question of the cause of the beta adrenergic effect on subjective anxiety remains unanswered. We have generally found propranolol to be more anxiolytic than metaprolol or nadolol.

The anxiolytic efficacy of beta adrenergic blockers has been compared to that of benzodiazepines in controlled studies. Wheatly noted that chlordiazepoxide (30 mg q.d.) was as effective as propranolol (90 mg q.d.).[264] Tyrer and Lader found diazepam (10 mg q.d.) more effective on subjective anxiety than propranolol (120 mg q.d.) in a small study.[260] Burrows et al. found oxprenolol (240 mg q.d.) equally as effective on subjective and somatic anxiety as diazepam (15 mg q.d.).[265] Kishman found oxprenolol (40 mg q.d.) superior to diazepam (2 mg q.d.) in reducing exam nerves without impairing cognitive processing.[266] The current consensus of opinion is that beta adrenergic receptor blockade is as effective as benzodiazepine receptor stimulation upon somatic anxiety and produces less cognitive impairment, but whether beta adrenergic blockade is as effective as benzodiazepine receptor stimulation upon subjective anxiety symptoms has not been established yet. Greenblatt and Shader have suggested a combination of beta blocker and benzodiazepine is more effective than either alone.[219]

The effectiveness of beta adrenergic receptor blockers in specific anxiety disorders has been established in a few disorders, and is being examined in others. Adjustment anxiety responds well to beta blockers, particularly the somatic anxiety component.[267] Beta blockers can be used on an as needed basis for unique stresses like exams and other performances, say propranolol 40 mg q.d., 1 hr beforehand.[268,269] Anxiety in social phobia is considerably

relieved by beta blockers, because somatic anxiety symptoms frequently add to the patient's embarrassment and thus to anxiety.[270]

Beta adrenergic blockers are somewhat effective in the anxiety associated with ETOH and opiate withdrawal, and in the post detoxification management of the anxious patient with secondary ethanol dependence.[271,272] Beta adrenergic blockers are somewhat effective in the management of panic disorder and agoraphobia with panic attacks where they act both on panic attacks and on anticipatory anxiety.[93] Propranolol has been considered the drug of choice for patients with anxiety associated with mitral valve prolapse which often accompanies agoraphobia with panic attacks; however, these patients also respond to tricyclics and MAOIs.[52] It will be interesting to see if the action of beta blockers to prevent tachycardia, elevated blood pressure, and elevated plasma lipids can reverse the demonstrated tendency of panic disorder patients to develop cardiovascular disease.

Beta adrenergic receptor blockade reduces anxiety in generalized anxiety disorder. Dartmouth's Matthew Friedman reports that beta adrenergic blockers reduce generalized anxiety in post-traumatic stress disorder, and they are his first or second anxiolytic choice in that disorder.[273]

Further research will clarify the effectiveness of beta adrenergic blockade in specific anxiety and fear disorders.

What concentration of beta blocker is necessary to produce anxiolysis? Plasma total propranolol concentration is not a good indicator of anxiolytic response, possibly because it is extensively bound to plasma proteins or because active catabolites play a role.[274] The degree of beta blockade can be assessed by measurement of heart rate, and this measure correlates to relief of anxiety.[93]

Beta adrenergic blockers are safe drugs to use.[275-280] High doses have been associated with central nervous system symptoms of depression, fatigue, insomnia, nightmares, and rarely delirium (2000 mg q.d.). Patients with heart failure may have exacerbation if given propranolol. There can be a hypertension and anxiety rebound after abrupt discontinuation of beta blockers. Patients with asthma may experience exacerbation when given beta blockers. Beta blockers should not be given to patients with diabetes mellitus because it can mask symptoms of hypoglycemia. Bradycardia and hypotension can occur, but are rarely problematic.

In view of the anxiolytic efficacy and safety of beta blockers, it is surprising that the U.S. Food and Drug Administration has not yet approved them for the treatment of anxiety.

Several pharmacokinetic considerations (see Table 9) are important in the use of beta adrenergic blockers as anxiolytics.[281]

Propranolol administered orally is extensively but variably catabolized in its pass through the liver. Thus, there is a 20-fold variance in plasma concentrations from a comparable dose in different patients. The mechanism of this catabolism is saturable, and it can be overcome by raising the dose.[282] 4-Hydroxy propranolol is one of the catabolism products which has comparable beta blocking properties to propranolol. Other catabolism products are nonactive naphthoxylactate, isopropylamine, propranolol, glycol, and propranolol glucuronides. The half-life of propranolol after chronic administration is about 4 hr; thus, propranolol must be given at least every 6 hr.[283]

Nadolol is a nonselective beta adrenergic blocker having similar affinity to propranolol but which is not catabolized. Its half-life is long (24 hr), and it can be administered once per day.[281]

Metoprolol is a selective beta-1 adrenergic antagonist having similar potency to propranolol upon this receptor. It is 100 times weaker as a beta-2 antagonist. It doesn't block beta-two mediated peripheral vasodilation or produce broncho constriction. Metoprolol is also extensively catabolized upon first liver pass, thus creating variability in systemic levels from a given dose. Catabolites include O-demethylated and hydroxylated compounds which are not

Table 9
PHARMACOLOGICAL CHARACTERISTICS OF BETA ADRENERGIC RECEPTOR BLOCKING AGENTS

Compound	Potency as beta blockers (Propranolol = 1.0)	Half-life in plasma (hr)
Nonselective (B_1 + B_2) adrenergic blocking agents		
Alprenolol	0.3—1	2—3
Bunolol	50	6
Nadolol	0.5	20
Oxprenolol	0.5—1	1—2
Penbutolol	5—10	26
Pindolol	5—10	3—4
Propranolol	1	3—5
Sotalol	0.3	5—12
Timolol	5—10	4—5
Cardioselective (B_1) adrenergic blocking agents		
Acebutolol	0.3	3—4
Atenolol	1	6—8
Metoprolol	0.5—2	3—4
Practolol	0.3	5—10
Tolamolol	0.3—1	3—6

pharmacologically active. The half-life of metaprolol in plasma is 3 to 4 hr, thus it must be given at least every 6 hr.[281]

E. Clinical Pharmacology of Tricyclic-Type and Monoamine Oxidase Inhibitor Drugs

The clinical pharmacology of antidepressants of the tricyclic and monoamine oxidase inhibitor classes has been discussed elsewhere in this volume in Chapters 2 and 4. The discussion in those chapters about how to prescribe tricyclics and about how to prescribe monoamine oxidase inhibitors apply equally whether the drugs are being used to treat depressive disorders or are being used to treat anxiety disorders. The time course of therapeutic response, dosages, and the plasma levels necessary to produce it, are similar whether anxiety disorders or depressive disorders are being treated. The molecular alterations, which in turn produce a therapeutic response produced by these drugs, are probably the same. The adjective antidepressant applied to these drugs is a historical accident and misnomer. They could as aptly be called anti-panics. The chemical structures of several tricyclic antidepressants is given in Figure 9.

The discovery that imipramine could block panic attacks in patients with agoraphobia and panic attacks was made by Klein and Fink in an uncontrolled study reported in 1962.[82] Sargant and Dally reported the efficacy of phenylzine to do that same thing the same year.[285] Since those pioneering studies, numerous well-controlled studies using several tricyclic and tetracyclic antidepressants and several monoamine oxidase inhibitors have confirmed the anti-panic effect of the "antidepressants."[26,228,286-292]

Within about 3 weeks of taking about the equivalent of 150 mg of imipramine P.O. q.d. or 60 mg of phenylzine P.O. q.d. panic attacks in panic disorder or agoraphobia with panic

attacks usually stop entirely.[26] Furthermore, if patients discontinue these medications, they often relapse into panic attacks. The conclusion that tricyclic and monoamine oxidase inhibitor antidepressants inhibit panic attacks in patients with panic disorder or agoraphobia with panic attacks can be reached from these data.

An adequate tricyclic or monoamine oxidase inhibitor dose which is maintained long enough produces total elimination of panic attacks in almost all patients with panic disorder or agoraphobia with panic attacks. An occasional patient who is premenstrual and trying to cope with a major stress (e.g., divorce) may have a sub-panic attack in spite of demonstrated optimum drug levels; however, this is quite unusual.

The anti-panic attacks efficacy of these agents is no subtle, statistically significant but clinically microscopic effect. Rather it borders upon the mythical "magic bullet." One will seldom be proven wrong if one assures the patient without equivocation that taking these drugs will cure the panic attacks, and such assurance does wonders for a patient's sense of security and trust of the physician. The courage that is necessary for confronting anticipatory fears and extinguishing them can be built upon that belief. The physician can bank on that.

A possible exception to this confident assertion about elimination of panic attacks by these drugs is the drug trazodone. While Sheehan reports that it is efficacious, that has not been our clinical experience.[26] In an uncontrolled clinical trial we placed four patients with agoraphobia and panic attacks plus compulsive personality on trazodone (300 mg q.d.) and four patients on desipramine (100 mg q.d.). At the end of 2 months, all the desipramine patients were asymptomatic for 5 weeks, but three of the four trazodone patients continued to have panic attacks at reduced frequency. The other trazodone patient became asymptomatic for the final 2 weeks. Contradistinctly, patients with major depression and compulsive personality treated with trazodone (300 mg q.d.) were markedly improved at 2 months. Our present experience suggests that noradrenergic potentiating tricyclics have proven their efficacy to stop panic attacks, and serotonergic potentiating ones haven't. Methodological problems in our small sample uncontrolled study having no plasma level determination make it a weak challenge to David Sheehan's observations. However, several well-controlled studies are needed to resolve this matter of the anti-panic efficacy of trazodone.

The tricyclic and monoamine oxidase inhibitor-type drugs also improve generalized anxiety in patients with panic disorder or agoraphobia with panic attacks. Whether this effect is independent of the anti-panic effect or caused by it is unknown. The effectiveness upon secondary anticipatory anxiety and established phobic avoidance is minimal at best. Other anti-anxiety measures, both pharmacologic and behavioral, need to be employed to solve these problems.

Obsessive-compulsive disorder is very difficult to treat and it is often unresponsive to psychotherapy, neuroleptics, ECT, and psychosurgery.[293] However, the efficacy of the tricyclic drugs to reduce anxiety in such cases can be clearly seen from the Western experience with clomipramine. A series of uncontrolled trials revealed clomipramine to be an effective drug in obsessive-compulsive disorder.[294-296] Controlled double-blind studies have confirmed the efficacy of clomipramine in obsessive-compulsive disorder.[216,297,298] A pharmacologically similar drug, doxepin, has been shown in an uncontrolled trial to be effective also.[299] Notriptyline also has been shown in double-blind study to be superior to placebo in the treatment of obsessive-compulsive disorder symptoms.[300] Thus, drugs of the tricyclic class are in general effective upon anxiety and obsessive-compulsive rituals in obsessive-compulsive disorder. Anxiety and rituals decline in parallel from 21 to 42%.[300]

Tricyclics which potentiate serotonergic neurotransmission work better than those which potentiate norepinephrine neurotransmission. Clomipramine has been shown to be more effective than nortriptyline in the reduction of anxiety and obsessive-compulsive symptoms.[300] Degree of improvement correlates with changes in CSF-5HIAA but not with MHPG.[94,301,302] Potentiation of clomipramine effects by L-tryptophan has been reported.[94]

More potentiation of serotonergic neurotransmission and more reduction in obsessive symptomatology can be obtained with a serotonergic tricyclic and L-tryptophan than can be had with a serotonergic tricyclic alone. This strategy is called precursor loading.

The dosages and plasma levels used for clomipramine treatment of obsessive-compulsive disorder are similar to clomipramine treatment of depression. Doses from 150 to 300 ng q.d. produce blood levels from 150 to 300 mg/mℓ and a plasma therapeutic window for these effects of between 150 and 250 ng/mℓ has been reported.[303,304]

F. Clinical Pharmacology of Clonidine

The use of clonidine as a psychotropic was pioneered by Gold, Redmond, and Kleber, who showed in a group of ten methadone maintenance outpatients that it blocked the panic anxiety and hyper-autonomic symptoms and signs associated with methadone withdrawal.[96,305] This anti-panic effect of acute clonidine was confirmed in single-blind and double-blind studies.[97,306] The anti-panic effect was confirmed by double-blind studies from other laboratories.[307] It has been shown also in the treatment of heroin, dilaudid, and oxycodone withdrawal.[308] The use of clonidine for opiate withdrawal is replacing the use of methadone in general clinical practice.

Dr. Thomas Uhde, who collaborated with Gold et al. in some of the initial studies, has extended the use of clonidine to the treatment of agoraphobia with panic attacks. Dr. Uhde et al. note that clonidine acutely is effective against panic attacks, generalized, and anticipatory anxiety in this disorder.[95] In a double-blind, randomized-design crossover study, intravenous clonidine (2 mg/kg) and placebo were given to 4 panic/agoraphobic patients, 24 normal controls, and 14 depressed patients. State anxiety was measured just before and 1 hr after the infusion by Spielberger S-T anxiety inventory. The panic-agoraphobic subgroup decreased baseline anxiety from 67.8 to 46.5 ($p<.05$), but placebo had no effect. Anxiolysis was also observed in the depressed. These observations are similar to those reported by Liebowitz et al. and Hoehn-Saric et al.[139,309] Acute administration of clonidine has anti-panic and general anxiolytic effects.

Tolerance develops to the anti-anxiety effects of clonidine, but it does not to the hypotensive effects. Thus, after about 3 weeks, the patient is hypotensive with ineffective anxiolysis.[95] Clonidine is effective acutely against panic attacks and generalized anxiety in agoraphobia with panic attacks, but it is not effective chronically because of tolerance. Thus, it can be used episodically for symptomatic relief, particularly in patients refractory to other forms of treatment.

After oral administration of clonidine, the blood pressure falls over about 20 min and this drop may persist for several hours. Some postural hypotension occurs, but the reflexive control of capacitance vessels is not abolished. The drop in blood pressure is secondary to decreased cardiac output at constant resistance. An exception is the cerebral vessels which increase resistance.[310] Patients may complain of light headedness which is probably secondary to both these effects. Other common side effects include dry mouth and constipation. Clonidine is effective at a plasma concentration of about 1 ng/mℓ, and its half-life is about 9 hr.[311] Abrupt discontinuation of clonidine can result in rebound anxiety and hypertensive crisis which begins about 12 hr after the last dose.[312-314] Patients should be cautioned about the need to take their regularly prescribed doses. Discontinuation of clonidine should be done gradually over several days.

G. Behavioral Treatment of Anxiety and Phobia

Folk wisdom has it that one has to face up to one's fears in order to overcome them, and this may be the central principle which is useful to keep in mind in the behavioral treatment of phobia. One can explore feelings about the feared object for hours and one won't get the patient any closer to it. The task of therapy is to design a program which repeatedly exposes

the patient to the feared object, and which doesn't let the patient avoid doing it. Some time later the patient will no longer be frightened by the original feared object. The patient has become desensitized to it.

The theories of Classical Conditioning (Pavlovian) explain how this works.[315] A neutral stimulus which is paired sufficiently often to an unconditioned aversive stimulus becomes a feared conditioned stimulus. This stimulus signals the phobic object. If the subject is then exposed several times to the neutral stimulus no longer coupled to the aversive one, eventually the stimulus will no longer be frightening or avoided. The response has extinguished. Obviously, extinction will not occur if the phobic object remains coupled to the aversive unconditioned stimulus.

Behavioral therapy techniques have been applied to anxiety responses which are not produced by previous conditioning, e.g., compulsive rituals.[316] The observation is that repeated exposure to the feared object, e.g., dirt for compulsive hand washers, leads to extinction of the anxiety and washing responses. Advances have been maintained through 2 years of follow up. Advances are significantly better than with relaxation therapy.

A number of different desensitization strategies have been developed by behaviorists and have been used in the treatment of phobic disorders. A complete discussion of these techniques is beyond the scope of this chapter.

One popular strategy makes use of another central principle of behavior therapy, that fear/tension are reciprocally related to joy/relaxation.[317] Patients are first conditioned to relax using a process called progressive relaxation. Then they are gradually exposed to a (from least to most) graded sequence of approximations to the phobic object. The relaxation reflex inhibits the tension reflex, and fear is kept at low levels until the patients, who have been exposed to the full phobic object, become desensitized. This strategy is called progressive relaxation and systematic desensitization.

If no attempt is made to keep the patient's anxiety low during exposure, then the strategy is flooding. Even though the patient's anxiety goes high, repeated exposure ultimately results in desensitization of the patient to the object.

How the patient is exposed to the object can affect treatment outcome. Some treatments utilize the patient's subjective images of the phobic object, some utilize filmstrips or pictures (imaginal desensitization), and some utilize the real object or situation (in vivo exposure). Investigators have demonstrated the superiority of real exposure to produce desensitization in agoraphobic type avoidance.[318-322]

H. Behavioral Treatment of Agoraphobia

Gelder et al. placed a mixed group of patients with agoraphobia, social phobia, or simple phobia in treatments consisting of (1) 9 months of once a week systematic imaginal desensitization, (2) 12 months of individual therapy, or (3) 18 months of group psychotherapy.[318] The mixed groups showed the greatest reduction in severity of main phobia and general anxiety with systematic imaginal desensitization. Eighteen months of group psychotherapy was consistently the worst option. Gillan and Rachman confirmed these results.[319] Systematic imaginal desensitization reduced symptoms on about 50%, group psychotherapy reduced them on about 15%.

Marks et al. exposed agoraphobic patients to six sessions of imaginal flooding vs. six sessions of systematic imaginal desensitization (50 min each).[320] Then there was a crossover and the same patient received the other treatment. Flooding was particularly effective in agoraphobia, and was significantly better than systematic imaginal desensitization. Contradistinctly, simple phobics in the same paradigm were treated equally well with either treatment.

Matthews et al. assigned 36 female agoraphobic patients (distribution between primary and secondary agoraphobia unclear) to treatment by in vivo exposure or imaginal flooding

in an 8-week crossover design.[321] In vivo exposure was significantly better than imaginal flooding in terms of assessment of safety in the phobic situation. Emmelkamp and Wessels separated fear from avoidance and confirmed that avoidance was reduced more by in vivo exposure.[322]

The conclusion of these experiments is that agoraphobic type avoidance is better treated by in vivo exposure than by imaginal flooding, systematic imaginal desensitization, individual, or group psychotherapy.

Johnston and Gath showed that diazepam and placebo enhanced the effectiveness of in vivo exposure in treatment of agoraphobic avoidance, and that diazepam was superior to placebo in this effect.[323] Hafner and Marks submitted 41 agoraphobics to in vivo exposure and either diazepam or placebo.[324] Results showed that diazepam potentiated in vivo exposure by increasing the exposure rate.

Ullrich et al. examined the effects of beta blocker (alprenolol) upon in vivo exposure.[325] Reduction in "autonomous anxiety" potentiated the exposure rate.

Beta blockers or benzodiazepines potentiate in vivo exposure treatment of agoraphobia by increasing the rate of exposure.

I. Treatment Protocol for Adjustment Anxiety

At the start of treatment, a 35-year-old male unemployed machinist with a mortgage he can't pay is worried about losing his home. He is a high school graduate who has been married for 7 years, and he and his wife have no children. He had worked for the same company for 12 years, and had been promoted over more senior employees repeatedly during that time. However, massive layoffs at his plant prompted by the recession finally got him and he has been out of work just over a year at the time he is first seen. His union benefits have run out, and he can't pay the mortgage on his house that he purchased 3 years ago. The patient's father never owned a home, and the patient has been proud he did. A normally adaptable and giving man, he has since become preoccupied by worry about losing his home. Although he had actively looked for work before, he has stopped looking. This is his first psychiatric contact with a chief complaint of "nervous."

Successful treatment of this man requires empathy and support besides medication. His worry about losing his home is in one sense a realistic response to real threat, but it now preoccupies him and limits his usual flexibility, thus it is adjustment anxiety. The patient has indicated he would like medication for his anxiety.

The patient's anxiety is clearly anticipatory and exogenous in origin. There is no evidence of depression, borderline syndrome, schizophrenia, or dementia which would indicate a need for neuroleptics or antidepressants. There are no spontaneous panic attacks or partial panic attacks to suggest the presence of endogenous anxiety. The patient has exogenous anticipatory anxiety and no evidence of phobic avoidance. Adjustment anxiety is the prime indication for benzodiazepines.

Which benzodiazepine? In accord with the theoretical considerations presented in the molecular biology of benzodiazepine section, we recommend a high-affinity benzodiazepine to maximize therapeutic efficacy at minimum side effects, lorazepam. Alprazolam is an equivalent choice.

Assessment of response to anxiolytic medications in general requires that specific anxiety symptoms are measured as targets of drug action. Where and when does the patient experience anticipatory anxiety and how much of it is experienced? In the measurement of anxiety in various mental disorders, we recommend the use of mood adjective checklists, or some other validated anxiety scale. Izard's mood adjective checklist, the Differential Emotive Scale-State Anxiety Inventory is particularly useful because it measures all seven fundamental motions simultaneously and only requires about 5 min for the patient to fill out.[4] These are filled out when or shortly after anxiety is experienced, and they enable good quantification

of target anxiety. Even with mood adjective checklist results, it is important to question the patient carefully about changes in target symptoms, the presence of new symptoms, or possible side effects. At the time the lorazepam script is given, the patient is instructed about anxiety record keeping and when and how to fill out the mood adjective checklist. A fairly accurate quantification of the patient's anxiety can often be estimated from clinical history, and this provides part of the baseline. If laboratory tests are pending, it is possible to have patients delay starting the medications until a small baseline anxiety record can be obtained.

About 2 weeks into benzodiazepine treatment one needs to reassess target symptoms. One must decide how much improvement has occurred and whether one's initial assumptions and plan were correct. Inability to detect a 25% reduction in anticipatory anxiety at this point would likely lead to an inappropriate decision to change medications, and this underlines the importance of quantification of target symptoms. Prior to the 2-week visit, we recommend that the patient get therapeutic drug monitoring of lorazepam level after 1 week of therapy. A level less than 200 ng/mℓ is taken as evidence for sub-therapeutic dose. Rickels has noted that response at 1 week is a good predictor of ultimate response.[239] We use the 2-week response similarly. If the patient doesn't respond at 2 weeks to a continuous dose of benzodiazepine which produces a plasma level of 750 ng/mℓ diazepam and desmethyldiazepam or the equivalent (200 ng/mℓ lorazepam), then the treatment should be considered a failure and another kind of anxiolytic selected.

Commonly the nonresponse problem is caused by inadequate dose. Benzodiazepines are often prescribed on an "as needed" basis. Even if they are prescribed on a continuous basis, patients often take them as needed to avoid "depending on" medication. Given recent insights into benzodiazepine receptor dynamics and the increasing use of short half-life compounds, the "receptor roulette" of as needed dosing is difficult to recommend. Attainment of a stable level of medication requires several days. Abrupt discontinuation of medication produces rebound anxiety. It is small wonder that initial attempts to correlate benzodiazepine level with clinical response using prn dosing schedules were unsuccessful. We recommend continuous, regular dosing which provides steady-state concentration of benzodiazepines and active metabolites, and thus constant benzodiazepine receptor stimulation. Changes in patient status are then unlikely to be caused by spurious side effects and are more likely to reflect changes in the patient's anxiety condition.

At his 2-week visit, the patient's anticipatory anxiety has dropped from 70% of maximum and 50% of his waking hours to 3% of maximum and 33% of his waking hours. He has been taking lorazepam 1 mg P.O. t.i.d., and his level is 225 ng/mℓ. He and his wife noted he is less nervous and more 'himself''. No side effects are reported. The decision is made to continue lorazepam 1 mg P.O. t.i.d.

At 1 month of therapy, the patient's anxiety is 20% of maximum and 30% of his waking hours. He is working hard at looking for work, and he is his normal self except for a few episodes of moderate anxiety associated with meetings about possible foreclosure at the bank. Lorazepam 1 mg P.O. t.i.d. was continued.

Four days later the patient calls with obvious euphoria to say he had been recalled at the plant. Lorazepam therapy is tapered over 1 week and discontinued.

If the patient has responded completely to benzodiazepine, then consideration must be given to how long to continue treatment and how to discontinue treatment. Resolution of the threat of the exogenous stressors is a reason to stop treatment, either because the problem is time limited or because the patient gives evidence of coping with it effectively. Some chronically anxious patients may benefit from continuous treatment over months or years, and there is evidence of lack of anxiolytic tolerance and lack of significant benzodiazepine dependence problems. They should continue on benzodiazepines as long as they need them. Whenever the decision is made to stop benzodiazepines, they must be tapered gradually.

The longer the treatment and the higher the dose the more likely withdrawal anxiety will complicate stopping treatment.

J. Treatment Protocol for Simple Phobia

At the start of treatment, the patient was a 40-year-old married female executive who had recently been promoted to vice-president for program planning and development for a major U.S. corporation. Ten years previously, her husband and son had been killed in a private plane crash. Since that time she has been unable to take plane trips secondary to intense anticipatory anxiety that the plane will crash. She knows intellectually that this is unlikely, yet she still fears. Her promotion requires that she participate in business meetings with the president of the company on transcontinental flights. She notes that diazepam "knocks her for a loop" and she is afraid to take it when her best cognitive skills will be required. She has only 3 weeks until her first business meeting in the sky and she is already worried. In addition, the patient's medical history is complicated by asthma.

Successful treatment of this woman requires that she rapidly overcome her fear of flying. Desensitization of her conditioned avoidance would appear to be the method of choice, but it is unlikely that this could occur fast enough unless a maximum speed of exposure approach were used. Benzodiazepine pre-treatment could help to increase the exposure rate, but if this needed to be continued into her first actual trip, she might make errors. We would recommend selection of metaprolol starting at 50 mg P.O. q.i.d., combined with in vivo exposure to airplane trips.

Target symptoms include anxiety associated with various steps in the patient's desensitization hierarchy, which can be measured as before by mood adjective checklist, and avoidance of plane flight. Heart rate can also be recorded, and the dose of metaprolol q.i.d. adjusted to a resting heart rate of 55 to 60 beats per minute.

Drug therapy can be tapered gradually when the patient is completely desensitized to plane flights and her aerial business meetings.

K. Treatment Protocol for Post-Traumatic Stress Disorder

The patient is a 29-year-old man who 3 months prior had suffered burns over 25% of his body in a car accident in which his wife and his children, ages 4 and 6, had burned to death. The patient, who was the driver, was trapped in the burning car and he had been unable to save his children from the fire after they were not killed by the collision. The patient was oriented and alert, and he isolated his affect almost to flatness in describing the events. He fidgeted continually and startled conspicuously when the telephone rang. He believed that somehow he should have gotten the children out and reports a recurrent nightmare of the crash and subsequent fire. He was without vegetative signs of depression, and he was at times superficially cheerful.

There are no systematic studies of the proper role of drugs, psychotherapy, and behavioral therapy in this disorder. Workers in the field have used tricyclics, monoamine oxidase inhibitors, beta blockers, and benzodiazepines in pharmacotherapy; however, there have been no comparative efficacy studies. The presence of recurrent nightmares which occur during rapid eye movement (REM) sleep has been used to justify treatment with the REM-suppressing tricyclics and monoamine oxidase inhibitors.[25,326,327] Friedman has noted that the generalized anxiety often responds well to beta adrenergic blockers, and that a combination of antidepressant and beta blocker is sometimes useful.[328] Among tricyclics, Friedman favors amitriptyline which differs from the others by being both a better serotonin agonist and REM suppressor.[25]

Phenomenologically, the clinical picture of generalized anxiety, repressed guilt, obsessive thoughts, and superficial cheerfulness resembles the old "smiling" depression. It is interesting that this guilt-anxiety syndrome; like depression, obsessive-compulsive disorder, panic

disorder, and social phobia; responds best to tricyclics and monoamine oxidase inhibitors. Further, it is interesting that the clinical impression of a careful psychopharmacologist like Friedman is that amitriptyline works better than other tricyclics. It brings up again the serotonin deficiency and guilt relationship which has been observed by Asberg in obsessive-compulsive disorder. Alprazolam, with its actions on anxiety and depression, may well be efficacious in post traumatic stress. We would welcome systematic studies of the relative efficacy of tricyclics, monoamine oxidase inhibitors, beta blockers, benzodiazepines, alprazolam, neuroleptics, clonidine, etc. in post-traumatic stress disorder. Further, neurotransmitter function and biological marker studies might contribute to differential diagnosis and treatment of post-traumatic stress disorder in ways which would improve the efficacy of treatment.

In the pharmacological treatment of post-traumatic stress, target generalized anxiety, guilt, and nightmares and treat with amitriptyline while monitoring amitriptyline and nortriptyline levels. Adjust dose to provide a nortriptyline level within the therapeutic window. Observe for changes in target symptoms at 1 month after reaching therapeutic levels. If clearly no response, discontinue amitriptyline and start propranolol. In case of a partial response, add propranolol. Adjust dose to produce a heart rate of 55 to 60 beats per minute. Monitor changes in target symptoms of generalized anxiety, guilt, and recurrent nightmares.

Pharmacotherapy and psychotherapy are used together in the treatment. A facilitated exploration of the traumatic event to assist controlled discharge of repressed guilt is important.

L. Treatment Protocol for Obsessive-Compulsive Disorder

At the start of treatment, a 20-year-old male engineering student presented a history of being unable to eat at restaurants because of the recurrent thought that he would vomit the meal. He had in fact never vomited at a restaurant, nor had he even become nauseated. However, when he knew he would be going to a restaurant he would become anxious, and this anxiety would increase driving to the restaurant. At the time he got the menu he would be very anxious, depersonalized, and he had recurrent intrusive images of vomiting which could not be repressed. He couldn't make himself eat even though he thought the whole problem was silly, and he knew that he would not vomit. His eating at home or at fast food stores was unimpaired, his appetite was good, and he hadn't lost any weight. He was otherwise his normal self; a very controlled, perfectionistic, and moral man who was somewhat rigid but who was well liked among his engineering peers. He had had one significant continuous relationship with a girl who was his neighbor which lasted 6 years. The onset of his symptoms began 6 months earlier when he discovered her smoking marijuana; and when she refused to stop, he cancelled their date for a formal dinner-dance and broke up with her.

Laboratory examination was remarkable for decreased platelet serotonin transporter. Sleep-deprived nasopharyngeal lead EEG was normal, and the patient had no unconscious episodes, hallucinations, or illusions. Dexamethasone suppression testing and TRH-thyroid stimulation testing may be useful in some patients to rule out major depression.

Successful treatment of this man's obsessive-compulsive disorder pharmacologically requires the knowledge that potentiation of serotonin neurotransmission is of proven value in obsessive-compulsive disorder regardless of the presence of depression, and l-tryptophan potentiates the actions of tricyclics or monoamine oxidase inhibitors. This particular patient has a platelet serotonin abnormality which further points the therapy toward serotonin.

Since the patient was consistently severely anxious and depersonalized in the restaurant at the point of getting the menu, the patient was instructed to eat dinner in a restaurant twice a week and fill out a mood adjective checklist just before reading the menu. He was also asked to rate depersonalization on a scale of one to ten and to globally rate his thoughts of vomiting on a scale from one to ten. Thus there were four abnormal target symptoms;

anxiety, guilt, depersonalization, and obsessive thinking which were measured twice a week before and during pharmacotherapy.

Selection of a tricyclic over a monoamine oxidase inhibitor was made on the basis of the greater relative safety and the absence of dietary constraints using the former. Trazodone was selected because of its specific and potent action to bind to 5-HT2 receptors, which were known to be abnormal in this man. Dose was begun at 100 mg P.O. b.i.d. while checking serum levels. The dose which produced 1000 ng/mℓ was maintained. When the patient demonstrated no adverse effects from trazodone after 3 days, l-tryptophan was added to the treatment regime starting at 500 mg P.O. q.i.d. while watching the serum tryptophan and tyrosine levels.

It should be noted that if the patient had evidence of complex partial seizures, epilepsy, or an abnormal EEG that the combination of trazodone and tryptophan theoretically could exacerbate the seizure problem. In such cases, a trial of carbamazepine might well produce symptomatic improvement.

Several obsessive-compulsive disorder patients we have treated became asymptomatic at 6 weeks on trazodone and l-tryptophan. In cases of significant improvement but residual symptomatology, one can obtain increased results by (1) increasing the tryptophan, (2) discontinuing both and starting an MAOI to be followed by increasing doses of l-tryptophan, and (3) addition of behavior therapy, specifically in vivo exposure, to the treatment plan.

M. Treatment Protocol for Social Phobia

At the start of treatment, the patient is a 32-year-old lawyer who is afraid to go to court. At times when he has managed to get there, his voice cracked, his knees knocked, his hands trembled, and he became so nervous he couldn't think and was disoriented. He is very aware of the inadequacies of his preparation, and feels like everyone in the court room is aware of them also. Occasionally when he is over-prepared, he has enough confidence to complete a trial. He has avoided going to court by doing legal research which doesn't require public display, and he is very capable one-on-one. However, this work is economically limited, and he is engaged to be married. He has always been shy and acquaintences think him aloof, but he is not asocial or paranoid. He had trouble dating because of no opening lines and impotence until he could overcome his self-consciousness at being naked. His anxiety is anticipatory of the scrutiny of others and he denies spontaneous attacks of anxiety ever. The patient tended to avoid eye contact on mental status.

Because of the symptoms overlap between social phobia and panic attacks with agoraphobia, a lactate infusion test could be diagnostic.

The target symptoms in this patient are anxiety and the self-conscious shame experienced during presentations at work. Shame is clearly increased by the symptoms of somatic anxiety, e.g., beta-adrenergic tremor. Combinations of antidepressants and beta blockers diminish the shame and anxiety pharmacologically, while in vivo exposure lessens conditioned anxiety in social phobia. Among tricyclics we have had good results with trazodone. Dosage should be increased until a plasma level of 1000 ng/mℓ is reached. Propranolol dosage should be increased to maintain pulse range of 55 to 60 beats per minute. When dosages are stabilized, in vivo exposure can begin. Reduction of shame in public situations seems to be the most important factor in overall improvement.

N. Treatment Protocols for Panic Attacks with Agoraphobia

At the start of treatment, a typical patient is housebound and has a succession of relatives and friends shuttling in and out so she will not be alone. She is generally anxious and this is punctuated by peaks of panic anxiety and depersonalization or derealization, particularly in the early morning and for a week or so premenstrually. Prior to becoming totally housebound, she could go out with a confidant to small stores or uncrowded supermarkets;

however, she wouldn't have contemplated small stores alone or crowded supermarket checkout lines. She was then unable to cross bridges, use elevators, or drive. In her house, thinking about these situations (e.g., being alone, leaving the house, waiting in line, etc.) provokes increased anxiety. She is socially phobic because she doesn't want acquaintances to see her so out of control. Being housebound has strained her relationship with her husband who must now do everything for her, and with her children who resent her not taking them to soccer practice, etc. Her fear of being alone is complicated by a realistic fear she may lose her husband. She has some depressed feelings because she has been sick and dysfunctional a long time, but is not suffering from major depression. Lactate infusion testing was positive for endogenous anxiety.

Successful treatment of this woman requires a directed attack at the target features of her disease: (1) panic attacks, (2) generalized anxiety, and (3) anticipatory fear of fear in situations when alone and potentially trapped. These actions must be coordinated so that she cannot experience a panic attack during extinction of anticipatory anxiety or doing that will be difficult.

Panic attacks stop after about 3 weeks of adequate doses of a tricyclic or a monoamine oxidase inhibitor. Tricyclics are safer than MAOIs and do not require a careful diet. Specifically, desipramine is very effective and among tricyclics has a minimum of anticholinergic and antihistamine side effects. Any of these drugs, including desipramine, is associated with peripheral hypersympathetic side effects for the first few weeks of treatment before tolerance develops to them. This early period can be associated with increased panic attacks, and patients usually perceive themselves to be worse in these weeks. Often they flee medication for these reasons. Also, they feel that they are being controlled by a drug that they sense by these side effects. In their compulsive personality structure, they stubbornly insist to control themselves. This is another major source of medication noncompliance. Patients who refuse medication don't get better. Compliance with treatment can be assured by (1) warning the patient in advance about side effects and how she is likely to feel about them, (2) emphasizing that they are temporary, (3) not increasing desipramine precipitously, (4) using two drugs in combination, and (5) measurement of drug levels to assure the patient is taking the drug(s) and the level is appropriate.

Symptoms of somatic anxiety and their troublesome sequellae in the mind of the secondary agoraphobic can be eliminated either by a benzodiazepine or by a beta blocker. We have used propranolol, nadolol, lorazepam, and alprazolam for this purpose and all will work. Beta blockers seem to be superior in that they produce less sedation than benzodiazepines and sedation often provokes medication noncompliance. However, alprazolam offers the added benefit of a direct, anti-panic effect. Beta blockers are approximately as good as benzodiazepines to lower general anxiety and somatic anxiety symptoms. Propranolol is preferred to nadolol because it seems to be more effective, but it is more troublesome in terms of rebound anxiety. Asthmatic patients can get metaprotol.

Propranolol can be raised to 120 mg P.O. q.h.s. within 1 week in most patients without bradycardia (less than 50/min) or significant hypotension. Titrate the heart rate to the 55 to 60 beats per minute range. Desipramine can be raised to 150 mg P.O. q.h.s. in 50-mg increments every 3 days in the presence of propranolol, but it requires several weeks of 25-mg increment increases otherwise. Thus, using the combination of desipramine and propranolol, in most patients panic attacks and general anxiety can be eliminated in 1 month of treatment. Desipramine plasma levels should be obtained to assure optimum effects. If this does not occur and the patient has any panic attack in the latter 2 weeks, the approach has failed. Repeat lactate infusion testing after it has been positive can help to assure the patient she won't panic.

After 1 month of treatment, the patient is still housebound but is comfortable and having no panic attacks. In vivo exposure, which is potentiated by the anticipatory anxiolytic effects

of propranolol, can now begin. The patient constructs a hierarchy of threatening situations, and the therapist then constructs a behavioral treatment plan based upon that hierarchy starting with exposure to less threatening situations and progressing to the most threatening situations. If during an exposure the patient's anxiety goes over 60% of maximum, then retreat and try again later. Progress depends upon exposure rate which is related to time spent in exposure. Exposure time can often be maximized by the use of para-psychiatric personnel. These persons are often desensitized former agoraphobics who have empathic understanding of how much and when to push the patient in phobic situations. Usually this desensitization hierarchy can be completed in 2 months. Thus, in 3 months the patients can go from housebound and panicky to driving alone to crowded supermarkets and waiting in the checkout line without anticipatory or panic anxiety. Propranolol can then be tapered and discontinued. The patient is maintained on desipramine, and the dose can usually be reduced.

If the patient's panic doesn't respond in spite of an adequate trial of desipramine, then another anti-panic agent must be used. Sheehan's report of the anti-panic effects of 6 to 10 ng q.d. of alprazolam and relative safety and convenience of benzodiazepines compared to monamine oxidase inhibitors make this an attractive second choice.[218] Alprazolam level of about 100 mg/mℓ is required for anti-panic action, compared to about 20 ng/mℓ for anxiolysis of anticipatory anxiety. Sheehan notes that patients must pass through two or three tolerance plateaus to reach this high dose, and he notes that that usually takes about 3 weeks. If at 1 month of treatment the patients have had any panic attacks in the preceding 2 weeks, then the trial is considered a failure and another drug trial is indicated.

Sheehan reports that phenylzine is the most effective drug against panic attacks,[26] and it should now be used. Patients must be carefully instructed about diet and the need to watch it carefully. If an 8-week trial at blood levels which produce 90% or greater inhibition of MAO in vitro doesn't eliminate panic attacks, then it has failed.

In practice, few patients will require the second choice of anti-panic drug. The combination of desipramine and propranolol eliminates panic attacks in most patients. The commonest cause of treatment failure is the patient's refusing to take the medication secondary to side effects. Occasionally attacks temporarily recur at times of extreme stress. Behavior therapy, specifically in vivo exposure, will take the patient to the final stage of extinguishing anticipatory fear of fear and agoraphobic situational avoidance.

V. A BETA-ADRENERGIC RECEPTOR HYPERACTIVITY HYPOTHESIS OF ENDOGENOUS ANXIETY

The "sine qua non" of panic disorder is the presence of panic attacks, which are probably induced by stress of some sort, nonspecific or perhaps separation. In this chapter we have reviewed data about panic disorder, and its response to psychopharmacological intervention which is summarized as follows:

1. Peripheral beta adrenergic or lactate stimulation of panic disorder patients, but not normals, results in a panic attack.
2. Acute central hyperadrenergic stimulation by amphetamine, or subacute desipramine, or phenylzine can produce panic attacks in these patients, and is associated with increased adrenergic transmission.
3. Chronic central hyperadrenergic stimulation by desipramine or phenylzine for about 3 weeks eliminates panic attacks and the response to lactate in these patients. Chronic administration to rats of desipramine or phenylzine results, after about 3 weeks, in down regulation of beta-adrenergic receptors in the brain and periphery, but not alpha-1 receptors.
4. Acute administration of the alpha-2 receptor agonist clonidine eliminates panic attacks

in panic disorder patients, and stops central adrenergic neuronal firing and turnover and presumably beta-adrenergic stimulation.
5. Beta-adrenergic blockade reduces panic attacks in panic disorder patients.
6. Chlorpromazine has been shown to make panic disorder worse, and is associated with up regulation of beta adrenergic receptors.
7. Panic disorder is a genetic disease probably having an autosomal dominant mode of inheritance.
8. Stress in normal individuals is associated with increased central adrenergic transmission, and so too in panic disorder patients.

We agree with the hypothesis of Klein et al. of endogenous anxiety in panic disorder[196] and we further posit that the previously mentioned observations are consistent with the hypothesis that panic disorder patients inherit an increased density of beta adrenergic receptors centrally and peripherally, which cause in the presence of stress extreme reactions called panic attacks which can be cured by pharmacological intervention which reduces that receptor increase or otherwise impairs the formation of the active beta receptor-adrenergic complexes.

VI. SUMMARY

The material in this chapter describes the phenomenology of fear and anxiety and the clinical occurrence and differential diagnosis of the symptom of anxiety. The recent distinction between endogenous anxiety and exogenous anxiety is defined. Successful pharmacotherapy depends upon correct diagnosis of the syndrome causing the anxiety, and this diagnosis helps to select an appropriate anxiolytic drug. Treatment options; including benzodiazepines, beta-adrenergic blockers, tricyclics, monoamine oxidase inhibitors, clonidine, tryptophan, behavior therapies, and combinations are presented, including indications, efficacy, side-effects, the role of levels, dosages, and pharmacokinetics. Emphasis is placed upon how to maximize efficacy in specific anxiety syndromes. Sample case protocols help to simulate how actual cases are managed. Having read this chapter, the physician will be theoretically and practically prepared to prescribe anxiolytics.

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Chapter 10

ALCOHOLISM

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TABLE OF CONTENTS

I. INTRODUCTION

The psychopharmacological treatment of alcoholics with concomitant psychiatric illness is a complicated, controversial, and critical clinical issue. This chapter will address some of the clinical aspects which we have encountered while treating alcoholics in an inpatient setting. It is not meant to be a review of the current literature regarding this topic, and so should be qualified as a summary of our empirical clinical experience. In this context we have attempted to unite the principles of Alcoholics Anonymous(AA) and psychiatry as they apply to patients with both alcoholism and major psychiatric illness. The alliance of these disciplines, which is often strained, is essential to insure proper clinical management of such patients.

Generally speaking, we have found that the vast majority of alcoholics do not require psychopharmacological or psychiatric intervention. In fact, the failure encountered by psychiatry in the treatment of alcoholism, relative to the success of AA, has contributed a great deal to the friction between these two disciplines. Certain psychiatric disorders will not respond to AA treatment, and require appropriate psychiatric and psychopharmacological therapy. Failure to identify these disorders usually precludes the effectiveness of AA in treating coexisting alcoholism. Untreated patients may continue drinking as a form of self-medication, or because the psychiatric problem has interfered with their participation in AA. As well as the prolonged and often needless suffering of certain psychiatric conditions, there are the everpresent dangers of suicide or violence. An integration of psychiatric and AA treatment is essential and feasible for the minority of alcoholics which require both approaches.

Although it is important to identify and treat medication-responsive psychiatric disorders which are seen in alcoholics, it is also important to avoid medicating alcoholics unnecessarily. There are two aspects to this issue. First, certain medications are relatively contraindicated for use in alcoholics because they are addictive or mood-altering substances. Alcoholics already have demonstrated their addictive tendency by their use of alcohol. Any use of alternative, similar agents will almost invariably lead to alcohol readdiction, or a substitution addiction. Sedative-hypnotic, anxiolytic, analgesic, and stimulant agents merely strengthen the pleasure-reinforced compulsion associated with alcoholism. Table 1 includes some of the medications that should be avoided in alcoholics. When medical or surgical conditions dictate the necessity of any of these agents, their use should be closely supervised and the possibility of recidivism anticipated. There are no psychiatric disorders which indicate the use of drugs from Table 1 in alcoholic patients.

The other aspect of using medications in alcoholics relates to their symbolic meaning. The alcoholic has self-medicated problems ranging from daily stress to emotional discomfort. Continued use of medications, even those without addictive or mood-altering characteristics, will reinforce the old compulsion of drinking. This is probably the major clinical reason for the anti-medication position of AA. Even alcoholic patients with medical or surgical problems requiring drug maintenance may experience a negative therapeutic effect with respect to their alcoholism treatment. Therefore, as with all medical situations, the psychiatrist must weight the benefits against the risks of psychopharmacological treatment. With this consideration in mind, we have largely restricted our psychopharmacological interventions to major depressive illness, manic depressive illness, psychosis, and panic disorder. Each of these situations will be discussed further.

II. AA — TREATMENT PHILOSOPHY

AA treatment is generaly regarded as the treatment of choice for alcoholism, and certainly is associated with the highest degree of success. This section will summarize some of the philosophical and practical aspects of AA treatment. An understanding of this treatment

Table 1
PHARMACEUTICAL AGENTS TO BE AVOIDED IN ALCOHOLICS

Hypnotics and Sedatives	Opioids
Benzodiazepines	Codeine
Barbiturates	Meperidine
Chloral hydrate	Propoxyphene
Ethchlorvynol	Levorphanol
Ethinamate	Fentanyl
Glutethimide	Methadone
Meprobamate	
Methyprylon	**Miscellaneous**
Methaqualone	
Paradehyde	Nitrous oxide
	Methylphenidate
	Elixir preparations

modality is crucial for the physician to effectively treat psychiatric illness in an alcoholic. The AA position asserts that the alcoholic lacks the internal power to stay sober continuously. Alcoholics are considered to be permanently disabled in this regard, and permanently at risk of readdiction to alcohol or other agents. There is no cure for alcoholism, and the compulsion to drink is a life-long pattern that must be approached with rehabilitation. Alcoholics tend to deny extensive psychological problems, including isolation, shame, guilt, loneliness, and other uncomfortable feelings. They use alcohol as a means of dealing with unpleasant feelings, and to perpetuate their entrenched denial of severe problems in their lives. They tend to have enormous dependency needs but poorly developed interpersonal relations. Given their intense needs, and their compulsive use of alcohol to avoid emotional discomfort, alcoholics are considered powerless to maintain sobriety by themselves.

The efficacy of AA is largely based on the use of a peer group to help the individual with his or her powerlessness over alcohol. The group accepts the alcoholic, in spite of inadequacies and past behaviors, and serves as a powerful and ever-present support system. The individual's powerlessness is offset by the peer group's strength. Dependency needs are met by the group, as is the hope of an escape from continued addiction. The pattern of compulsive drug use is replaced by communication, emotional closeness, shared experiences, and the work of helping others attain emotional and spiritual balance.

In the inpatient setting, alcoholics are detoxified and immediately placed in peer groups lasting thoughout the day. Education regarding alcoholism, as well as confrontive but non-punitive group sessions, serve as practical means of changing compulsive patterns. Patients are expected to be honest and responsible in their desire to achieve sobriety. After a 4- to 6-week hospitalization, the alcoholic is expected to become an active AA member in his community, with daily meeting attendance during at least the first 3 months. In this way, dependency on the inpatient unit is therapeutically transferred to the community group, which continues indefinitely. Families of the alcoholic are considered, by definition, to have pathological patterns which must be changed through education and treatment. Families tend to compensate for the alcoholic's behavior, and thereby enable continued addiction. Familial patterns associated with alcoholism include the manipulation and control of the alcoholic family member and protection from the consequences of alcohol-related behaviors. Families often become negativistic, cynical, and isolated. They usually require treatment for their own psychological health, and to allow for the alcoholic's recovery. Families are effectively treated through attendance at community Al-Anon or Al-A-Teen self-help groups, which are strongly supported by the inpatient AA program.

The principles of AA are designed to obliterate the compulsion of drinking. This pleasure-reinforced compulsion is very difficult to alter and must be replaced by newly learned patterns. The philosophy of AA includes a series of steps, or traditions; these steps include the intellectual and emotional realization of powerlessness over alcohol, and that protests to the contrary represent denial. In order to overcome denial, the alcoholic must "surrender" to the group, and so accept the group's objectivity and strength. This surrender often has spiritual or religious associations, and should lead to feelings of hope and strength as the alcoholic transcends his denial. Honesty and newly formed, interpersonal relationships replace the old patterns of denial. He is encouraged to review past behaviors which have led to intense guilt or poor self-esteem. The AA group serves as an understanding, accepting, and nonjudgmental society where needed changes can be made. Continued review of the 12 steps of AA and active attendance at meetings can gradually replace the compulsion of alcohol use.

The AA approach addresses the psychological needs of the alcoholic in a number of ways. Alcoholism is an illness for which there is no cure, and AA furnishes a means of dealing with the illness. Alcoholism is considered by AA to have no known pharmacological antidote, and the reliance on medications to deal with emotional disorders opposes the AA approach. Rather, the AA group and principles replace compulsive drug use. For this reason, we are very specific in stating that psychopharmacological treatment of the alcoholic is indicated for certain concomitant psychiatric diseases, and not for alcoholism per se. Furthermore, the use of medications by alcoholics can symbolically recruit memories of self-medication with alcohol, and often causes friction with AA groups. Therefore the clinical indication for psychopharmacological treatment must significantly outweigh the disadvantages, and should be continually reassessed.

III. SELF-MEDICATION HYPOTHESIS

Although most alcoholics do not have major psychiatric diseases, there are subgroups which suffer from affective, psychotic, or anxiety disorders. These patients frequently began to use alcohol as a means of obtaining symptom relief. The process of using alcohol to "treat" an underlying psychiatric illness is referred to as self-medication, and is a problem which is often clinically unappreciated. Very frequently the underlying psychiatric illness will predate compulsive alcohol use, and such use may continue until the underlying psychopathology is corrected. This situation is paralleled in medicine or surgery, where chronic pain often leads to self-medication and subsequent addiction to alcohol, analgesics, or tranquilizers. In the case of psychiatric disorders, however, there is usually a highly effective treatment. These disorders should therefore be properly diagnosed and treated. Failure to do so will usually lead to continued self-medication, and complications associated with both alcoholism and the coexisting psychiatric disorder.

Before concluding that self-medication is operating in an alcoholic patient, it is crucial to examine whether coexisting psychiatric symptoms are actually caused by alcoholism. Alcohol-induced psychosis, depression, and anxiety disorders are very frequently seen. A careful history can be helpful in clarifying this issue, with particular attention to whether the psychiatric disorder preceded alcoholism. However, even with a clear-cut history of preceding psychiatric illness, one cannot rule out the presence of a superimposed, alcohol-induced disorder. In addition, preceding alcoholism does not rule out an unrelated and subsequent onset of psychiatric illness. This is especially possible for many affective disturbances which typically develop in the third or fourth decade of life. Therefore, the issue of cause and effect is often confusing and inconclusive.

In our experience, most psychiatric symptoms seen in alcoholics are a result of alcoholism rather than major psychiatric illness. These symptoms frequently include insomnia, depressed

mood, guilty thoughts, anergia, decreased libido, irritability, suicidality, and anorexia. Furthermore, such symptoms tend to clear after 1 to 2 weeks of sobriety in most alcoholics. Because the above symptoms are generally used to make psychiatric diagnoses, the clinician must be very careful to consider the influence of alcohol in symptom generation. Psychiatric diagnoses should not be made while the patient is actively drinking, or during the first 2 weeks of sobriety. Psychopharmacological treatment, unless required on an emergency basis, should be reserved for syndromes persisting beyond this 2-week "wash-out" period.

The majority of alcoholic patients with psychiatric symptoms will improve within 2 weeks of sobriety. However, a certain percentage of these patients will continue to suffer from psychiatric symptoms. Often these symptoms will even worsen with sobriety, raising the question of an existing, underlying psychiatric illness. Frequently such patients will use alcohol or other substances as an attempt to self-medicate their problems. These patients will have great difficulty maintaining sobriety as they become overwhelmed by painful psychiatric symptoms. They often have a long history of recidivism, and have trouble getting engaged in AA treatment. They may be misunderstood by AA groups, considered to be resistent to treatment, stubborn, or unwilling to surrender control. A great deal of suffering and frustration can be avoided if these patients are properly diagnosed and treated.

Before proceeding to a discussion of specific psychiatric syndromes often encountered in alcoholics, there are a few general principles that should be reviewed. Alcoholics who are actively drinking should not be medicated as outpatients. In general, these patients require hospitalization, detoxification, and then psychiatric evaluation for symptoms persisting beyond 2 weeks of sobriety. One exception regarding pharmacological treatment is in the hospitalized psychotic or manic alcoholic, who usually requires antipsychotic medications on an emergency basis. Actively drinking alcoholics should not be medicated because existing psychiatric symptoms will often disappear with sobriety, and alcohol can interact adversely with psychotropic medications. Therefore, an alcoholic already being treated for a major psychiatric disease who begins to drink again should be rehospitalized or otherwise confirmed to be sober if pharmacological treatment is to continue. Often random, supervised blood or urine samples are indicated to insure that the patient is alcohol free. Finally, the alcoholic with a psychiatric illness must be encouraged to remain an active member in AA. The psychiatrist should clearly define AA as the treatment for alcoholism, and psychiatric intervention as the treatment of the psychiatric disorder. The patient should not be allowed to minimize the entrenched patterns of compulsive drinking, even though self-medication has been a factor. The psychiatrist cannot assume that successful treatment of the psychiatric disorder will eradicate the alcoholism. AA treatment should be seen as an essential modality, and should usually be a prerequisite to on-going psychiatric or psychopharmacological treatment.

The next several sections will discuss psychiatric diseases most commonly seen in alcoholics. These include major depression, mania, panic disorder, and psychotic illnesses. The actual use of pharmacological agents, when indicated, is essentially the same as has been described in this volume. We will not therefore go into detail regarding the choice and management of medications unless there are differences related to coexisting alcoholism. These differences tend to involve the means by which a diagnosis is made, and how the need for medications is explained to the patient without interfering significantly with AA treatment. When no difference between alcoholic and nonalcoholic patients are specified, the reader can assume our approach would be identical to that described in previous sections.

IV. AFFECTIVE DISORDERS

A. Major Depressive Illness

It has long been appreciated that alcoholics have an unusually high incidence of major

depressive illness. This incidence has been reported to range from 28%[1] to 59%[2] if lifetime prevalence rates are measured. Since it has been estimated that there are at least 10 million alcoholics in this country,[3] even the most conservative reports would indicate that a large number of patients have both alcoholism and major depression. It is not clear how many of these patients have alcohol-induced depression, or are self-medicating their depression with alcohol. This section will address the identification and treatment of alcoholics with coexisting major depressive illness.

It is likely that a large number of alcoholics with major depression remain untreated with respect to their mood disorder. This unfortunate situation is probably due to several factors. First, many depressed alcoholics are actively drinking and generally not seen by physicians. Even those who see physicians seldom see psychiatrists who would be more likely to recognize a mood disorder. In fact, there are a number of neurovegetative symptoms that are present in both depression and alcoholism, making the diagnosis of depression problematic. These symptoms include insomnia, anorexia, depressed mood, guilty thoughts, anergia, and decreased libido. Thus, even the psychiatrist well versed in symptom-based psychiatric diagnoses will often have great difficulty diagnosing depression in the alcoholic.

Alcohol probably often causes neurovegetative symptoms through a complex combination of cerebral toxicity and withdrawal symptomatology. In addition, the lonely and demoralizing lifestyle of most alcoholics certainly contributes to depressive symptomatology. Alcohol-induced neurovegetative and psychological changes, however, tend to reverse quickly with sobriety and supportive hospitalization. Frequently the most florrid depressive syndromes, with extensive neurovegetative symptoms, will clear completely within 2 weeks of sobriety. This 2-week "wash-out" period allows the clinician to distinguish an alcohol-related, organic affective syndrome[4] from a major depressive illness. Observation during the 2-week "wash-out" period is sufficient treatment for most alcoholics presenting with mood disturbances, allowing for the avoidance of antidepressant medications.

Laboratory testing for major depression in the alcoholic can be extremely useful in confirming the clinical diagnosis. As with the psychiatric examination, however, timing is extremely important. The dexamethasone suppression test (DST) is specific for depression in the alcoholic if performed after 3 weeks of sobriety.[5] Nonsuppression of plasma cortisol at this time is confirmatory of major depressive illness, although certainly not a necessary finding. If the DST is performed earlier, especially within 1 week of active drinking, "false positives" are frequently seen and are not helpful in confirming the presence of major depression.[5,6] Careful studies regarding the sensitivity and specificity for depression of the diurnal cortisol test in alcoholics are lacking. We have, however, found this to be a useful adjunct to the DST. The other widely used neuroendocrine test in the evaluation of depression is the thyrotropin-releasing hormone (TRH) test. A blunted thyroid stimulating hormone (TSH) response to TRH has been extensively reported in patients with major depression.[7,8] The TRH test, however, is not specific for depression in alcoholics.[5] Alcoholism is associated with markedly blunted TSH responses in the absence of depression, limiting the use of this test in alcoholics. We routinely perform DST and diurnal cortisol testing after 3 weeks of sobriety in alcoholics who have a persistent depressive syndrome according to DSM III criteria.[4] These neuroendocrine parameters, in conjunction with a careful past and present psychiatric evaluation, will identify most alcoholic patients with major depressive illness.

Before proceeding to a discussion of treatment for major depression, certain other diagnostic considerations should be mentioned. Alcoholics are susceptible to a number of medical diseases, some of which can mimic depression. Thyroid abnormalities are often seen in alcoholics and can be evaluated with the TRH infusion test. Augmented TSH responses or abnormalities in T3, T4, or baseline TSH could indicate the need of thyroid hormone replacement. Alcohol-induced, pseudo-Cushing's syndrome is characterized by a transient but marked elevation in plasma cortisol,[9] and can be ruled out by measurements of plasma

or urinary cortisol, or with the 2-mg dexamethasone suppression tests. Hepatic or pancreatic disease, often seen in alcoholics, can also mimic depression. Medical illnesses associated with depression have been described in this volume, and should be carefully ruled out during the evaluation process.

Once the diagnosis of major depression has been made in the alcoholic, treatment with antidepressant medications should be considered. As we have mentioned, only the alcoholic who has been sober for at least 2 weeks is a candidate for antidepressants. Typically, this patient will be hospitalized in an AA-based treatment unit, attempting through treatment to overcome the compulsion of alcohol use. The issue of administering an antidepressant medication becomes a somewhat delicate matter. On the one hand, the patient should not conclude that depression is the only problem, and its treatment will end all problems with alcoholism. This would sabotage AA treatment and usually lead to recidivism and compulsive drinking. On the other hand, the patient should realize the need for medications and the presence of a coexisting biological depressive illness. The success by which a psychiatrist negotiates this treatment depends greatly upon his communication with the AA staff. An open and mutually respectful relationship between psychiatrists and AA staff is a prerequisite to the successful management of nearly all patients with alcoholism and psychiatric disease. The patient should be approached well before the use of antidepressant medications. Biological aspects of the depressive illness are best emphasized, including family history or positive neuroendocrine findings. The patient should be educated regarding the biological nature of major depression, and the risks of self-medication with alcohol if the depression is not treated. The AA staff should support the need for medications when indicated, and also be educated about psychiatric illnesses. Antidepressant medications should be carefully described as nonaddictive substances with no acute mood-altering effects. Antidepressant effects of these medications are best explained as the restoration of normal, balanced mood rather than an artificial or elevated mood state. Continued explanation of the disease concept of major depression is usually necessary in order to avoid intense conflict in the alcoholic over taking medications. Focus upon neurovegetative symptoms of depression will often convey the biological aspect of this disorder. When a patient is extremely resistant to taking antidepressants, it is often useful to involve the family and AA counselor in discussions with the patient. However, in spite of a sensitive and well-coordinated approach, many alcoholics with major depression will refuse medications or will prove noncompliant. For this reason, the issue of noncompliance should be openly discussed throughout treatment.

The pharmacological treatment of the depressed alcoholic does not differ significantly from that of nonalcoholic, depressed patients. Tricyclic antidepressants are usually very effective, provided plasma levels are adequate and properly monitored. The same pharmacological strategies described in previous sections of this volume can be used with alcoholics, as long as no addictive or potentially abused substances are used (see Table 1). Lithium, monoamine oxidase inhibitors (MAOI), and new-generation antidepressants can be administered as outlined in this volume. Blood levels should be regularly monitored since the alcoholic is often likely to be noncompliant. Noncompliance can result from reactivation of compulsive drinking, AA group pressure, or denial of the depressive illness. These issues should be openly discussed in treatment. If recidivism to alcohol use occurs, the patient will often become depressed in spite of antidepressant medications. These patients should be rehospitalized with renewed attention to their refractory alcoholism.

B. Mania

The alcoholic patient experiencing an acute manic episode represents a psychiatric emergency and is best admitted to a locked psychiatric facility. When these patients are in an AA-based rehabilitation unit, they usually require transfer to a psychiatric unit where external controls and specialized staff skills are more appropriate to their clinical condition. These

patients must first be stabilized psychiatrically before they can participate effectively in AA treatment. This section will address those aspects of manic alcoholic patients which are not present in their nonalcoholic counterparts. Otherwise, the acute management of these patients is identical to that for mania in general.

The first distinction to be made clinically in the alcoholic presenting with manic-like symptoms is whether the patient is experiencing delerium tremens. It is assumed that the reader is familiar with the identification and treatment of this potentially lethal syndrome. These patients must receive appropriate medical treatment immediately and will usually stabilize quickly with respect to their psychiatric symptoms. Similarly, alcohol withdrawal can mimic an acute manic episode and should be carefully assessed and treated with detoxification. Antipsychotic treatment may be indicated if hallucinosis or paranoia are present. These patients have a medical basis to their psychiatric symptoms and tend to stabilize much more rapidly than manic patients. Transfer to a locked psychiatric unit can often be avoided with aggressive medical and psychopharmacological treatment.

In general, physicians are well aware that alcohol intoxication can mimic acute mania, and detoxification should be completed before a manic diagnosis is entertained. Less appreciated, however, is the frequency by which alcoholics abuse other substances which could generate psychiatric symptoms. For this reason, we recommend antibody-based urine or plasma screens for drugs of abuse. In particular, cocaine, amphetamines, phencyclidine, and hallucinogens can be associated with a manic presentation. Careful questioning of family or friend informants will often clarify significant substance abuse which might explain a seemingly manic syndrome. As with withdrawal-associated manic symptoms, those related to substance intoxication tend to clear spontaneously or with transient antipsychotic treatment.

In patients with a persistent manic presentation that cannot be explained by substance intoxication, delerium tremens, or alcohol withdrawal, the diagnosis of acute mania should be tentatively made. These patients must be stabilized psychiatrically before their alcoholism can be addressed. Manic symptoms should be treated with antipsychotic medications and lithium treatment is usually indicated. These patients often have a past history of mania or depression, as well as a family history of affective disorder. Frequently these patients have used alcohol to self-medicate their mood disturbances. It cannot be assumed, however, that stabilization of their manic depression will also reverse their alcoholism. Compulsive patterns of alcohol use, even if originally used to ameliorate psychiatric symptoms, tend to become entrenched and tenacious. Intensive AA-based treatment is indicated once the patient has attained psychiatric stabilization.

As with major depressive illness, education regarding the need for continued medications is critical with manic depressives. Compliance with lithium therapy is often problematic, and should be closely monitored. A coordinated approach with AA treatment is best facilitated by transfer from the psychiatric to AA rehabilitation unit. There, during a 4- to 6-week stay, the patient can address coexisting alcoholism. Noncompliance with lithium can precipitate the reemergence of mania and subsequent use of alcohol. For this reason, alcoholics with manic depression are particularly likely to relapse to both disorders, necessitating a well-coordinated AA and psychiatric treatment.

C. Schizophrenics

The schizophrenic patient with alcoholism presents a very difficult and often tragic treatment dilemma. The use of alcohol by schizophrenic patients often exacerbates psychotic symptoms, or leads to noncompliance with antipsychotic medications. Involvement in AA-based treatment, however, is often precluded by the unrelatedness and social impairment associated with the psychotic disturbance. Many of these patients remain chronically psychotic, actively drinking, and outside the reach of the health care system. Others become

chronically hospitalized in state psychiatric institutions. This section will deal with some aspects of schizophrenia and psychosis when associated with alcoholism.

The acutely psychotic, alcoholic patient is very likely not to have schizophrenia. Therefore, a careful diagnostic evaluation of such patients is critical for their proper management. Psychotic symptomatology can be associated with alcohol intoxication, alcohol withdrawal, delerium tremens, and post-intoxication states. These psychotic states tend to be less persistent than schizophrenia, and usually clear within a few days of sobriety. Antipsychotic medications are indicated once medical stabilization has been attained. Psychotic patients should also be suspected to have abused other substances, and antibody-based urine and blood screening for substances of abuse are indicated. Another common cause of psychosis in the alcoholic population is organic brain syndrome. Alcohol-related dementia is often associated with hallucinations and paranoia, and should be managed with antipsychotic medications when present. Psychotic, alcoholic patients require a complete medical and neurological evaluation before an accurate psychiatric diagnosis can be made. Often the diagnosis of schizophrenia can only be definitively made at a future time after a long period of sobriety.

If psychotic symptoms persist beyond the first 2 weeks of hospitalization, and are not associated with any of the causes mentioned, a full psychiatric evaluation should be pursued. The patient should be evaluated as is any other psychotic patient. The existence of previous episodic or chronic psychoses may indicate the presence of schizophrenia or of a psychotic affective disorder. Neuroendocrine testing with the DST may assist in the delineation of a mood component, and could indicate the use of lithium. The initial psychiatric evaluation and stabilization of these patients is best performed in a psychiatric unit. Psychopharmacological treatment with antipsychotic medications is usually indicated.

Once an alcoholic patient with schizophrenia has been stabilized psychiatrically, AA treatment should be attempted. Because schizophrenia is such a heterogenous disorder, it is often difficult to predict which patients will tolerate and benefit from AA treatment. Many will do well with AA meetings, and benefit from the structure and support system. Others, however, may become disorganized in AA meetings and tend to decompensate. Schizophrenic, alcoholic patients should be exposed to AA treatment while still hospitalized so that their response can be assessed under controlled conditions. Those who can benefit from AA treatment have a better prognosis because repeated alcohol can be curtailed. Frequently, these patients will do well in an AA-based, supervised residential community. This structure, in conjunction with careful monitoring of antipsychotic medications, is often the best approach to the alcoholic with schizophrenia.

The schizophrenic patients unable to tolerate AA treatment often are the more withdrawn, treatment-refractory schizophrenics. These patients often tend to self-medicate psychotic symptoms with alcohol. Although alcohol may afford transient relief from hallucinations or delusional experiences, the long-term effect is almost invariably destructive. Such patients tend to be noncompliant for their antipsychotic medications, and characteristically have frequent rehospitalization. Continued alcohol use contributes to their chronic psychosis and lack of responsivity to neuroleptic medications. Often chronic hospitalization is required to afford any degree of psychiatric stabilization.

D. Panic Disorder

Most alcoholics complain of anxiety and have used alcohol to deal with this feeling. Many alcoholics, however, have panic disorder with incapacitating panic attacks and anticipatory anxiety.[10,11] We have found that large numbers of alcoholics complain of panic disorder preceding alcohol use. These patients often used alcohol initially to suppress anticipatory anxiety or actual panic attacks. Once addicted, they may experience increased panic symptoms during periods of abstinence. Thus, even though alcohol intoxication often affords

some symptom relief initially, patients often require ever-increasing doses of alcohol to successfully ward off panic symptoms. Self-medication with alcohol may reduce the threshold for the next panic attack, contributing to continued self-medication and addiction. Due to the severity of their psychiatric symptoms, these patients are at great risk of alcohol recidivism if panic symptoms remain untreated. In addition to patients whose panic disorder preceded alcoholism, some patients develop panic attacks after becoming alcohol dependent. It is unclear whether chronic alcohol use can induce panic disorder, or whether a preexisting vulnerability is merely unmasked by alcoholism.

The identification of panic disorder in an alcoholic is usually fairly obvious. Patients will complain of panic attacks, generally characterized by palpitations, diaphoresis, chest or abdominal pain, fear of impending doom, flushing, and tremor. Since many of these symptoms are seen with alcohol withdrawal, this medical syndrome should certainly be ruled out and treated. Also important to rule out are medical conditions which can mimic panic disorder. These include hypoglycemia, pheochromocytosis, hyperthyroidism, and severe mitral valve prolapse. In addition, an antibody-based urine and plasma screen for drugs of abuse should be performed. Patients with opiate, barbiturate, or benzodiazepine use are often physically addicted to these substances. Withdrawal syndromes associated with any of these drugs can be indistinguishable from panic disorder. Frequently, patients with panic disorder have been prescribed addictive medications by physicians unfamiliar with the proper pharmacological management of this disorder.

If panic symptoms persist beyond detoxification, and sequential urine drug screens remain negative, the alcoholic patient should be suspected to have panic disorder. A careful psychiatric evaluation should address past history and patterns of self-medication. Phobias should be carefully explored, as well as related avoidance behavior. We have found that roughly 40% of all alcoholics admitted to our inpatient unit have at least one phobia. Although the incidence of panic attacks is substantially lower than that of phobic behavior, it is nevertheless very high in the alcoholic population. Also useful in the evaluation of panic disorder is an echocardiogram reading. We have found that 60 to 70% of alcoholics with panic disorder have mitral valve prolapse. This serves not only as a marker for this disorder, but may indicate responsivity to propranolol.

The treatment of choice for panic disorder is pharmacological. In general, the same approach should be used in discussing medications with these patients as was outlined with the depressed alcoholic. Alcoholics with panic disorder, however, tend to be less resistant to taking medications. They are more apt to minimize their alcoholism than their panic disorder. Care should be taken to explain that, even though self-medication with alcohol probably occurred, they nonetheless have entrenched addictive patterns and require specific AA treatment.

The treatment of panic disorder in alcoholics does not differ significantly from its treatment in nonalcoholics. Tricyclic antidepressants are usually effective in low doses, and should be employed after their nonaddictive action is explained. If tricyclic antidepressants are not effective, monoamine oxidase inhibitors can be used. In patients maintained on antidepressants, it is advisable to schedule once-a-day administration. This minimizes the frequent use of medications which might reinforce old patterns of self-medication.

In patients with mitral valve prolapse, treatment of panic symptoms with propranolol is often effective. These patients will usually present with predominant cardiac symptoms such as tachycardia, palpitations, and chest pain. Propranolol can be started in doses as low as 10 mg three times daily, and is often effective in low doses. Dosage can be increased as indicated clinically. Generally, since propranolol is a recognized "medical" medication, as opposed to an antidepressant, alcoholics are less conflicted about taking it. We have used propranolol extensively in the treatment of alcoholics with panic disorder. It is often effective and can also be used in combination with antidepressants.

As with affective and psychotic disorders, alcoholics with coexisting panic disorders should be educated as to the nature of their illness. Education regarding panic disorder should focus on the danger of self-medication and the need for pharmacological compliance. In general, these patients do not show significant noncompliance provided their medications are effective and side effects are tolerable. Care should be taken to explain the dangers of alcohol and tranquilizer use, not only as they relate to readdiction but also their adverse effect upon panic disorder. Random blood or urine screens for drugs of abuse are initially indicated. Education about alcoholism is best provided by AA meetings, and these should be supported by the treating psychiatrist. As with the other conditions described, a combined psychiatric and AA treatment plan is the key to recovery.

V. CONCLUSIONS

This chapter has reviewed our clinical experience in the pharmacological treatment of alcoholics with coexisting psychiatric disorders. We have described the major psychiatric illnesses encountered in the alcoholic population and attempted to identify problems specifically associated with alcoholism. These problems involve both diagnostic- and treatment-related issues. Probably the most important diagnostic theme with the alcoholic population is the need for an observation period uncontaminated by the presence of alcohol administration. Transient depressive, manic, psychotic, and anxiety states will often clear spontaneously during the first 2 weeks of sobriety. For this reason, observation should replace aggressive pharmacological treatment when possible. This also allows for a comprehensive medical evaluation of conditions which might mimic psychiatric disorders. Treatment considerations involved in alcoholics with psychiatric illness are complicated. Optimal clinical management often requires both pharmacological treatment for the psychiatric disorder, and AA treatment for alcoholism. The psychiatrist should be familiar with the AA approach and support this system as a means of minimizing readdiction. Education of the patient regarding the psychiatric illness is critical, and serves to minimize conflict between AA and pharmacological approaches. In general, the treatment of psychiatric illnesses depend upon recovery from active alcoholism. Similarly, due to the elimination of self-medication, successful treatment of the psychiatric disorder will allow for recovery from alcoholism. The interdependence of these coexisting problems necessitates a coordinated, mutually respectful approach by both AA and psychiatric disciplines.

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Chapter 11

NARCOTIC ADDICTION

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TABLE OF CONTENTS

I. INTRODUCTION

Opiate addiction poses special diagnostic and treatment problems for the physician. This chapter will provide a historical overview and an update on prevalence and new theories about opiate use and abuse. Special attention will be devoted to ways to diagnose and treat coexisting psychiatric disorders and alcoholism in opiate addicts. Finally, nonopiate treatments for detoxification and maintenance treatment of detoxified opiate addicts will be discussed.

II. HISTORICAL OVERVIEW

Opiates are among the oldest psychoactive drugs used by man. Their production and apparent use predates writing. *Papaver somniferum* has been cultivated and harvested for its opiate content, as well as for its edible seeds, for over six millenia. It is clear that their early uses included analgesia. In early Assyrian art (from 4000 B.C.), recognizable images of the opiate poppy capsule can be seen, some bearing the longitudinal slashes of the sort still employed to harvest the opiate-bearing latex. *Papaver somniferum*, the opium poppy, is vividly displayed in Egyptian tomb art and early medical papyri. In fact, traces of opiates have been recovered from the interiors of funeral "unguent" or "perfume jars" of the 18th through 28th dynasties, suggesting that the narcotic contents were treasured commodities to be taken and preserved for the afterlife.[1] Opiates were apparently abused in ancient Greece and in the Persian Empire. While we do not know the extent of opiate abuse, we do know that opiate intoxication was responsible for the death of the famous Arabic physician Avicenna in 1037.[1] *Papaver somniferum* was cultivated extensively in the domains of the Ottoman Empire and spread through the trade routes that their merchants followed, both westward into Europe and eastward to southeast Asia. For this latter area, the cultivation of the poppy was rapidly established, with eventual use of its products as intoxicants. By the early 19th century, there was a significant addict population in both India and Java.[1] However, it was in China in the 19th century that opiate addiction found the environment it was ideally suited to exploit.

The Chinese grew *Papaver* species as an ornamental garden plant before 1800, because of its multitude of petal colors of pink, red, lavender, and white. They rarely used it as medical treatment.[1] From Indonesia through Canton and from India through Nepal and the Himalayas, opium was imported into China over the strenuous but ineffective objections of the Chinese Manchu authorities. Their attempts to eradicate the profitable narcotic trade led to war with Great Britain in 1839, which China lost. Even without the military defeat, however, the issue had largely been decided by the fact that there were millions of addicts in China by then. The addicts of China at that time used opium in much the same way as is done in Southeast Asia now and by the working and upper class cocaine abuser in America: by smoking, eating, drinking, or sniffing it.

At this same time in Europe, opiates were so widely used as "tonics" that little concern was attached to their intake. In England, the drug was relatively pure, easy to obtain and inexpensive.[2] This unholy trinity leads to a drug problem. Opium was taken in pills of two to three grains or dissolved in alcohol and drunk under the name of laudanum. De Quincey[3] wrote that opiates were better and less expensive than alcohol. He used them himself both for self-prescribed medicinal purposes and for their ability to stimulate reverie and euphoria. Many other notables from that era were apparently opiate-dependent, and indirectly advocated their use.

America was not immune to the powerful lure of the poppy. A survey in San Francisco at the turn of the century, reported by Emboden,[1] showed approximately 1 in every 400

people were abusing opiates, with the largest cohort of users being American middle-class women. By this time purified derivatives of poppy latex, such as morphine were available. The emergence of opiate addiction and opiate withdrawal as problems were closely associated with availability of parenterally administered drugs. It was just such an addiction that Eugene O'Neil so tragically documented in "Long Day's Journey Into Night," an affliction seen at painfully close quarters in the dramatist's own mother. The growing awareness of the medical profession of the dangers of morphine, once considered a panacea, led to a search for medications capable of breaking this pernicious habit. Solutions to the problem were frequently much more inane than abstinence. In his 1884 paper "On Coca", Sigmund Freud proposed that cocaine would serve admirably in a detoxification regimen from morphine.[4] For the next 100 years medical experts, pharmaceutical companies would follow in Freud's footsteps. For example with opiate abuse, addiction, and withdrawal, increasingly recognized attempts were made by various pharmaceutical companies to separate the potent analgesic properties of the opiates from their dependency-inducing properties. Bayer Company therefore introduced the "nonaddictive" opiate called heroin in 1890, and Winthrop Laboratory introduced the "nonaddictive" opiate meperidine (Demerol®) in the 1940s. Further search for new "nonaddictive" narcotics led to drugs with both agonist and antagonist qualities such as cyclorphan,[5] pentazocine,[6] and cyclazocine.[7] Unfortunately, these drugs often had psychotomimetic side effects and/or significant abuse potential.

III. OPIATES TODAY

The current prevalence of narcotic abuse for the induction of euphoria is difficult to estimate, but the estimated prevalence of narcotic addiction is three to five times that of schizophrenia. Although narcotics-related crime and addiction are distinct liabilities, opiates are a tremendous benefit to those suffering from pain. Euphoria and analgesia are only two of the effects of opiates; they affect level of arousal, respiration, appetite, libido, smooth muscle activity (in ciliary muscle of the eye, gut, and blood vessels) and sleep. How could a given drug influence so many systems? Finding the answer to this question is the story of the discovery of the endorphins.

The presence of both agonists and pure antagonists for opiate action suggested the possibility of opiate receptors in the body. Corroborating evidence for their existence came from Mayer et al.,[8] who found that the analgesia produced by electrical stimulation of the periaqueductal gray matter in rats was partially blocked by naloxone. Following a research paradigm proposed by Goldstein et al.,[9] three groups of investigators independently discovered high affinity, stereospecific opiate receptors in mammalian brain tissue.[10-12] Teleologically, there was no reason to expect that mammalian brain tissue would contain receptors for a plant alkaloid. Accordingly, efforts to find a naturally-occurring compound which interacted with this mammalian brain receptor were begun. This led rapidly to the identification of the family of "endogenous morphines" called collectively the "endorphins." These are discussed further below.

As reviewed by Gold et al.,[13] even prior to the discovery of endorphins it was known that specific narcotic antagonists as well as agonists existed. The first narcotic agonist used clinically was nalorphine, given with morphine in an attempt to confer analgesia without respiratory depression.[14] Nalorphine was found to have mixed agonist and antagonist activity, and unfortunately led to dysphoria or psychosis in some subjects. The latter made this medication somewhat less than clinically acceptable. Other mixed agonist/antagonists were cyclorphan, pentazocine, and cyclazocine as noted above.

Because of the ability of cyclazocine to block the effects of other opiates,[15] attempts were made to treat opiate addicts with it. Once adequate blood levels were obtained, exogenous narcotics did not produce euphoria.[16] Later, a pure opiate antagonist, naloxone, was

synthesized[17] and used in an attempt to discourage former addicts from the use of opiates. This was unsuccessful, probably due to the short period of naloxone action within the body.[18] Because of rapid turnover, an addict could experience euphoria within 24 hr of discontinuing naloxone, making it only a minor deterrent. This lead to the synthesis of a longer-acting, orally effective narcotic antagonist, naltrexone,[19,20] which is currently being evaluated for efficacy in prophylaxis against relapse in recently detoxified addicts.[13] Naloxone remains the mainstay of emergency opiate overdose treatment.

For the heroin addict, drugs are both a way of life and a way of coping with life. They produce euphoria, banish despair and provide oblivion. Because of this connection, therapists have often been reluctant to do much more than to allow continued dependence on legal narcotics during treatment. Physicians in methadone programs have already accepted that it is appropriate to prescribe some medications in the treatment of the narcotic addict. However, the physicians and methadone program staff wish to diminish the patient's reliance on exogenous compounds to solve all of life's problems. This creates a dilemma for the narcotic addict patients. Physicians and drug abuse treatment staff lose sight of the boundary between a drug of abuse and a medication prescribed and taken as directed. Trying to maintain a drug program dogma, they find themselves on the one hand under pressure by patients seeking drugs, especially minor tranquilizers, and on the other hand, thinking themselves of whether it would really hurt to prescribe something because they believe that patients could benefit from use of a particular medication such as an antidepressant or antipsychotic agent. These problems are made more difficult by relatively few controlled studies about the use of psychotropic medications in the treatment of narcotic addicts; the differences between detoxified or maintained drug addicts; the lack, until recently, of adequate tools for accurate diagnostic assessment; pressure of time and too many patients. In addition there are the pressures of other staff either in the direction of not wanting the physician to prescribe any "drugs" or wanting the physician to prescribe medications that will in some almost magical way solve the patient's problems.

IV. PSYCHIATRIC DISORDERS IN OPIATE ADDICTS

There has been more chaos than consensus concerning the incidence and prevalence of various psychiatric disorders or symptom clusters in drug addicts. Confusing the picture even more is the effect of methadone on any underlying emotional problems. Does methadone lead to depression or improve it? Does it suppress the symptoms of schizophrenia to some degree or worsen such symptoms? Does narcotic detoxification produce depression or unmask depression? The presentation of psychopathology with patients maintained on methadone may be quite different from that when the same patient is on a very low dose or when not on methadone. At times, immediately following withdrawal, there may be an emergence of symptomatology even where the detoxification has been slow and stress has been minimal. Is this a withdrawal phenomenon or the reemergence of a self-medicated syndrome. Symptoms of panic-anxiety, depression, psychosis, or mania have been observed under such circumstances. This chapter will review what is currently known about the use of psychotropic drugs in the treatment of methadone-maintained patients.

Before dealing with the psychopharmacological treatment of opiate addicts, it is important to have a picture of the prevalence of psychiatric disorders in these patients. Information for making diagnostic judgments are collected using the Schedule for Affective Disorders and Schizophrenia (SADS). On the basis of this information collected, the methadone-addicted subjects are classified by the Research Diagnostic Criteria (RDC), which are a set of operational diagnostic definitions with specific inclusion and exclusion criteria for a variety of nosologic groups.

Using the SADS-L, diagnoses are made for both the current time period and for a lifetime.

For current psychiatric illness, depression is the most commonly diagnosed symptomatic condition; 23.8% of the sample met criteria for major depression at this evaluation. Other affective disorders, including minor depression (2.3%), manic disorders (0%), and hypomanic disorder (0.9%) were less infrequently diagnosed, as were schizophrenia (0.2%) and schizoaffective disorders (1.5%). Only small percentages of the sample were in current episodes of panic (0.9%), obsessive-compulsive (1.3%), or generalized anxiety (0.9%) disorders. However, a substantial minority had a current phobia (9.2%) or had abused alcohol to a degree that they met criteria for alcoholism (13.7%).

With respect to the lifetime RDC diagnoses, 86.9% of the addicts surveyed met the criteria for some psychiatric disorder — exclusive of drug addiction — in their lifetime. These data are consistent with the interpretation of reports of post-detoxification panic, anxiety, depression, and mania resulting from the discontinuation of a potent psychopharmacological treatment.

Looking at the lifetime rates of specific disorders, the most commonly diagnosed disorders were major depression 53.9%, alcoholism 34.5%, antisocial personality 26.5%, intermittent depression 18.8%, labile personality 16.5%, phobic disorder 9.6%, schizotypal features 8.4%, minor depression 8.4%, other psychiatric disorders 6.8%, hypomanic disorder 6.6%, and generalized anxiety disorder 5.4%. All other disorders, including schizophrenia, schizoaffective disorders, mania, cyclothymic personality, obsessive-compulsive disorder, panic disorder and Briquet's disorder were found in less than 5% of the sample. When affective disorders are combined, it is apparent that opiate addicts are at high risk, in that 74.3% met the criteria for some affective disorder. When compared to alcoholics, narcotic addicts are much more medically and psychiatrically ill.

A. Schizophrenic Disorders and Neuroleptics in Opiate Addicts

The incidence of psychosis, usually schizophrenic reactions, in opiate addicts has been estimated from as low as 1%[21] to as high as 19%.[22] The recent Yale study puts the combined figure for schizophrenic and schizoaffective disorders at less than 2%.[23] This low rate does not suggest that an over representation of schizophrenic patients exists in methadone programs. The relation of opiates and endogenous opiate-like substances to schizophrenic symptoms is controversial, but the use of the neuroleptics to treat such symptoms in methadone patients is not. In general, these medications should be used cautiously after a careful diagnostic interview and evaluation because of the likelihood of hepatic and other physiologic abnormalities in addicts. Lower doses of antipsychotics with more frequent blood levels than normal can often be employed. Unlike some of the other categories of psychotropic drugs discussed in this chapter, these medications are usually not abused by addicts, especially when monitored, and the problem more often is getting the patients to continue taking them when they are indicated.

B. Minor Tranquilizers in the Treatment of Anxiety Disorders in Opiate Addicts

The data from the Yale study indicated that approximately 10% of their opiate addicts are diagnosed as having an anxiety disorder. It has been noted by a number of authors that diazepam has become a popular drug of abuse among opiate addicts and in methadone programs.[24-29]

Although benzodiazepines have been shown in numerous controlled studies to be useful in treating anxiety in nonaddict patients, the problems in this population are which addicts need benzodiazepines and whether the abuse potential outweighs the clinical usefulness. The abuse potential in methadone patients may be greater than in alcoholics.[30] There has also been increased attention of late to the problems of diazepam withdrawal even at lower doses than are frequently required by methadone patients.[31] Under these circumstances, it appears prudent to attempt to treat anxiety by counseling, training in biofeedback and other

relaxation techniques, or environmental manipulation and not use benzodiazepines. Occasionally, when other methods have been unsuccessful and the clinician is convinced of the presence of a serious anxiety disorder, diazepam may be used if care is exercised. Monitoring plasma levels may be helpful in ensuring compliance and reducing abuse. Potential misuse is suggested by requested refill of prescriptions earlier than due, supposedly lost prescriptions, requests for increasing doses, and desire for indefinite use.[29]

C. Antidepressants in the Treatment of Affective Disorders in Opiate Addicts

A number of studies have demonstrated the presence of depression in a significant proportion of opiate addicts,[32-38] a finding consistent with the clinical theories of Wurmser[39] and Khantzian.[40] They suggest that a main problem for the typical addict is regulation of affect and vulnerability to dysphoria. In the recent Yale study,[23] approximately 24% of their sample were diagnosed as having a current major depression while three fourths were noted to have either chronic or episodic depressive disorders. The efficacy of both pharmacotherapy and psychological treatments in depressive disorders had been demonstrated in several recent controlled clinical trials.[41] There is agreement on the high incidence of current and past affective disorders in opiate addicts and methadone-maintained patients. There is less agreement over what to do about this finding and even less agreement as to whether the cause is psychological, psychosocial, or biological. Since there appears to be substantial change in depressive symptoms during the first 3 to 6 months on methadone without specific pharmacotherapy, it is probably best not to intervene with pharmacological therapy until it is seen whether spontaneous remission will occur. Antidepressant medication should be considered for those patients who meet descriptive and neurobiological criteria (e.g., DST, or TRH testing abnormalities) for a diagnosis of active major depression. They may also be considered for those patients who do not improve after 1 to 3 months or for those abusing stimulants who may be trying to self-medicate. Current diagnostic tools such as the SADS, RDC, DSM-III,[42] and symptom rating scales such as the Beck Depression Inventory[35] have been shown to be useful in assessing depression in methadone patients and should be employed prior to beginning pharmacotherapy. For programs with limited psychiatric staff, the Beck, either the 13-item[43] or 5-item version,[44] would be a useful screening tool to indicate which patients should then be more intensively evaluated. Major depression neurobiological subgroups of addicts with depression may exist and require specific pharmacotherapy.

D. Lithium in Opiate Addicts

The Yale study[23] did not turn up any current patients diagnosed as manic but found 0.9% to be hypomanic. In their study, lifetime rates were 0.6% manic, 6.6% hypomanic disorder, 5.4% bipolar 1 or 2 and 0.4% schizoaffective, manic type. Thus, there may be a significant number of bipolar patients in methadone clinics for whom lithium might be a useful treatment or prophylactic agent.

E. Alcoholism and the Use of Disulfiram in Opiate Addicts

Abuse of alcohol by recently opiate-detoxified patients or patients maintained on methadone has been recognized as a serious problem since the early 1970s. Until recently, however, there was disagreement as to whether the alcohol problems began while on methadone, or were due to it (such as looking for alternative way to get high since heroin use was blocked), or preceded program entrance. Studies examining this issue have found that alcohol use often preceded opiate use and that up to 25% of patients on methadone were abusing alcohol concurrently.[23,46]

Theories as to why some methadone patients abuse alcohol tend to fall into two categories, one stressing underlying psychiatric and psychosocial adjustment problems and the other focusing on a "generic hunger for a high" created by the patient's inability to get high on

heroin while on methadone. In addition, alcohol has opiate receptor stimulatory effects and other effects which could bias the addict toward increasing use during methadone dose reduction. Carroll et al.[47] suggest that, "These two explanations are not antagonistic. In fact, they are complementary, and we suspect they are both valid partial explanations for this phenomenon." Gerston et al.[46] list a comprehensive program as "a combination of supportive environments and psychotherapy, crisis intervention, and an emphasis on control of drinking". They also note that whereas one study found success to be correlated with number of therapeutic modalities available,[48] an "exhaustive literature review found that minimal or no treatment at all had the same effect on abstinence as more than minimal treatment".[49]

F. Conclusion

Alcohol problems often may have preceded entrance into methadone maintenance programs for most patients and, therefore, the program cannot be "blamed" for it. However the consequence to such alcohol abuse can be devastating and programs are well advised to try to diagnose and treat it. Alcoholics Anonymous programs and disulfiram can be a useful treatment adjunct in this regard combined with counseling.

It has been said that many of the physicians who treat addicts are like the addicts themselves in one respect — they are looking for a drug to do magical things. We have summarized the psychopharmacological treatment of a variety of psychiatric problems that may accompany narcotic addiction. It has been shown that many of the patients do have accompanying or underlying psychiatric illnesses, with affective disorders being most common. Methadone may have a direct impact on the expression or emergence of a number of psychiatric symptoms, but as yet its role is not clear. As far as the various psychotropic medications are concerned, neuroleptics for schizophrenics and lithium for manic disorders are generally agreed upon. Minor tranquilizers for anxiety and MAO inhibitors for depression are both seen as problematic in this population — the former because of the possibility of abuse, the latter because of the danger of drug interaction associated with the addict's life style. Tricyclic antidepressants may have a role in treating panic disorders in low doses and major depression in higher doses in methadone-maintained patients. Blood levels should be used routinely to individualize dose, monitor compliance, and prevent abuse. Finally, abstinence-based programs (e.g., A.A. or disulfiram) are useful in treating the alcoholic and/or the methadone patient if he will take it. A behavioral contingency program using methadone as a reinforcer may be necessary to accomplish this. Therapeutic drug monitoring and the identification of diagnostic subtypes of patients may improve the efficacy of existing pharmacological treatments. Concomitant severe psychopathology has been associated with poorer opiate-free outcome and longevity while on methadone. Chemical and psychological approaches that can reduce the severity of the illness could significantly improve the quality of patients' lives both during and after methadone maintenance.

V. GENERAL COMMENTS ON TREATING OPIATE ADDICTION

The abuse or use of narcotics causes a rather specific opiate receptor-mediated effect on the brain and body. This means that narcotic addicts might be very useful population for expanding our knowledge of the role of the endorphin system in vivo. Endorphins, in turn, offered promise for a more comprehensive theory of addiction and understanding opiate addicts.

Opiate addicts, as a patient group, are specifically manipulating their endorphin system and mood through their drug of choice. This endorphin connection may explain the overrepresentation of affectively ill people in narcotic addicts and some of the other special problems of this group of patients. Until (or unless it doesn't happen) endorphin theories

explain this patient group, we need to offer more than a cheap, long-acting narcotic — methadone.

The treatment of opiate addiction is a complex and often frustrating task. Opiate addiction is an illness which is subject to great prejudice and misunderstanding, and opiate addicts are generally viewed by society with disdain and ostracized. It is necessary to understand the psychological and physiological forces that form the underpinnings of opiate addiction before the provider of care can transcend societal prejudices and develop an objective strategy of treatment. Such an understanding also provides the empathy necessary to relate to these patients, and coincidentally leads to some surprising speculations regarding possible roles of natural opiate systems in the brain. The purpose of this section will be to review some of our clinical research data which have led to our structured treatment program for opiate addiction.

Before proceeding to a framework for understanding opiate addiction, it is useful to examine some of the reasons why addicts are misunderstood. The recreational use of opiates seems difficult to justify in light of the perils of opiate addiction. The injection of street heroin of unknown potency can easily lead to lethal overdose. Drug-related medical illness, such as malnutrition, numerous forms of hepatitis, vasculopathies, tetanus, tuberculosis, and other infections can cause morbidity or mortality regardless of social class. The necessity of obtaining drugs disrupts job performance and social ties, and opiates become the addicts' preeminent focus. Procurement of illegal drugs is a dangerous task, exposing the addict to risks of assault, blackmail, death, or incarceration at the time when judgment is often impaired by drug intoxication or abstinence symptoms. Psychiatric complications, particularly depression, can lead to prolonged suffering and even suicide. The development of withdrawal symptoms and panic are always hours away, constituting a firm reinforcement of continued addiction. Sociopathic activities, often employed to avoid withdrawal symptoms and obtain drug supplies, cause others to suffer and increase social isolation. These and other hazards associated with opiate addiction contribute to the general lack of understanding of what could motivate individuals to become or stay opiate dependent.

Opiate addiction becomes more comprehensible in light of classical conditioning theory as described by Wikler.[50] The euphoric effect of opiates, probably mediated through endogenous opiate systems in the human brain, is a "positive reinforcer". This means that the euphoria of opiate intoxication makes repeated use more likely, even before physical addiction develops. The strength of this positive reinforcement is enhanced when individuals have underlying feelings of "dysphoria", such as anxiety or depression. Therefore, certain individuals who have psychiatric symptoms are more susceptible to the positive reinforcement of opiate euphoria, and these individuals may in fact use opiates to self-medicate feeling of dysphoria. Other individuals may use opiates initially as a result of peer pressure, adventurism, or curiosity.

Once an individual begins to use opiates repeatedly, due to the positive reinforcement of euphoria or other reasons, an insidious negative reinforcer develops. This takes the form of the abstinence syndrome, as extremely uncomfortable withdrawal symptoms emerge with physical drug addiction. Furthermore, physiological tolerance leads to progressively increased doses of the drug, and even more severe withdrawal symptoms. A cycle is thus begun whereby positive reinforcement (drug euphoria) alternates with negative reinforcement (withdrawal symptoms), providing strong impetus for continued drug use. This cycle is further strengthened if preexisting psychiatric symptoms are being self-medicated or if opiate-induced neurochemical or neuroendocrinological imbalances emerge to further sustain self-medication. This latter situation will be discussed further in relation to opiate-induced depression.

The power of the psychological and physiological entrapments of opiate addiction is demonstratd by the addict's decision to remain in the hazardous drug environment even after

tolerance develops and opiates no longer produce as much euphoria. In fact elements of the drug environment can themselves lead to conditioned abstinence symptoms.[51] Just as Pavlov's dogs began to salivate after hearing a bell which had been associated with feeding, addicts often experience abstinence symptoms and craving upon exposure to elements of the drug environment. Seeing buildings where drugs were bought, smelling burning matches, or meeting drug-using friends can precipitate strong urges and abstinence symptoms even in detoxified patients. This classical conditioning further fortifies the addictive process and has specific treatment ramifications. Since merely the presence of the environment is potent enough to induce drug craving and withdrawal symptomatology, patients attempting to achieve a drug-free state must actively limit access to both drugs and conditioned elements of the drug environment. This requires hospitalization initially, on the most concrete level, but later patients are taught to terminate friendships with addicts, move from old neighborhoods, and change jobs if drug exposure is present. Otherwise, the force of conditioned abstinence symptoms will often lead the patient back into addiction. In addition, the use of the long-acting opiate blocker, naltrexone, if available, reduces the lure of opiates by eliminating the positive reinforcement of opiate-induced euphoria.

As has been previously mentioned, exogenous opiates, such as heroin or methadone, appear to exert their psychological and physiological effects by acting upon the endogenous opiate system of the brain. Specific opiate binding has been known to exist in the brain since 1972,[52-54] and in 1975 two types of natural opioid peptides were discovered. These were beta-endorphin,[55] and the smaller enkephalin peptides.[56,57] Although endogenous opioid peptide systems have yet to be characterized with regard to their functional roles, it is likely that they are somehow related to mood regulation. This is suggested by the euphoriant action of administered opiates, which is completely blocked by the opiate receptor antagonist naltrexone. Furthermore, opioid peptides are most concentrated in brain regions traditionally associated with mood regulation, such as the hypothalamus, locus coeruleus, amygdala, and certain other limbic system structures. A description of known neuroanatomical and functional characteristics of endogenous opioid peptides has been reviewed elsewhere,[58] and suggests that these opioids have important connections with catacholamine systems of the brain, which in turn are implicated in mood regulation and affective disorders.[59]

The connection between mood regulation and opiate agents is underscored by reports of extremely high prevalence rates for depression in opiate addicts. Rounsaville et al.,[60] using the Schedule for Affective Disorders and Schizophrenia (SADS)[61] as a diagnostic instrument, found that 17% of opiate-addicted individuals suffered from major depression by Research Diagnostic Criteria (RDC)[62] and 48% had suffered from RDC major depressive illness in the past. Furthermore, of addicts with past major depression, 5.6% had depressive episodes preceding their drug abuse, and 94.5% were secondary depressives.[60] This supports the notion that the tremendously high prevalence of major depression in addicts is somehow caused by the addiction, rather than preceding initial drug use. It seems unlikely that widespread, preexisting depressive illness would give rise to opiate use as a form of self-medication. In fact, given the extremely hazardous task of procuring opiates, and the relative passivity associated with depression, it would be surprising to see initial opiate use occurring in the context of a major depression. At Fair Oaks Hospital, 50 consecutive patients were interviewed 3 weeks after opiate detoxification with a SADS interview. We found a 32% point prevalence of RDC major depression and a 10% point prevalence of RDC minor depression. Interestingly, shortly after the potent psychoactive opiates are discontinued, and after withdrawal symptoms have abated, the prevalence for major depression nearly doubled as compared to the 17% point prevalence for major depression in addicts taking opiates.[60] This raises the possibility that opiates can ameliorate the very depressive symptoms that they appear to precipitate, thereby further reinforcing their continued use and bolstering the entrapment of addiction. We have found that the use of antidepressants in the post-detoxi-

fication period is often indicated by the severity of depressive symptoms and serves as a deterrent to recidivism. Careful attention to post-detoxification depression, and appropriate treatment when present, is a crucial treatment strategy. Generalized lack of appreciation of this critical complication of opiate use may partially explain the high recidivism rates seen in opiate addiction.

Given the high prevalence of depression in post-detoxified opiate addicts, the euphoria caused by opiate intoxification, and the presence of endogenous opiate systems in limbic structures of the brain, it is tempting to speculate that endogenous opioid peptides are involved in mood regulation and perhaps in the pathophysiology of affective disorders. Gold has presented diverse evidence that is consistent with a depletion of endogenous opioids in individuals chronically addicted to opiates.[63,64] This depletion of naturally occurring opiates with heroin or methadone use has been hypothesized to result from chronic stimulation of a feedback system by the exogenous opiates, resulting in the endogenous opiate system being "turned off". It has been suggested that a compromised endogenous opiate system gives rise to withdrawal symptoms once exogenous opiate use is abruptly terminated.[65] It appears possible, in addition, that a compromised endogenous opioid system may give rise to depressive symptoms. The addict may use exogenous opiates daily to prevent both abstinence symptoms and depression, leading to further depletion of endogenous opiates and the perpetuation of addiction.

Just as exogenous opiate agonists deplete endogenous systems, it is theoretically possible that exogenous opiate antagonists might reverse this process. Naltrexone is a long-acting opiate antagonist which has been used in post-detoxified opiate addicts to maintain the drug-free state.[59] By blocking the opiate receptor of the brain, naltrexone prevents subjective and physiological effects of exogenous opiates. Patients taking naltrexone will not experience the opiate high, and cannot become readdicted. This prevents the conditioned process of addiction previously described. Naltrexone has been reported to cause dysphoria in normals, but not in post-addicts, suggesting that in the post-addicts the effects of opiate receptor antagonists may be different.[66] In addition, the opiate antagonist naloxone causes a release of or displaces beta endorphin from opiate receptors in humans.[63] This naloxone-induced surge in endogenous opiate release is consistent with the notion that naltrexone administration to addicts might release ACTH and endorphins, and may reverse the endogenous opiate depletion caused by chronic opiate addiction. Alternatively, naltrexone may increase opiate receptor sensitivity or receptor numbers. Further research is required to determine whether these are beneficial effects of naltrexone. However, in light of its proven efficacy in blocking the opiate high, and the possibility that it may aid in reversing chronic endogenous opiate depletion in opiate addicts, the use of naltrexone appears to be an important adjunct in the treatment of these patients.

We have reviewed some of the aspects of opiate addiction which may not be widely appreciated. The high prevalence of depression in these individuals, particularly when they attempt to become opiate free, serves to impede their sobriety and may lead to actual self-medication with opiates. This cycle of opiate-induced depression, followed by self-medication with more opiates, is similar to the pattern seen with opiate-induced abstinence symptoms. Careful attention to depressive symptoms, and treatment with antidepressants when indicated, can serve to neutralize this particular entrapment of opiate addiction. Furthermore, naltrexone treatment, aside from eliminating the positive reinforcer of drug-induced euphoria, may reverse the endogenous opiate depletion hypothesized to cause depressive and abstinence symptoms.[59] This possibility can be addressed as we develop more precise methods of measuring endogenous opioids and understanding their physiological roles. A more sophisticated understanding of endogenous opioid pathways can only serve to improve our treatment of opiate addiction, and may even cast light on the physiology of mood regulation.

VI. NONOPIATE TREATMENTS FOR ADDICTS

A. Clonidine and Related Agents for Opiate Withdrawal

Support for the endorphin-locus coeruleus connection in opiate withdrawal, and by extension for endorphinergic mechanisms of addiction, can come from nonopiate treatments of withdrawal. If it is postulated that hyperactivity of the Locus Coeruleus (LC) system after release from opioid suppression is the mechanism of withdrawal, then treatments (opiate or nonopiate) which decrease this hyperactivity should lessen withdrawal signs. Aghajanian and his group[67-70] first suggested that receptors might exist on the body of the locus coeruleus cell for norepinephrine and epinephrine. Further studies confirmed the existence of these alpha-2 receptors.[71] Clonidine, an alpha-2 agonist, was found to bind these receptors, leading to a decrease in norepinephrine release[72,73] and turnover.[74,75] The inhibition of LC firing by clonidine is blocked by the alpha-2 antagonist piperoxane, but not by the opiate antagonist naloxone.[68,70] This indicated a second, completely separate nonopiate inhibitory control on LC noradrenergic activity. When clonidine was given to withdrawing opiate addicts, it succeeded in abolishing the vast majority of the signs and symptoms of withdrawal.[76-78] The clinical use of clonidine for rapid, nonopiate detoxification has since become widespread[76,77] with verification of its efficacy from all independent investigators who have studied its effects.[79-82] Both heroin[83] and methadone addicts[84] have been successfully detoxified with clonidine with excellent results.

The implication of the original noradrenergic hyperactivity hypothesis, that the locus coeruleus was hyperactive in opiate withdrawal symptoms,[85] led to a number of testable hypotheses. Among them were that nonopiate treatments could bypass the dysfunctional endorphin-LC connection and terminate LC activity and signs and symptoms by augmenting alpha-2 feedback inhibitory receptors. In addition to clonidine, other nonopiate inhibitors of LC activity should then also be found which ameliorate opiate withdrawal symptomatology. Clonidine markedly reduces the severity and absolute number of symptoms and signs of opiate withdrawal by putting alpha-2 mediated[86-88] "brakes" on the rebound increases in central noradrenergic LC function by augmenting presynaptic alpha-2 adrenergic function. Clonidine is a potent inhibitor or brain NE release by stimulating alpha-2 adrenergic receptors at the nerve terminal and also decreasing noradrenergic neuronal activity by binding to alpha-2 receptors located somatodentritically.[86-89] We know that these alpha-2 receptors are distinct from opiate receptors located on the LC (3).

On the basis of this theory, other alpha-2 agonists, for example lofexidine[78,90] and aldomet,[91] have been successfully used in treatment of acute opiate withdrawal with efficacy similar to clonidine. Clonidine also functions as an anxiolytic.[92] The primary adverse reactions of clonidine involve hypotension, sedation, irritability, and insomnia,[93,94] usually not of sufficient magnitude to lead to discontinuation of medication. The confirmaion of the efficacy of various nonopiate (clonidine, lofexidine, etc.) and opiate (morphine, methadone, endorphin) locus coeruleus inhibitors lends strength to the hypothesis of LC-noradrenergic hyperactivity in opiate withdrawal, and by extension, to the importance of the endorphinergic system in creating the conditions leading up to that withdrawal.

The endorphin hypothesis of opiate addiction has already generated many novel treatments for addiction. One of the most useful has been the use of clonidine and other alpha-2 adrenergic agonists, enabling many addicts, especially those maintained for years on methadone, to undergo a relatively comfortable detoxification. Opiate free is now an acceptable and attainable outcome measure. In addition it has made the detoxification process faster, increasing the viability of naltrexone as a next step for the recovering addict. This theory and clonidine may have rescued an important treatment from the ranks of orphan drugs. For the large proportion of methadone addicts who have a propensity for involvement with other drugs, inpatient clonidine detoxification decreases the likelihood of use of alcohol or sedative-

hypnotic cross or readdiction. Rather than the drawn-out process of gradual methadone reduction, often undertaken as an outpatient, the addict can now undergo detoxification within 2 weeks or less. The elucidation of the endorphin-locus coeruleus connection has also generated important hypotheses for further research into the involvement of endorphins in panic disorder, affective disorder, alcohol withdrawal, and more interest in understanding the role of endorphins in addiction, acute withdrawal, protracted withdrawal, and relapse.

Now that we are all looking for it carefully, protracted abstinence syndrome is becoming more commonly recognized. An endorphin-LC mechanism has been proposed to explain this syndrome. As effective treatments for this syndrome are developed, the continued high relapse rate of detoxified addicts into opiate abuse should be lessened. Preliminary results with the use of endorphin potentiating or stimulating treatments such as the use of acupuncture, transcutaneous nerve stimulation, tricyclic antidepressants, and vigorous exercise are encouraging, but must undergo detailed, controlled study before they may be wholeheartedly espoused by treating physicians. Recognition of relapse rate and the prevalence of the protracted abstinence syndrome brings home the lesson that opiate detoxification is not a cure, and that a rigorous hospital program combining pharmacological treatment with structured psychosocial recovery program, skill training, and psychotherapy are at the present time necessary to lower the toll of the illness. Detoxification is really just the beginning of the treatment. Opiate addiction is a substance abuse problem waiting for an A.A.-like successful cure-oriented program.

B. The Clinical Use of Naltrexone Maintenance in Detoxified Opiate Addicts

The advent of methadone maintenance in the treatment of opiate addiction introduced the concept of eliminating dysfunctional drug use rather than drug use itself. Methadone clinics have provided the addict with a stable source of drug, eliminating the disruptive need to procure supplies. Substitution of heroin with methadone enables the avoidance of illegality, and the exposure to the criminal life style and multiple medical illnesses so often associated with drug-seeking behavior. The psychological craving is reduced and the individual can function more effectively as the cost and frequency of drug taking decreases. However, methadone maintenance is not in itself a treatment but rather a drug delivery system which is not acceptable to all individuals. Many individuals desire complete abstinence or prefer treatment in a private setting where they can reduce the risk of exposure to criminal elements. Others are abstinent but in danger of relapse.

Naltrexone maintenance is a very effective treatment for opiate addiction as long as it is taken. Obviously, a treatment program designed to maximize compliance with naltrexone is of critical importance. Naltrexone will reliably prevent opiate addiction from occurring, so that the success of a treatment program for chronic relapsing addicts is totally a function of its success with the compliance issue. Eventually, plasma naltrexone levels will help insure and supervise compliance. In our multimodality treatment program at Fair Oaks Hospital, the patient is initially given naltrexone as an inpatient, once a clonidine detoxification process has been successful as measured by a symptom-free naloxone challenge. We have found that treatment is more successful when naltrexone is perceived as a privilege to be earned in treatment, as active participation and motivation for improvement are demonstrated.

As was mentioned earlier, opiate addicts have a high frequency of several psychiatric disorders (e.g., panic anxiety and major depression), and so the ability to correctly identify and treat these underlying problems while maintaining naltrexone is often an important consideration. In selective patients, we have used naltrexone in combination with many psychotropics, including nortriptyline, desipramine, amitriptyline, imipramine, doxepin, tranylcypramine, phenelzine, chlorpromazine, perphenazine, thiothixine, thioridazine, fluphenazine, propranolol, lithium, benztropine, trihexylphenidyl, and diphenhydramine. We

have observed no clinical or biochemical complications related to drug interaction of any of these agents with naltrexone. In essence, the pharmacological treatment of patients with psychotropic medication, when indicated, is greatly enhanced by coincident administration of naltrexone since the possibility of obfuscation by opioids is eliminated. It allows the patient an opiate-free period to experience proper trials of pharmacological treatments with therapeutic monitoring and without the usual avenue of self-medication by opiates.

Development of the effective, long-term opiate receptor antagonist naltrexone, as described by Gold et al.,[13] offers great potential benefit in the treatment evaluation and treatment.

The establishment of programs for detoxification from heroin has received governmental support due to the direct alleviation of the physical problems and the relatively low cost. This detoxification process has generally been carried out with methadone, and more recently, clonidine and other clonidine-like medications have been shown to be effective nonopiate agents for the treatment of opiate withdrawal symptoms. Unfortunately, opiate addiction involves more than physical dependence on a drug. The establishment of a psychological conditioned response greatly undermines the individual's freedom of choice. The necessity of continually obtaining supplies of drugs is disruptive to job performance and social ties. Friends and family are substituted by suppliers of drugs and even the basic drives for food, shelter, and sex become secondary to the daily ritual of drug attainment and consumption. Intense craving can occur with protracted abstinence for periods greater than 1 year even though most physical symptoms of withdrawal have subsided, making successful treatment even less likely.[95]

The development of naltrexone has provided an important treatment alternative for post addicts, even before we fully understand the disease and can treat it more effectively.[96] Taken orally three times weekly, naltrexone will completely prevent euphoric effects of opiates, removing the ability and incentive to relapse. Also, the long half-life in the body allows the imposition of delay between opiate urge and ingestion, with a chance to overcome impulsivity. The partial abolition of alcohol euphoria as well is a real benefit, considering the great number of ex-opiate addicts who go on to become alcoholics. Finally, naltrexone blockade tends to stimulate endorphin production and may shorten the time needed for endorphinergic systems, previously suppressed, to return to normal. Naltrexone is still undergoing extensive clinical evaluation but may one day be available for widespread use in opiate and other addictions (gambling and eating).[13,97]

For researchers working in this area, it seems as if we know nothing with certainty and progress is very slow. However, it is rare that medicine has seen so rapid an explosion of knowledge as that concerning the endogenous opiates, and rarer still that the theoretical knowledge has paid such rapid dividends in the clinical treatment of the patient. We anticipate continued progress in the future.

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Chapter 12

THE ROLE OF THE LABORATORY IN PSYCHIATRY

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TABLE OF CONTENTS

I. INTRODUCTION

All psychiatrists utilize the laboratory and laboratory testing to a certain extent. Until recently this utilization has been limited and predominantly focused on medical advances which occurred greater than 25 years ago. The screening of new psychiatric patients and hospital admissions for syphilis, gross medical problems, gross infectious or hematopoetic disease (urinalysis; CBC with differential), and pregnancy testing (females) is so commonplace that most psychiatrists instinctively order tests on new outpatient referrals and all inpatients. This use of the laboratory of the 1960s continues even though changes have occurred in the patterns and types of psychiatric referrals and frequency of disease entities which have a psychiatric presentation. The yield for all laboratory tests changes with clinical setting and over time. For example, nearly all new admissions have a test (RPR) for syphilis while the yield is closer to 0 than it is to 1%. But no psychiatrist would want to miss the diagnosis of syphilis even if only to prevent embarrassment and indefensible malpractice suits. For many, this "admission profile" of tests such as a complete blood count (CBC), urinalysis, multitest chemistry profile (such as the SMA), RPR, drug screen, and pregnancy test is ordered without thought. When the laboratory is used in this manner it is not unusual to find that the busy practitioner has not reviewed even these "severely limited" data very carefully even though in some cases suspicious data existed which could have led to a correct diagnosis. Remembering that as many as one out of three "major depressive episodes" turn out to be secondary (secondary to a known medical or related illness), it is difficult to imagine that a psychiatrist can make a complete differential diagnosis and rule out of active consideration all competing illnesses using only this admission panel and a screening physical exam.

The usefulness of the laboratory is not limited to one type of test or procedure. It is not limited to new evaluations or admissions but impacts in many areas of psychiatric practice. However, it is only recently that psychiatrists have begun to recognize the relatively wide scope of these applications. Of those psychiatrists who utilize existing laboratory resources, many become familiar with only one application of the laboratory to inpatient practice, such as the use of therapeutic drug monitoring, or neurochemical testing of urine, or the applications of psychoneuroendocrinology to diagnosis or identification of biologically relevant state markers, and so on. These are as limited viewpoints in many ways as those psychiatrists who only test urine to rule out diabetes. We see that the clinical laboratory is a major component of the practice of medicine, though the laboratory, in the same way that a person can still walk though crippled, is not indispensable in psychiatric evaluation and psychopharmacological treatment.

Laboratory tests in use in medicine vary with respect to *sensitivity* and *specificity*. *Sensitivity* describes the ability of the test to correctly identify through an abnormal or positive result a percentage of patients with a given syndrome (true positives). The remaining, unidentified patients are the false negatives. *Specificity* is a measure of the ability of the test to exclude false positive patients. *Confidence level* is a term used to describe the likelihood that an abnormal laboratory result in a given population will identify the true positives. Good clinical practice or laboratory medicine requires neither perfect sensitivity, specificity, nor confidence level. This is not necessary or even expected. With any diagnostic or laboratory tests, it is simply the physician's responsibility to become familiar with the uses and limitations of each particular test in various specific psychiatric syndromes. For these and other reasons, laboratory tests can never replace physicians. Diagnosis in laboratory medicine is often based on the review of the results derived from a number of unrelated tests, each with a different sensitivity and specificity. The best example of this is the use of the laboratory in the diagnosis of various endocrinopathies or even autoimmune diseases. Some of the most

commonly used laboratory tests in these diseases have very low sensitivity or specificities although the results of sequential, provocative, or additive tests can make important contributions to the diagnostic process.

Some psychiatrists entered psychiatry with a hope of leaving the stethoscope, physical exam, blood, and urine to others. These psychiatrists are becoming very disappointed. Diagnostic testing is here to stay, although which specific tests are useful or outdated will remain in flux.

II. DIAGNOSTIC TESTING

A. Drug Abuse Detection

The ability of clinicians to rapidly document the abuse of prescription of illicit drugs is critical in accurate diagnosis and development of appropriate treatment plans for psychiatric patients. Given the fact that many admissions to psychiatric services have used drugs and/or alcohol near the time of admission which relate to the presentation, maximizing detection is the main issue. Failure to detect drugs of abuse results in failure to address the diagnostic issue of drug-related, drug-contributed, or drug-independent syndrome. A blood alcohol and additional testing for particular drugs of abuse should be ordered on all new evaluations, patients, or admissions unless there is some very good reason not to.

General medical laboratories performing routine "drug screens" frequently generate negative results which are difficult for clinicians to understand. Even known abusers and patients maintained on barbiturates frequently return with negative results. Patients rarely admit to drug use, but even when they complain of taking or smoking something and becoming paranoid, manic, depressed, or psychotic, the drug screen sometimes still is negative. Important and commonly abused psychoactive compounds such as methaqualone (quaalude) marijuana, tetrahydrocannabinol (THC), phencyclidine (PCP or "Angel Dust") or heroin (morphine) are not tested for in most "drug screens" and other important drugs of abuse such as amphetamine and cocaine cannot be easily detected in low or sub-lethal doses in the typical drug screen. Simply by drinking citrus juice or taking vitamin C and acidifying the urine makes even high-dose detection of cocaine and amphetamine very unlikely. These problems are not a result of laboratory error or incompetency but instead reflect technical limitations. Let the consumer beware: in this case the psychiatrist is the consumer. Psychiatrists are simply unaware of the sensitivity of the various drug abuse detection tests for drugs in question or even whether the test they ordered can ever detect the drug they are trying to measure, and therefore they cannot decide on drug-induced, drug-related, or naturally occurring etiologies. The failure to order correct test(s) or understand the limitations of the test(s) ordered very frequently results in misdiagnosis, confirming or adding to a psychiatric stigma, and treating someone who has a drug or alcohol problem in the wrong treatment program or with inappropriate medication. The assumption that the patient who is psychotic, with a past history consistent with schizophrenia or mania, who presents with a negative "drug screen" *and* who responds to haloperidol, is a schizophrenic or manic is wrong. Cocaine, amphetamine, other stimulants, and even PCP can cause the same behavior and not be detected in the usual "drug screen".

Drugs can be detected in human urine by any of several analytical techniques, including colorimetry, gas chromography, flurometry, and antibody-based assays. High-pressure liquid chromatography, gas chromatography with mass spectroscopy, and other specific techniques can be used to quantify and detect most drugs of abuse in blood. Quantitative and specific blood testing for cocaine and amphetamine can add to the clarity of diagnosis of affective states, blood PCP is used in the differental diagnosis of psychotic states, and plasma methadone can be used on admission to document safe dose and level of tolerance. Quantitative assays in blood, while sensitive and specific, are costly. They are critical in certain clinical

situations and irrelevant in others. The routine "drug screen" ordered performed by most general laboratories uses the rapid, inexpensive, thin-layer chromatographic (TLC) technique. Being fast and inexpensive are the main virtues of the TLC tests. This traditional toxicology urine screen is in fact less than ideal for psychiatrists' use as a rapid documentation of sub-toxic levels of a known or unknown drug in a random sample of urine. TLC screens are technically cumbersome and involve crude and highly interpretive methods. When the physician is testing for drugs which TLC methods can identify, when the quantities ingested are large, and when the sample is obtained shortly after the drug abuse event, the TLC tests may be useful. This is the case while other more specific and reliable testing is pending. TLC is of little use in testing for admission, forensic psychiatry, differential diagnosis, or establishing a drug level baseline. Since identification in urine of the low dose use and abuse which is the most common type of abuse seen in the psychiatric patient is desired, antibody-based or Gas Chromatography (GC) capillary, or GC/MS methods are preferable. We have found urine antibody screening methods useful in most clinical situations to give a sensitivity and specificity up to 50 times superior to TLC results for certain drugs of abuse. In addition, antibody-based assays can readily identify synthetic opiates, marijuana, methaqualone, THC, and high concentrations of PCP.

The clinical uses relate to the questions being asked by the hospital or psychiatrist. For example, identifying the psychotic patient who has in fact used cocaine, amphetamine, or PCP is of critical importance in the clinical setting. Many of these patients are unwilling or unable to admit to drug use, and when they do the exact drug taken is always a mystery. Every psychiatrist recognizes that these drugs are in the differential diagnosis, but only a few will vigorously rule it out of active consideration with a detailed history and the specific laboratory tests. In many cases, especially first break cases, both urine (antibody) and plasma (GC or GC/MS) testing should be ordered. These practices will depend on the patient population in question. In one study, 145 consecutive patients seen in the psychiatric emergency service of an urban public hospital were tested specifically for PCP. A surprisingly high 43% of the patients showed positive plasma PCP levels. In other reports, cocaine or cannabis has been shown to produce a clinical picture very similar to that seen in euphoric or panic states and even schizophrenia. Both drugs are easy to identify in blood and urine. The major reason that these tests are not utilized is the psychiatrists false belief that a drug "screen" will suffice.

The treatment plan for the depressed patient who by testing is found to be in a post stimulant state, a low-dose barbiturate, or alcohol abuse state or a person on a self-styled quaalude or marijuana maintenance program is specific and markedly different from that of the atypical or pure endogenously depressed patient, especially if the depression clears once the patient is off drugs of abuse. Similarly, drug-related or induced euphoric or psychotic states require special attention and specific treatment lest they continue or recur. Typically, patients minimize and rationalize drug use and deny the association of alcohol and other drugs with their chief complaint. Answers like "I drink at times", "all people smoke pot," and "I do a little" can be evaluated with quantitative testing. Quantitative testing and a medication- and drug-free trial can make the diagnosis and provide for appropriate and effective aftercare.

Inpatient treatment units in hospitals, especially adolescent units, often set limits on acceptable behavior, including prohibitions against bringing drugs or alcohol onto the unit by patients or visitors or taking drugs while in the hospital or on a hospital pass. In many hospitals, a common consequence of "proven" drug use is discharge of the patient or transfer to a more restrictive facility. Considering the false positives and negatives of TLC techniques and given the drastic response of staff to such drug use by inpatients, antibody-based assays or blood levels are indicated in such cases to preserve the integrity of the

inpatient program, insure accuracy, and enable hospital staff to remove patients who are pretending to be in treatment but wasting valuable resources and needed bed space.

All analytical methods have limitations. Sample integrity, time of day of the sample, time and dose of the last drug ingestion, as well as drug structure, half-life,and affinity for brain and their lipophilic profile, all affect the length of time the drug remains detectable in a urine sample. In psychiatry, quantitative testing on serum or supervised first-void urines are necessary for a definitive diagnosis. The measurement of urinary specific gravity should be done in all urine drug testing samples to eliminate the possibility that the sample has been tampered with and diluted with tap water.

In freestanding specialty hospitals where patients are generally referred for evaluation and treatment after failing in outpatient treatment, a complete drug abuse evaluation is essential. A comprehensive drug abuse evaluation includes, at a minimum, antibody-based tests for opiates (morphine equivalents), barbiturates, alcohol, amphetamine, benzodiazepines, methaqualone (quaaludes), methadone, phencyclidine (PCP), cocaine, and cannabinoid (marijuana and THC); simultaneously, urine specific gravity is measured. Although a comprehensive drug abuse evaluation, including all the common drugs of abuse, is indicated in many cases, in some patients with a clear presenting symptom, limited testing may be more cost-effective. For example, evaluation of a newly admitted patient with natural or drug-related euphoria should at least include specific testing for amphetamines, cocaine, benzodiazepines, methadone, opiates, PCP, methaqualone, and alcohol. Positives by any method should be confirmed in duplicate and confirmed by a second, independent method. Patients admitted in a suspected drug withdrawal, drug intoxicated, or drug-related psychiatric state should have blood testing immediately for the suspected drug(s) while the urine can be taken as soon as possible for comprehensive evaluation. First void urine is preferred for demonstrating drug use, abuse or drug related states. Once an admission comprehensive urine test is completed, a repeat test can be helpful in distinguishing drug abuse/use since admission vs. drug decline in levels following admission.

B. Hepatitis

Hepatitis is a nonspecific term like pneumonia. It means simply inflammation of the liver just as pneumonia means inflammation of the lung. The similarity continues because both can be caused by agents infectious and chemical.

In drug addicts, we are most concerned with viral hepatitis. Most of this hepatitis is transmitted by sharing needles. Hepatitis B was formerly called serum hepatitis and is most often linked to drug abuse. Hepatitis B virus can be transmitted in 0.00004 mℓ of blood.[1] One milliliter of blood from a carrier with HBsAG + and HBeAb + contains 1 trillion HBsAg particles.[2] Drug addicts also show an increased rate of hepatitis A, formerly infectious hepatitis, and non-A/non-B hepatitis, both of which can also be transmitted by dirty needle sharing. To add some confusion, many addicts also abuse alcohol and have a superimposed alcoholic hepatitis.[3] Accordingly, it is important to be as specific as possible about causes of hepatitis in drug abusers.

C. Hepatitis B

Hepatitis B has been classically associated with drug abuse and is in fact used by the DAWN (Drug Awareness Warning Network System) to track patterns and distribution of heroin throughout the U.S. as it spreads to different population groups.[4]

Great strides have been made in hepatitis research in the last 10 years. For anyone treating or planning to treat cocaine, amphetamine, or opiate addicts, it will pay to review some of these advances. The Hepatitis B virus may be detected serologically as three different antigen groups in a patient's blood (see Table 1). The first group is Hepatitis B surface antigen, HBsAg. This was previously known as the Australia Antigen (Au antigen) or Hepatitis

Table 1

HBsAg —	Hepatitis virus is circulating in the blood
HBsAb —	Hepatitis B exposure and/or infection or vaccination
HBcAg —	Should not be seen in blood, only in liver cells during viral replication
HBcAb —	Evidence of active hepatitis infection
HBeAg —	Patient is infectious; chronic active hepatitis, cirrhosis
HBeAb —	Asymptomatic carriers of HBsAg; chronic persistent hepatitis

Associated Antigen (HAA). Its presence in blood indicates that the intact virus is present circulating, and may be found throughout the body and all its secretions.[5]

Hepatitis B core antigen (HBcAg) is the center of the virus and is never present in blood even during Hepatitis B virus replication, when it is found only in liver cells.

Hepatitis B antigen (HBeAg) is another part of the core of the virus and is found in peripheral blood. It is the best indicator of how infectious a patient is at any point in time, either acutely or clinically. It is also found in patients with chronic active hepatitis and cirrhosis.

Antibodies exist to all these antigens. HBsAb demonstrates previous Hepatitis B exposure and possibly, but not necessarily, infection. It is also present in individuals vaccinated with Hepatitis B vaccine. The presence of HBsAb indicates immunity to future infection. HBcAb provides evidence that active hepatitis infection has occurred at some time in the past. HBeAb is often found in asymptomatic carriers of HBsAg and in individuals who have chronic persistent hepatitis.[5] Of i.v. drug abusers at Fair Oaks, independent of social class and whether cocaine or opiates were abused, 35% have HBeAb, indicating that they are at much higher risk to develop chronic liver disease.[6]

Serologic evidence of previous Hepatitis B infection with either HBsAg or HBsAb present in drug abuser's blood is between 50.9% and 86% of i.v. drug abusers.[6-11]

At Fair Oaks Hospital, we have found 86.2% of suburban i.v. drug abusers have HB antibodies, either HBsAb, HBcAb, or HBeAb, as opposed to 6.3% in non-i.v. abusers.[6] This was seen in upper as well as lower social class users of cocaine and/or opiates. Cocaine users were as likely as opiate users to have hepatitis.

D. Hepatitis A

Hepatitis A, formerly called infectious hepatitis, is transmitted primarily by an oral/fecal route, but it can also be transmitted parenterally. It produces a milder hepatitis than Hepatitis B and may be especially mild in children. It is not associated with any chronic liver disease.

At present, there is no readily available test to detect Hepatitis A virus in blood. Evidence of active infection is obtained by the presence of acute IgM antibodies and evidence of past infection is obtained by convalescent antibodies IgG.

Many authors have shown that there is no difference in antibody evidence of previous Hepatitis A infection between urban i.v. addicts and controls. At Fair Oaks, however, we have studied a suburban population and find a striking difference between i.v. and non-i.v. drug abusers' convalescent IgG Hepatiis A antibodies. Of non-i.v. drug abusers, 6.3%, as compared to 41.4% for i.v. abusers, show these antibodies.[6] The Hepatitis A rate is less than half the Hepatitis B rate, demonstrating that the Hepatitis B is much more transmissable than Hepatitis A by i.v. routes, but that Hepatitis A still can be transmitted parenterally.

E. Non-A/Non-B Hepatitis

Non-A/Non-B Hepatitis requires a diagnosis of exclusion.[12] It is made by finding evidence of active hepatitis without antigen or antibody evidence of Hepatitis A or B infection. It may be caused by a variety of agents, including Epstein, Barr Virus, Cytomegalovirus, Delta Agent[13] (see below), surreptitious alcohol or drug abuse, and others. Norkrans et al.[14]

have clearly demonstrated that two episodes of non-A/non-B hepatitis can occur in the same individual. More worrisome is that non-A/non-B hepatitis can progress to chronic forms of hepatitis just like Hepatitis B and unlike Hepatitis A. It can also be transmitted parenterally.

F. Delta Agent Hepatitis

A newly discovered cause of hepatitis is the delta (δ) agent. It has an RNA genome and it cannot reproduce without the help of Hepatitis B virus. It is also transmitted parenterally and has been found in 31 to 64% of addicts in Italy, Denmark, Switzerland, Ireland, and California.[13]

Since this agent needs the Hepatitis B virus to replicate itself in human liver, it may actually produce a second hepatitis and account for a biphasic elevation in liver enzymes seen in many addicts with hepatitis.[14] This may explain at least a portion of the multiple hepatitis attacks reported in i.v. drug abusers and attributed to non-A/non-B hepatitis.

At the least, all drug patients with possible intravenous use should have a comprehensive hepatitis evaluation which includes all of the tests listed above.

G. Alcoholic Liver Disease

Many authors report that opiate abusers often use and abuse alcohol concomitantly with the opiates.[15] This can lead to alcoholic liver disease and cirrhosis. Novic et al.[3] concluded that most of the chronic liver disease they saw in a group of opiate addicts was not due to previous hepatitis B infection but was secondary to alcohol abuse.

H. Chronic Liver Disease in Addicts

Chronic liver disease is found in significant numbers of drug abusers. Sorting out the causes and natural progression of chronic liver disease in this population is very difficult. Most studies are complicated by the patients being on methadone maintenance which allows them to continue to abuse i.v. narcotics, other drugs, and alcohol. This problem is so severe that Novic et al.[3] found 82.6% alcohol abuse in former narcotic users who had chronic liver disease. Alcohol cirrhosis was found on liver biopsy of 52.2% of his patients.

One study does exist in which 320 totally drug-free former i.v. narcotic addicts at Daytop Village were studied on admission and 6 months later. During that drug-free period, transaminase abnormalities fell from 39% to 22% and persisted thereafter. Of these addicts, 15 to 20% were found to have chronic persistent or chronic aggressive hepatitis 6 or more months after stopping drug abuse. Serial liver biopsies showed some improvements while others did not progress; 58.4% showed evidence of previous Hepatitis B infection.[11]

From this study, it is clear that chronic liver disease develops in drug abusers as a secondary complication of acute viral hepatitis. It can be caused by either Hepatitis B or non-A/non-B Hepatitis viruses even when the addict has stopped all drug and alcohol abuse. Fair Oaks i.v. patients (35%) were found to be at risk for this complication by virtue of HBeAb in their blood.[6] The only bright spot in this situation is provided by Arthurs et al.[16] who claim that chronic, active hepatitis is less severe and chronic, persistent hepatitis regresses more in drug abusers than in nondrug abusers.

III. DIAGNOSTIC NEUROENDOCRINE TESTING

After medical, endocrinological, and other tests are ordered and found negative, psychiatric diagnostic tests are ordered and used as confirmatory tests for diagnosis of active major depression and as adjuncts to assess and confirm responses to treatment. Of these diagnostic/prognostic tests, the most extensively studied and the most consistently reported abnormalities in major depression are hypersecretion of cortisol failure to suppress cortisol secretion after dexamethasone administration,[17-23] and blunted TRH-induced TSH response.[24-28] These tests

should not be used to screen patients or normals for depression, but to confirm a clinical diagnosis and assess response to treatment.

Normalization of the DCT or the DST after *successful* treatment has been reported in many studies. It has been shown that depressed patients who show apparent clinical recovery, but whose DST remains abnormal, are at serious risk for early relapse. When the DST remains abnormal, continued DST abnormalities may indicate the need for continued somatic treatment and observation, if not alternative antidepressant treatment or ECT. Normalization of the DST has been used to determine when to discontinue treatments in a course of electroconvulsive therapy and it appears that the DST returns to normal before clinical response to antidepressants in patients who are on their way to recovery.

An abnormal DST may identify patients for whom treatment for depression may be indicated, although they carry other presumptive diagnoses such as schizoaffective depression, severe character disorder, dementia, or catatonia. In fact, a positive DST may have more power in prognosis, medication prediction, and relapse prediction than any other component of the diagnosis. In addition, nonsuppression in depression in children and adolescents may support use of medications in such cases where diagnosis is more complex. Results at the present time regarding the ability of the DST to predict response to a particular antidepressant are conflicting, but the data support biological treatment responsiveness.

Thyroid stimulating hormone (TSH) response to Thyrotropin Releasing Hormone (the TRH test) is useful in confirming a major, unipolar depression diagnosis and relapse prognosis as demonstrated in our studies[24,25] and data reported in the literature.[26-28] Patients with unipolar depression, but not other depressed patient groups or controls, have reduced a maximal TSH response, or a ΔTSH of ≤ 7 μIu/mℓ. The actual cut-off for ΔTSH varies according to TSH assay methodology.

TRH testing has also been shown to predict high relapse potential in depressed patients when these patients are retested at the time of supposed clinical recovery and found to have contained TRH test abnormalities.[29] Our data and data in the literature also suggest the potential utility of pre- and post-treatment TRH testing in psychiatric treatment decision making. In the differential diagnosis of mania vs. schizophrenic psychosis, a blunted TSH response to TRH may help identify the manic patient. Using both the DST and the TRH Test, abnormalities in either can confirm the diagnosis of major depression (and particularly unipolar depression) with high diagnostic confidence, and with few false positives, especially when combined with a careful clinical interview. Any comprehensive evaluation program should use the DCT, DST, and TRH test to increase identification of true unipolars to 80 to 90%. When all testing is negative a reexamination of other examinations and tests is in order to again rule out a secondary illness. Like the DST and DCT, the utility of the TRH test in inpatient psychiatry is becoming clearer. Its primary use is in the identification of hypothyroidism. Its secondary usefulness is in confirming a diagnosis of active major depression. In addition, *changes* in the TSH response to TRH in depressed patients have been used to predict response in a manner similar to the predictive utility of the DST. In some studies it appeared that nearly all depressed patients who failed to show a significant increase in ΔTSH after ECT relapsed within 6 months, while the majority of those who showed a change in ΔTSH after ECT remained asymptomatic during the same time period.

Many of the symptoms of hypothyroidism are similar to the symptoms of depression. In hypothyroidism, depression, aneragia, and/or changes in cognition are common, all of which usually improve with replacement therapy. Grades of hypothyroidsm exist and can be identified using the TRH Test. We have clearly demonstrated that failing thyroid gland has a behavioral presentation and can only be diagnosed by either waiting until the patient is overtly hypothyroid or by doing a TRH test.

In our experience the TRH/thyroid test identifies hypothyroid patients who are misdi-

agnosed by descriptive criteria and mislabeled as psychiatric. The TRH test also identifies thyroid hormone responders.

The etiology of hypothyroidism is diverse. Autoimmune mechanisms, however, are frequently implicated and can be screened for with relative ease.[30-32] In symptomatic patients, high antibody titers are considered evidence of an autoimmune disease process involving the thyroid gland. Patients with an increased ΔTSH and positive antibodies are diagnosed as suffering from symptomless-autoimmune thyroiditis ("SAT").

A. MHPG

While there has been some disagreement about where the MHPG comes from and critical arguments about the misuse of urinary MHPG as a diagnostic test for depression, most studies support the use of the MHPG test to predict response to nonadrenergic medication. As such, MHPG is the only well-validated pretreatment prognostic indicator.

B. Vitamin Deficiency

Folic acid deficiency has been widely reported in psychiatric patients, alcoholics, drug addicts, epileptics maintained on anticonvulsant medications, women on oral contraceptives, and other patients (e.g., malnutrition, malabsorption, pregnancy) who may have no other evidence of anemia. A firm link between folic acid level and depressive mood has only recently been made, with research studies demonstrating an abnormally low folate level in 20 to 40% of nonanemic depressed patients. Other studies show that folate deficiency is more common in depressed patients and B_{12} deficiency more common in psychotic patients. Folate deficiency can impair monoamine (e.g., norepinephrine) synthesis in the brain (folate is the co-enzyme for tyrosine hydroxylase). While folate deficiency is treated with replacement, it is unclear whether folate depression exists as a distinct entity or as a precipitant of an underlying vulnerability or as a life-style side-effect of depression. We suggest folate and B_{12} levels in the context of a comprehensive neuropsychiatric evaluation, especially in at risk patients. B_6, vitamin C, tryptophan, tyronine, other vitamins and amino acids may be indicated in certain situations and important in detecting unusual but reversible disease. Finally, environmental and chemical toxicology will emerge as a new and important form of "psychiatric illness". Deficiencies may be of two types: absolute or relative.

IV. THE FUTURE

What may have limited the implementation of laboratory advances by psychiatrists has been the "training lag" and conflicts between schools of psychiatrists. The frequent failure to evaluate drug abusers and homosexuals for the various forms of hepatitis, the failure to adequately assess for nutritional state, and so forth suggests that many clinical psychiatrists have fallen far behind. Many psychiatrists view the use of laboratory procedures as incompatible with their own theoretical approach to the patient and others will not draw blood. Other physicians have unrealistic expectations of the infallibility of laboratory systems. Psychiatrists argue about which mode of therapy or school of thought should be used in clinical practice so it is no surprise that unanimity is elusive with regard to the laboratory. Physicians in other branches of medicine do not find a laboratory test useless or suspect if it fails to have 99% or greater accuracy. They learn that laboratory testing is one component in the diagnostic and treatment process. The DST, for example, is neither indispensable nor dispensable. Recognizing the inherent imperfections frequently leads to the next diagnostic refinement instead of nihilistic return to nothingness. Psychiatrists need to have on-hands experience with the full spectrum of psychiatric laboratory tests to find out what syndromes they have been missing and to improve their patient evaluation and treatment as well as to

impact upon the use and improvement of such procedures. Finally, new tools and techniques developed since residency often necessitate additional post-residency training. Hospitals need to determine what patient groups in the catchment area need which testing. Physicians and hospitals need to test consecutive admissions and analyze their local experience to determine which testing procedures have clinically justifiable yield, to justify their expense and use while others are eliminated and new tests are tried. It would not be surprising to see marked differences between the data of a general hospital (acute, crisis) and a teaching hospital, specialty or referral hospital data. In addition, regional differences are likely. For general hospitals or outpatients physicians to look to the tertiary centers for these protocols is like looking for water in a desert — a waste of time. They must and will be developed by those with experience with typical patients.

The future of psychiatry without doubt will involve a synthesis of biological and psychological approaches to the patient. The trend toward more accurate diagnosis and safer and more effective treatment is accelerating. The laboratory will become more and more essential in diagnosis and documentation of appropriate utilization of psychiatric services.

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INDEX

A

B

C

D

E

N

O

P

R

S

T

V

W

Y – Z