CONTRIBUTING AUTHORS

Naomi Breslau, Ph.D.
Director of Research, Department of Psychiatry
Henry Ford Health Sciences Center, Detroit, MI.
Professor of Psychiatry, Case Western University School of Medicine,
Department of Psychiatry, Cleveland, OH.
Clinical Professor, Department of Psychiatry, University of Michigan School of
Medicine, Ann Arbor, MI.

J. Christian Gillin, M.D.
Professor of Psychiatry
Director, Mental Health Clinical Research Center
University of California, San Diego, CA.

Jack Gorman, M.D.
Professor of Psychiatry
College of Physicians & Surgeons, Columbia University, New York, NY.
Deputy Director of Research
New York State Psychiatric Institute, New York, NY.

Donald F. Klein, M.D.
Professor of Psychiatry
College of Physicians & Surgeons, Columbia University, New York, NY.
Director of Research
New York State Psychiatric Institute, New York, NY.

Rachel G. Klein, Ph.D.
Professor of Clinical Psychology
Chief, Division of Psychology
College of Physicians & Surgeons, Columbia University, New York, NY.

Thomas Roth, Ph.D.
Director of Research, Research Administration
Division Head, Sleep Disorder Center
Henry Ford Health Sciences Center, Detroit, MI.
Clinical Professor, Department of Psychiatry, University of Michigan School of
Medicine, Ann Arbor, MI.
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The burden of psychiatric disorders in the United States has been shown recently to be unexpectedly high. Nearly 50% of persons 15 to 54 years of age have suffered at least one disorder in their lifetime and nearly 30% have experienced at least one disorder within the last year. Psychiatric disorders include mental disorders, such as schizophrenia or major depression, and psychoactive substance use disorders, primarily alcohol and illicit drugs. An important discovery was that 14% of the population had three or more disorders in lifetime, and that the major portion of the burden of psychiatric illness in the population was concentrated in this small fraction with a history of multiple disorders. Persons who have suffered from multiple disorders have a far more serious course, with greater chronicity and more severe impairment. The majority of persons with psychiatric disorders have received no professional treatment and fewer yet have received treatment in the mental health specialty sector. Even among persons with three or more psychiatric disorders in lifetime, less than half have ever received mental health services.

We focus in this report on selected psychiatric disorders: schizophrenia, mood disorders, severe anxiety disorders, and severe disruptive behavior disorders in children, attention deficit/hyperactivity disorder and conduct disorder. For each disorder, an expert in the field presents a summary of the available information, following a uniform outline, which begins with a clinical description, continues through epidemiology, suspected causes and mechanisms, treatment, centers of excellence and service delivery, and concludes with a commentary on future directions. A brief summary is presented in the paragraphs below.

- Schizophrenia is a severe mental illness that affects one percent of the population, worldwide. Symptoms typically become manifest in late adolescence or adulthood and, for the majority of cases, the illness dominates the patient's life. Complete remission is rare, and at least one-third of patients suffers a progressive deterioration with loss of functional capacity. Approximately 10% of patients with schizophrenia die by suicide. Against this bleak picture, research has made substantial progress, particularly in the last decade, toward identifying the sources of pathology in schizophrenia and developing effective and safer therapeutic agents. It is now believed that negative symptoms, which include loss of affect and motivation, apathy, and anhedonia, are the core enduring symptoms of schizophrenia. Schizophrenia is often complicated by other psychiatric disorders, including depression, personality disorders, and substance abuse. Schizophrenia is at least in part genetic. The risk of schizophrenia in first degree relatives is 10%, tenfold the risk in the general population. Suspected environmental causes include
obstetric complications, head trauma and prenatal exposure to infection. Antipsychotic drugs, introduced in the United States in the 1950's, have remained the major treatment modality in schizophrenia. "Atypical antipsychotics", which have been introduced recently, have the advantage of preventing adverse side effects and are superior in the treatment of negative symptoms. Psychosocial treatments, especially rehabilitation and family therapy, together with medications have been shown to reduce the risk for rehospitalization. A major issue in service delivery concerns community based services for patients who a generation ago would have been in long term state hospitals. To date, community services and housing for patients out of institutions have been largely a failure. Major research efforts continue to be devoted to biologic mechanisms, the development of new drugs and psychosocial treatments. Perhaps the greatest need remains in the delivery of care area, including the coordinated design of psychiatric care, housing, general medical care, social services, and rehabilitation.

- Mood disorders affect nearly 20% of the population in lifetime. The most prevalent among them is major depression, 16%, while mania affects about 1% of the population. The most devastating aspect of major depression is the high risk of suicide. Major depression, and even depressive symptoms that do not fulfill diagnostic threshold for major depression, is associated with social and physical impairment as severe as that attendant on chronic medical illnesses.

Depression is approximately twice as common in females than in males. Persons with the disorder tend to suffer from other psychiatric disorders, primarily anxiety disorders. In the majority of cases, major depression is a recurrent and impairing disorder with high societal costs. Mood disorders are familial, with stronger genetic factors in mania than in major depression. Antidepressants and mood stabilizers are the mainline form of treatment for depression and mania. Patients with recurrent major depression and bipolar disorder are now frequently maintained on long-term drug therapy, to prevent relapse and recurrence. Unfortunately, only a relatively small proportion of persons with depression seek treatment. A major public health concern is the recognition, diagnosis, and effective treatment of major depression.

- Although symptoms of anxiety are widespread in the population, in most instances, these symptoms do not meet criteria to be designated as disorders. The most common anxiety disorders are the phobias, with 14% of the United States population meeting criteria in lifetime. The major portion of the phobic disorders
is specific phobia, which represents an unreasonable fear of an object and efforts to avoid it. Anxiety disorders are approximately twice as common in females than as in males. The anxiety disorders tend to co-occur and most persons with, say, panic disorder have a history of other types of anxiety disorders, such as phobia or generalized anxiety disorder. This section of the report focuses on the severe anxiety disorder: panic disorders, obsessive compulsive disorder, post-traumatic stress disorder, and social phobia.

**Panic disorder** is characterized by recurrent and unexpected panic attacks, involving intense fear and a cascade of somatic symptoms of distress. The disorder affects 1.5-3% of the population in lifetime and has an onset in adolescence or early adulthood. The disorder, especially when accompanied by agoraphobia, is associated with significant distress and social impairment. There is strong evidence for genetic transmission. Pharmacologic treatment for panic disorder has been used effectively. There is evidence that psychosocial treatments, including behavior and cognitive therapies, have an important role in treatment.

**Obsessive-compulsive disorder (OCD)** is a rare disorder, affecting less than 1% of the population. It is characterized by uncontrollable intrusive thoughts or distressing impulses (obsessions), and repetitive, ritualized behaviors, such as hand washing, counting, or checking (compulsions). The sex-difference in OCD is less pronounced than in other anxiety disorders. OCD has an early onset, long duration and a low rate of remission. There is evidence of genetic transmission and a link with Tourette’s syndrome. Effective treatment consists of combining pharmacologic agents and specialized behavioral therapies.

**Post-traumatic stress disorder (PTSD).** Research on PTSD has focused primarily on Vietnam combat veterans attending Veterans Administration Medical Centers. The definition of PTSD connects a specific category of stressors - catastrophic (traumatic) events - with a distinct syndrome, which consists of symptoms of reexperiencing (e.g., recurrent nightmares), avoidance, numbing of emotions, and hyperarousal. The disorder can occur in the general population (i.e., not under special circumstances of war or disaster). Rape, physical assault, severe car accidents, and other experiences that involve threat to life might lead to PTSD. Approximately 8-10% of the general population have been affected with PTSD in lifetime, with women having double the risk of men. The overall likelihood that exposure to traumatic events will lead to PTSD is relatively low (25-30%), and most of those who have experienced trauma do not meet full criteria for PTSD.
Persons with a history of psychiatric disorders are far more likely to develop PTSD if exposed to traumatic events. Psychopharmacologic agents have limited efficacy, although they are often used to alleviate associated symptoms. Psychosocial therapies have been found to be effective.

Social Phobia affects approximately 13% of adults in the USA. The disorder is characterized by fear of social or performance situations. Fear of embarrassment or humiliation leads to avoidance of social situations, interfering with social and occupational functioning. Two subtypes of social phobia have been discerned, generalized and non-generalized, with the former being a far more severe disorder. Females and African-Americans are at greater risk for social phobia than males and whites, respectively. The disorder has an early onset and is frequently lifelong. Treatment for the disorder includes medications as well as psychotherapy. Pure performance anxiety, as distinct from generalized social phobia, is treated effectively with beta blockers.

- Attention Deficit/Hyperactivity Disorder (ADHD) affects 3 to 5% of elementary school-age children, with boys predominating. The disorder is characterized by excessive inattention, motor activity, and impulsivity. Most of the important domains of the affected children's life are affected deleteriously. There is parent-child conflict, behavior problems in school, poor academic performance and peer rejection. Conduct disorders, depression, and anxiety disorders have been found to be elevated in children with ADHD. Generally, symptoms of ADHD become less manifest during adolescence and adulthood. However, during adolescence, many children with ADHD develop conduct disorders and in turn also acquire drug abuse and dependence. Those who follow this path have a very poor adult outcome. A family history of ADHD is the strongest antecedent identified. Stimulant treatment is highly effective. No other treatment approach has approximated the positive effects of stimulant medication. A large ongoing study is examining the value of extended medication and psychosocial treatment. The field awaits this study's results for definitive conclusions.

- Conduct disorder consists of a chronic pattern of rule breaking that often leads to school expulsion, familial strife, social rejection, drug abuse, and, in the extreme, trouble with the police and institutionalization. It is a common condition that affects mostly boys. Social, familial and genetic factors influence the likelihood of conduct disorder. Social circumstances include inner city dwelling, poverty, inadequate schools, and exposure to peers with conduct disorder; familial factors
include large family size, overcrowding, alcoholism and drug abuse in parents, and inconsistent and harsh discipline. ADHD frequently occurs with Conduct disorder, especially among those with an early (preadolescent) onset. In a substantial proportion of cases the disorder develops into adult antisocial personality disorders. Treatment is geared to modifying parental behavior, to foster prosocial behavior in the child. A modicum of success has been achieved, especially for programs that intervene in all aspects of the child’s life. Stimulant treatment ameliorates conduct disorder symptoms. Because of our ability to identify children at high risk for conduct disorder, efforts at prevention have been initiated. Their outcome holds promise, but their ability to prevent conduct disorder is unclear.

Several areas of high priority for future research have been emphasized.

- The need for research in the organization and financing of long-term psychiatric care for patients with schizophrenia. Despite progress in drug development, schizophrenia remains a disabling condition, and patients with the disorder require a high level of medical and social services to improve quality of life and prevent a deteriorating course. The challenge involves coordinating of psychiatric and social services, to bring together state of the art medical therapies and rehabilitation.

- In respect to major psychiatric disorders, especially the anxiety disorders, substance use disorders, and childhood disruptive behavior disorders, the scientific grounds will be greatly strengthened by studies that use twin methodology to discern genetic from environmental influences. The development of a large twin registry of children and adults will provide a rich scientific resource that will enable the study of genetic-environmental factors in specific disorders and in their relationships with comorbid disorders.

- Advances in pharmacologic treatment of major depression have not been matched by improvements in the detection and effective application of treatment to those affected. A research priority remains the development and testing of clinical effectiveness in the treatment of depression within health care systems. Among these concerns are the detection of depression, treatment of episodes, and prevention of recurrence.

- Of special concern in urban areas is the high prevalence of traumatic events and PTSD. While the disorder is relatively common in the community, most of what
is known about it comes from research on Vietnam veterans treated in Veteran Administration Medical Centers. Apart from being based on all male samples, the research findings are limited greatly by the social and biographical characteristics of the population, including prolonged social impairment and high rates of substance abuse. Research on samples from the general community is needed, including females and persons who had suffered a variety of types of trauma.
I. Clinical description

Schizophrenia is defined as the presence of at least two core signs and symptoms for at least six months. The core symptoms are delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms (see below). For a significant portion of the time since onset of the disturbance one or more major areas of functioning, such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset. The group of core symptoms is often referred to as "psychotic symptoms." It is important to note that psychotic symptoms can occur in other illnesses besides schizophrenia, including mania, severe depression, drug or alcohol intoxication, brain tumors, and metabolic disorders. Hence, careful diagnostic efforts, including appropriate medical evaluation, is essential before the diagnosis of schizophrenia may be made.

Traditionally, schizophrenia has been subdivided into paranoid, undifferentiated, catatonic, disorganized, and hebephrenic types. In paranoid schizophrenia there is a predominance of hallucinations and delusions, centered around ideas of persecution. In disorganized type there is a predominance of disorganized speech and behavior. Catatonic schizophrenia, a relatively unusual form, involves severe motoric abnormalities and abnormal movements. Undifferentiated schizophrenia is diagnosed when a mixture of core symptoms is present. Residual schizophrenia involves a prolonged state of symptoms usually following acute exacerbations.

These subdivision, although traditional and maintained in the most recent diagnostic guide of the American Psychiatric Association (the DSM-IV), have actually provided little direction to clinicians or scientists. That is, the subdivisions do not seem to identify patients with homogeneous underlying abnormalities in biological function nor do they separate different patterns of response to medication. Therefore, scientists have attempted to identify more useful subdivisions of schizophrenia.

Perhaps the most important of these is the distinction between positive and negative symptoms. The positive symptoms are the flagrant and typically come to clinical attention immediately, often in an emergency situation. They include hallucinations, delusions, disorganized speech, and grossly abnormal behavior. These symptoms usually erupt in late adolescence or early adulthood for the first time and are generally responsive to traditional antipsychotic medications. The negative symptoms include loss of affect, alogia, avolition, and anhedonia. These may precede positive symptoms, co-occur with them, or follow their
resolution. Negative symptoms have been notoriously difficult to treat with traditional antipsychotic drugs, which may actually worsen them.

Reliable instruments have now been developed to differentiate positive from negative symptoms. A variety of biological findings seem to distinguish patients with predominantly positive versus negative symptoms. Clinically, it is now believed by many that negative symptoms are the truly enduring symptoms of schizophrenia, perhaps developing slowly in many people for years before the first manifestation of positive symptoms and lingering long after positive symptoms have subsided. Negative symptoms appear to be related to biologically demonstrable abnormalities in discrete brain regions and to disordered memory and cognition. The newest medications for schizophrenia—the "atypical antipsychotics"—appear uniquely capable of ameliorating negative symptoms of schizophrenia.

A further refinement of the negative symptom concept has been the development of the idea of a "deficit syndrome." This refers to an enduring state of social and cognitive symptoms that is not caused by traditional antipsychotic drugs. This may be the real key aspect of schizophrenia, but further research is required to better define it.

Another perplexing variant of schizophrenia is called "schizoaffective disorder." Patients with schizoaffective disorder have the traditional symptoms of schizophrenia but in addition manifest symptoms of mood disorder, including depression and mania. Although recent research suggests that schizoaffective disorder is closely allied to schizophrenia, there is still debate about whether it is more properly seen as a severe variant of bipolar mood disorder (formerly called manic-depressive disorder).

A spectrum of personality disorders is also now linked to schizophrenia. The two most important of these are schizoid personality and schizotypal personality. The former involves a socially isolated state and the latter a set of nearly psychotic symptoms that never develop into full-fledged psychosis. There is evidence that these "schizophrenia spectrum" disorders are genetically linked to schizophrenia such that parents with one of them may transmit a gene to their offspring that leads to the developing of full-fledged schizophrenia in subsequent generations. This is critical information in pursuing genetic markers for schizophrenia.

II. Epidemiology

Schizophrenia affects approximately one percent of the world's population. Males and females are affected at equal rates, although women tend to develop schizophrenia
somewhat later in life than men and also have more mood symptoms and better prognosis. Several epidemiological observations are now driving research into the possible causes of schizophrenia.

Two such observations have suggested an infectious disease etiology for schizophrenia: the greater prevalence of schizophrenia in urban compared to rural areas of the world and the slight increase of late winter/early spring birth of people who later develop schizophrenia in the Northern hemisphere. Because infectious agents, particularly viruses, are more readily transmitted in crowded population centers, the increased prevalence of schizophrenia in cities might be attributable to maternal infection during pregnancy that interferes with fetal brain growth. As discussed below, there is other evidence suggesting that viral infection of a pregnant woman during the second trimester of pregnancy may increase the risk that the offspring will later develop schizophrenia. Because babies born in late winter/early spring are in the second trimester of gestation during the winter, a time when infectious diseases are more prevalent in the Northern hemisphere, the increased rate of late winter/early spring birth among patients with schizophrenia is compatible with this emerging notion.

It is also noteworthy that recent research suggests that the course of schizophrenia may differ somewhat between developed and third world countries. Although schizophrenia itself occurs at the same rate in all countries, in third world countries the pattern of illness follows a more episodic course than is seen in the developed world. Each episode of schizophrenia in the third world appears to be briefer and lead to more complete remission than is seen in wealthier countries. This finding needs considerable research attention because it may point in the direction of putative causes of schizophrenia.

Schizophrenia tends to be recognized in individual patients in late adolescence to early adulthood, with a somewhat later onset in women compared to men. The sex differential is of interest and studies have attempted to understand if differences in gonadal hormones may be responsible for it. Specifically, there is limited evidence that female hormones may have an anti-dopaminergic effect, thereby mimicking some of the actions of antipsychotic medication.

It is important to note when discussing age of onset of schizophrenia, however, that there is a disparity in many cases between the first manifestation of behavioral abnormalities and the time schizophrenia is first diagnosed. Until obvious positive psychotic symptoms become apparent, it is likely that prodromal stages will not be identified as schizophrenia. Hence, age of onset data are probably significantly
compromised. A relationship between childhood asociality and later development of schizophrenia has been observed. Similarly, subtle motoric abnormalities in early childhood may be found in those destined to develop obvious schizophrenia. Finally, high-risk studies in which children of parents with schizophrenia are followed from an early age have suggested that a range of emotional, cognitive, and physiological abnormalities exist in many children years before the first obvious psychotic symptoms are seen. These observations are critically important, because they redirect research from an exclusive focus on obvious, positive psychotic symptoms to probably much more central and long-lasting developmental abnormalities.

Schizophrenia is also more common among socioeconomically disadvantaged people. There are two possible explanations: poverty causes schizophrenia ("social causation") or schizophrenia causes poverty ("social drift"). Research fairly clearly indicates that the latter is the case. By virtue of its devastating effect on the ability to function, schizophrenia reduces the ability of the patient to complete education or maintain employment. Because schizophrenia is at least in part a genetic illness (see below), once a person with schizophrenia becomes impoverished it is highly likely that future generations will also be born into poverty.

III. Natural course

Approximately one-third of patients with schizophrenia develop a waxing and waning course, with remission possible for fairly long periods of time. Another one-third develop a stable and chronic illness with no remissions. The remaining one-third develop a chronic, deteriorating course with progressive loss of function. Schizophrenia rarely, if ever, disappears on its own. It is associated with increased medical morbidity and mortality and a high suicide rate. Understanding the reasons for suicidal behavioral among patients with schizophrenia is a prime target of current research. Unfortunately, traditional antipsychotic drugs have had surprisingly little effect in altering the long-term course of schizophrenia, their effect is in reducing acute exacerbations and positive symptoms. There is currently great hope that newer agents will have a more powerful effect on chronicity. As discussed below, psychosocial therapies also reduce some of the adverse effects of chronic schizophrenia.

Schizophrenia is frequently complicated by other psychiatric illnesses. Following an acute episode of illness, usually characterized by an increase in positive psychotic symptoms, many patients develop "post-psychotic depression." This is often mistaken for negative symptoms, deficit syndrome, or the result of side effects of antipsychotic
medication. Because post-psychotic depression has been shown to respond to antidepressant medication, it is important to makes this diagnosis early.

Perhaps the most plaguing comorbidity with schizophrenia involves the concomitant presence of substance abuse. For a variety of reasons, patients with schizophrenia have high rates of alcohol abuse. They also abuse illegal drugs, including stimulants such as cocaine. Most of the substances exacerbate the psychosis and interfere substantially with treatment. Programs have been created in many states specifically to deal with the "dual diagnosis" problem of schizophrenia plus substance abuse and there are a few promising leads of treatments that may be particularly useful for this group.

Patients with schizophrenia may also suffer from a variety of personality disorders, including borderline personality disorder. The latter greatly complicates the response to treatment intervention and often results in prolonged hospitalization. It is unclear if borderline personality overlaps biologically with schizophrenia, but this should be further researched.

Patients with schizophrenia develop medical illness, often fatal, at higher rates than comparable persons in the general population. The widespread use of cigarettes among patients with schizophrenia may be one factor. Recent studies also suggest that schizophrenia may be associated with abnormalities in the brain regulation of heart function, which may increase the risk of coronary artery disease and lethal arrhythmia. In addition, patients with schizophrenia generally have decreased access to health care services and probably receive much poorer medical attention than the general population. Finally, an interesting observation is that patients with schizophrenia have abnormally high threshold for pain detection and may therefore not report medically threatening events in a timely fashion. The biology of altered pain perception in patients with schizophrenia is currently under active research investigation.

Schizophrenia demands an inordinate use of health care and social services. Schizophrenia remains one of the few psychiatric disorders for which hospitalization is commonly required. Outpatient care is usually chronic and newer medications are expensive. Because few patients with schizophrenia are able to remain employed and therefore to maintain private health insurance, the burden of caring for patients with schizophrenia generally falls on public sources. Patients with schizophrenia generally require public assistance in addition to governmental health insurance; state governments still maintain hospitals specifically for the care of patients with chronic mental illness, most of whom have schizophrenia.
Schizophrenia is also associated with homelessness. Approximately one-third of homeless in the United States have schizophrenia. This challenges governmental agencies to provide appropriate levels of social services and municipally-funded shelter.

One of the great difficulties in the economics of schizophrenia is funding the use of the newest antipsychotic medications. Some studies suggest that the newer medications actually lead to an overall reduction in the costs of caring for patients with schizophrenia, because they reduce the need for hospitalization and increase functional capacity so that employment becomes possible. However, the new drugs are clearly substantially more expensive than older agents, straining the budgets of the governmental agencies that must pay for them.

There is a great need for services research in schizophrenia. More effective methods of delivering psychiatric care, keeping family involvement, insuring medical care, and preventing homelessness are critically required. The proper distribution of newer and more expensive medications must be determined.

IV. Suspected causes

1. Genetic factors

There is no question that schizophrenia is at least in part a genetic illness. Family studies have shown that although the risk of schizophrenia is 1%, the risk is 10% for first-degree relatives of people with schizophrenia. Twin studies compare the rate of concordance of schizophrenia between identical twins (also called monozygotic or Mz twins) and fraternal twins (dizygotic or Dz). The concordance rate (i.e. the rate at which both twins have the disorder) is 50% for Mz twins but only 10% for Dz twins. Because Mz twins have the same genes while Dz twins are no more genetically similar than ordinary brothers and sisters, this finding implies a genetic cause of schizophrenia. Finally, studies have looked at the occurrence of schizophrenia among people whose parents have schizophrenia but who were adopted away from them during infancy and raised in families without schizophrenia. Such studies find a high rate of schizophrenia among these "adopted away" individuals, indicating that genetic factors are more powerful than environmental factors in causing schizophrenia.

Modern molecular genetic techniques have successfully led to the location of genetic markers for a variety of illnesses including muscular dystrophy, Huntington's disease, spinal muscular atrophy, cystic fibrosis, and Wilson's disease. These techniques are now being applied at several laboratories in the United States and abroad in an attempt to find
the abnormal gene or collection of genes that predispose to schizophrenia. This work is
difficult because it is not yet certain whether such a gene(s) causes schizophrenia itself or
illnesses within the "schizophrenia-spectrum." Also, the clinical picture of schizophrenia
is somewhat heterogeneous and therefore it is likely that no single gene causes all cases of
the disorder.

At present, a marker on chromosome number 6 is the strongest genetic finding,
although much work needs to be done to confirm this finding. It is believed that genetic
markers will be identified for schizophrenia if funding support continues at least at the
present level.

It is also likely that abnormal genes will ultimately tell only part of the story of the
cause of schizophrenia. There are a number of compelling reasons to believe that non-
genetic factors are required to interact with abnormal genes in order for schizophrenia to
develop. At least five of these so-called "epigenetic" factors have been studied:

2. Obstetric complications

Patients with schizophrenia are born from pregnancies with a higher than expected
number of obstetrical complications, both during the pregnancy itself and during the
delivery. More powerful methods are now being used to confirm these findings.

3. Head trauma

Patients with schizophrenia have histories of significant head trauma at a higher
rate than the general population. One current idea is that head trauma disrupts the "blood-
brain" barrier that normally protects the brain, thereby allowing toxic substances which
may interfere with normal brain function to enter.

4. Prenatal exposure to infectious agents

A compelling body of research now suggests that maternal infection during the
second trimester of pregnancy may predispose the offspring of that pregnancy to develop
schizophrenia later in life. The evidence is strongest for influenza infection, but other
viruses and infectious agents are currently being studied.
5. Immunological injury

One way that infection during gestation might injure the developing brain is by provoking an "autoimmune" reaction in which antibodies generated to attack the infectious agent become misdirected and attack the fetus' own brain cells. A number of studies have shown increased immunological activity in some patients with schizophrenia and one group has identified a specific abnormal autoantibody in patients with schizophrenia.

6. Prenatal nutritional deprivation

Recent research has shown that people exposed in utero to severe nutritional deprivation during the Dutch Famine Winter of 1944-45 have a significantly elevated rate of developing schizophrenia. Vigorous research is now underway to identify the exact nutrients that are necessary to prevent this from occurring.

It is important to emphasize that these epigenetic factors are believed to impact on the development of schizophrenia early in life, generally during fetal gestation. They probably combine with genetic factors and their variety may explain the different clinical pictures observed among patients with schizophrenia.

V. Biological mechanisms and correlates

1. Neurotransmitter abnormalities

The discovery that the traditional antipsychotic medications shared the property of blocking the ability of a single neurotransmitter, dopamine, to bind to one of its postsynaptic receptor, the D2 receptor, stimulated a 30 year research endeavor to validate the "dopamine hypothesis." According to this hypothesis, schizophrenia is caused by a relative excessive activity of dopamine in the brain. Antipsychotic drugs were postulated to work in schizophrenia by blocking dopamine's effects.

Other lines of evidence were marshaled in support of the dopamine hypothesis. Most notably, drugs that increase dopaminergic activity in the brain, such as amphetamines, were noted to produce psychotic symptoms in some previously psychiatrically healthy individuals and to worsen psychosis in patients with schizophrenia. However, a number of problems with the hypothesis have now been recognized. The psychosis produced by amphetamines, for example, is largely limited to paranoid symptoms and does not model the complete clinical picture of schizophrenia. Antipsychotic drugs block the D2 receptor after just a few doses but often take weeks to have any
appreciable effect on the patient's symptoms. Finally, as discussed later, a whole new class of antipsychotic drugs, called "atypical" agents, was introduced into the United States in 1990. These drugs are at least effective as the traditional antipsychotic drugs but are much less potent D2 receptor blockers. Although there remain several reasons to continue to consider dopamine as an important part of the pathogenesis of schizophrenia, including the fact that successful treatment with antipsychotic drugs has been shown in several studies to lead to a reduction in the first metabolite of dopamine (HVA) in blood, it is now widely acknowledged that dopamine cannot be the whole story.

Adding to the complexity is the recent discovery that the dopamine system has not two types of receptors, as previously believed, but at least five. The different subtypes of dopamine receptor have different physical and molecular properties and are also distributed differently in the brain. Of particular interest are the D3 and D4 types. It has been shown that some of the new antipsychotic drugs have particularly strong affinity for D3 and D4 receptors and much weaker affinity for D2. D3 and D4 receptors appear to be located mainly in limbic areas of the brain, the hypothesized location from which positive symptoms are generated in schizophrenia. They are underrepresented in the basal ganglia and therefore drugs that bind to them do not cause the range of serious neurological adverse side effects that are seen with the traditional drugs. A great deal of research is now needed to further characterize the subtypes of dopamine receptor and determine their role in schizophrenia.

The atypical antipsychotic drugs are also strong blockers of serotonin (also known as "5-HT") receptors in the brain. This finding has led to a "serotonin" hypothesis of schizophrenia in which the ratio of dopamine to serotonin blocking activity is postulated to be the key element in the success and safety of an antipsychotic drug. The first of the new antipsychotic drugs, clozapine, also has activity at noradrenergic receptors. Taken together, it is clear that new research considering the role of neurotransmitters other than dopamine and receptors other than the D2 receptor is critically needed.

One of the most prominently discussed neurotransmitters in the schizophrenia area today is glutamate. Neuroscientists have developed a strong interest in glutamate because it is now known to play a key role in many basic neuronal processes and to be a major component of the memory system. It is also known that excessive glutamate release following traumatic head injury and stroke is responsible for much of the subsequent brain damage. Hence, pharmaceutical companies are currently developing glutamate antagonists to be given following traumatic brain injury and stroke. Glutamate appears to have an antagonistic relationship with dopamine such that deficient glutamatergic neurotransmission leads to excessive dopaminergic activity. Hence, the possibility arises that deficient
glutamate activity in brain may be involved in schizophrenia. Evidence supporting this idea has begun to accumulate and comprises one of the most active areas in schizophrenia research. A related area involves the brain's major inhibitory neurotransmitter, GABA, which depresses dopamine neurotransmission and may also be deficient in schizophrenia. This work involves clinical scientists, brain imaging, neuropathology, and molecular biology.

2. Neuroanatomical findings

It was first shown several decades ago that many patients with schizophrenia have an enlargement of the fluid-filled spaces of the brain, called the ventricles. This implies a decreased amount of actual brain tissue. As brain imaging technology progressed dramatically, neuroimaging studies in schizophrenia became one of the mainstays of research, revealing several important abnormalities. Using modern magnetic resonance imaging (MRI) techniques, two main areas of abnormality have been identified. A number of studies have shown decreased mass of the temporal and limbic areas of the brain in schizophrenia. This appears at the earliest stages of the illness and is not thought to be secondary to antipsychotic drug treatment or to any deteriorating process created by the disease itself. Rather, scientists now believe that structural abnormalities in temporal and limbic areas of the brain are developmental in nature, probably occurring during fetal life in those destined to develop schizophrenia. They probably mediate many of the cognitive and memory abnormalities seen in schizophrenia. The second area of the brain implicated in MRI studies is the thalamus. Although more recently identified as a possible site for schizophrenia pathology, the thalamic findings are extremely interesting because the thalamus is believed responsible for integrating and relaying stimuli from the external world to other parts of the brain for interpretation and action. Hence, thalamic abnormalities may be responsible for the distortions in reality perception common in schizophrenia. Furthermore, the thalamus is an important part of the brain for pain detection. Patients with schizophrenia have long been known to have a very high threshold for pain, hence an abnormal thalamus would be consonant with the clinical observation. A final set of structural abnormalities involves the symmetry of the brain. The normal human brain has left-right asymmetries in a number of areas which are apparently missing in many patients with schizophrenia.

Another type of brain imaging is called "functional imaging." Here, instead of looking at the size and shape of brain structures it is actually possible to study the function of discrete regions of the brain under a variety of conditions. Using dynamic measures of brain blood flow and metabolism, many investigators have found a decrease in activity in the frontal lobes of the brain in schizophrenia, so-called "hypofrontality." This is
postulated to be responsible for the negative symptoms of the illness. One important strategy is to challenge the brain of patients with schizophrenia and comparison normal subjects with cognitive tasks. Such activation studies reveal previously undisclosed abnormalities in the brain of patients with schizophrenia. For example, studies in which a neuropsychological task is performed during positron emission tomograph (PET) scanning of the brain revealed reduced activation in the dorsolateral prefrontal cortex in patients with schizophrenia. Similar abnormalities have been shown during an olfactory task with another functional brain imaging technique, single photon emission tomography (SPECT).

Magnetic resonance imaging has also been adapted recently for functional studies. A form of MRI, called magnetic resonance spectroscopy (MRS), has been used to show abnormalities in phospholipids that comprise the membranes of brain cells and is also now being employed to map out the amount of glutamate in brains of patients with schizophrenia compared to normal controls. This kind of work will be greatly enhanced as larger magnets are put into place. Magnets approaching five tesla in strength (the usual magnet for MRI is 1.5 tesla) are now being tested. Finally, functional MRI (fMRI) is increasingly studied in schizophrenia. It has several advantages over PET and SPECT: fMRI does not use any ionizing radiation and can therefore be done safely on multiple occasions and also used with children and also has much better resolution than PET or SPECT. In general, brain imaging promises to be one of the most fruitful areas of research in schizophrenia, revealing the location of abnormalities in brain.

3. Neuropathology

The study of abnormalities in the brains of deceased patients with schizophrenia has now become revealing because of major technological advances in neuropathology and the increasing cooperation of families of patients with schizophrenia. Because the brain rapidly decays after death, it is crucial to use advanced preservation techniques so that postmortem studies can be conducted. These studies have recently revealed a number of important findings. One set has shown abnormalities in discrete regions of brain that are almost certainly developmental in nature, arising during prenatal life. Another has revealed a decrease in cells with receptors for the neurotransmitter GABA. A third set of findings involves reduction of a type of structural brain cell (called "MAP-2") that are needed to support proper brain function. There is a critical need to develop brain banks to permit this research to continue.
4. Neurophysiology

Several abnormalities in brain function in schizophrenia have been detected with relatively simple techniques that are safe and non-invasive. These neurophysiological abnormalities have led to important insights into areas of the brain and basic processes that are disordered in the illness.

Normal individuals have a robust response to a startling stimulus, such as a loud tone. However, after repeated administration or if a less startling stimulus is presented immediately before the startling one, the response in the normal individual is typically diminished. Patients with schizophrenia, however, do not show this normal blunting of response and are therefore said to have abnormal "gating." Such studies are very important because they can also be performed in animals. Scientists have been able to create gating abnormalities in laboratory animals with a variety of techniques, thus modeling the abnormality in humans with schizophrenia. They are then able to correct the abnormality in the animal with medications. Hence, animal models of gating abnormalities promise to be an important method for drug development.

Neurophysiological tests can also be used to help genetic research. As discussed earlier, it is now widely believed that first-degree relatives of people with schizophrenia who do not themselves have the illness may nevertheless be silent carriers of genes predisposing to schizophrenia. Non-invasive and relatively inexpensive neurophysiological tests can be used to detect such carriers. For example, it has been shown that patients with schizophrenia have a distinct abnormality when asked to visually track an object moving back and forth on a screen. Such eye-tracking abnormalities are also found in approximately fifty percent of their first-degree relatives. Eye-tracking studies are now being used to assist genetic researchers to better define the population of people who may be carrying genes for schizophrenia.

Other neurophysiological tests enable scientists to identify brain regions that are abnormal in schizophrenia without the expense of formal neuroimaging technologies. Use of evoked potentials and the dichotic listening test, for example, have shown abnormalities in left temporal regions of the brain in schizophrenia that are also identified with MRI and PET studies. Abnormalities in heart rhythm have also been used to indicate regions of the brain that may be involved in schizophrenia.

There is now tremendous optimism that the causes of some forms of schizophrenia can be learned in the next 10 to 15 years. It is likely that this will occur only if a diverse
group of scientists from a variety of fields cooperate. Progress will need expertise in neuroimaging, genetics, molecular biology, neurophysiology, and neuropathology.

VI. Treatment

1. Typical agents

Antipsychotic medications are the hallmark of the treatment of schizophrenia. Unlike other types of psychiatric illness, there is little debate that medication is a necessary component for virtually all patients. Currently, antipsychotic medications are divided into two categories, typical (or traditional) and atypical. As the atypical agents become dominant in the next five to ten years it is likely that this terminology will need to be altered.

The typical agents were first introduced into the United States in the late 1950's with the approval of chlorpromazine (Thorazine). All of the typical agents have in common the property of blocking the actions of the brain neurotransmitter dopamine at one of its receptors, called the D2 receptor. Many typical antipsychotic agents were subsequently marketed and include such familiar names as Haldol, Prolixin, Mellaril, and Stelazine. These drugs are unquestionably effective in treating the positive symptoms of schizophrenia. Approximately 70% of patients with schizophrenia manifesting hallucinations, delusions, and thought disorder will realize clinically meaningful benefit from the typical antipsychotics.

However, numerous drawbacks have long been noted with the typical agents. First, at least 30% of patients do not have a response even for their positive symptoms and the drugs are relatively ineffective for negative symptoms. In fact, it has been argued that for some patients the typical antipsychotic drugs worsen negative symptoms. Second, the typical agents cause a host of serious neurological and medical adverse side effects. Because they block dopamine in the basal ganglia, the typical antipsychotic drugs produce reactions called extrapyramidal side effects (EPS) that include muscle rigidity (dystonia), restlessness (akathisia), and tremor (Parkinsonism). A rare but potentially fatal side effect is the neuroleptic malignant syndrome (NMS). Finally, after sustained use of antipsychotic drugs there is a substantial risk for development of the movement disorder called tardive dyskinesia (TD). This is characterized by involuntary muscle movements, usually beginning in the face. Although usually reversible after medication is stopped, irreversible cases of TD can occur.
2. Atypical agents

For almost 20 years no new antipsychotic drugs were introduced into the American market, despite the obvious shortcomings of the existing typical agents. The approval of clozapine, however, has revolutionized our approach to the treatment of schizophrenia. Because clozapine is a relatively weak dopamine blocking agent, it was called an atypical antipsychotic. It has a number of unique clinical properties. At least one-third of patients who are refractory to typical antipsychotic medications respond favorably to clozapine. It is also effective for the negative symptoms of schizophrenia. Finally, clozapine has little if any potential to cause EPS, NMS, or TD.

Unfortunately, one serious potential side effect of clozapine has limited its use. Approximately one percent of patients who take the drug develop a blood disorder called agranulocytosis in which a key cell in the immune response is suppressed. If left unchecked, agranulocytosis is usually fatal. As long as clozapine is stopped immediately once there is a drop in the white blood cell count, the problem almost always resolves. However, patients on clozapine must have a weekly complete blood cell count (CBC) which is both inconvenient and expensive. Other less serious side effects of clozapine include weight gain, which often leads the patient to stop the medication, increased salivation, and somnolence.

A second atypical agent was subsequently introduced. Risperidone has similar pharmacological properties as clozapine and less chance of causing EPS than typical drugs. Although it is widely seen as the proper first-line drug for patients with schizophrenia, it is not as potent as clozapine and, at higher doses, can cause EPS.

Two new atypical agents are about to be approved by the FDA, olanzapine and sertindole. Two others are in late stages of testing, sertindol and ziprasidone, while a host of atypical agents are in earlier phases of clinical trials. There is great optimism that one or more of these new drugs will be similar to clozapine in efficacy, without the risk of agranulocytosis.

3. Depot preparations

Another area of concern is the use of long-acting or depot preparations of antipsychotic drugs. These are given by injections, usually once or twice per month, and permit ongoing antipsychotic therapy without taking pills on a daily basis. Two depot preparations are available in the U.S., fluphenazine decanoate and haloperidol decanoate, and a third is under investigation. These preparations are particularly useful for patients
who frequently stop taking the medication and relapse. Depot preparations are widely used in Europe, but are underutilized in the U.S. for unclear reasons.

4. Treatment of negative symptoms

The atypical antipsychotic drugs are clearly better for negative symptoms than the typical agents, but typical agents are still widely prescribed. Because of this, investigators have attempted to find adjunctive treatments that would ameliorate the negative symptomatology. A host of agents have been reported in the literature to be useful, including mazindol, yohimbine, fenfluramine, and antihistamines, but very few properly controlled trials have been done. Because negative symptoms produce long-term impairment, improvement of the treatment of negative symptoms is seen as a priority for research.

5. Use of benzodiazepines

Until recently, antipsychotic drugs in large amounts have been used for the emergency treatment of acutely psychotic patients, usually when they are violent. This is effective but produces many side effects. More recently, it has been shown that more benign medications in the benzodiazepine class can successfully calm an acutely psychotic patient so that lower initial doses of antipsychotic medication can be used. However, studies are needed to refine these techniques.

6. Psychosocial treatments

Although almost all patients with schizophrenia require antipsychotic medication, there is evidence that focussed and specific psychosocial interventions are also helpful. The two best studied to date are rehabilitation and family therapy. Rehabilitation treatments are aimed at improving social and functional skills of the patient. These have been shown to work in concert with medication to reduce the risk of rehospitalization and speed reentry into successful community living. Effective rehabilitation therapy is patient specific but conducted according to procedures shown by research to work. Manuals and videotaped training sessions are available. Family therapy has also been shown to work in concert with medication. The focus here is not on uncovering abnormal family dynamics or placing blame on family members. Rather, effective family therapy of schizophrenia attempts to educate family members about the illness, alert them to early warning signs of relapse, and help the family cope with the severe impairment that schizophrenia often entails.
VII. Service delivery

Through the 1950's and early 1960's patients with schizophrenia were typically institutionalized in hospital centers administered by state governments. The "deinstitutionalization" movement then occurred, primarily for two reasons. First, the availability of the first generation of antipsychotic drugs enabled many patients to realize reduction in the most socially disruptive symptoms and return to community living. Second, seminal research studies showed that patients with schizophrenia could do as well or better if treated in the outpatient setting with support from family and community services. Most states then began, with encouragement from the federal government, a massive discharge of patients from hospitals. Today, this effort is largely seen as a failure, mainly because the promised community mental health centers and community housing for patients with schizophrenia were never adequately funded by state or federal governments. Many patients entered a revolving door scenario of repeated admissions and discharges from acute care hospitals. Others entered the criminal justice system after committing minor crimes while psychotic. Others were sent to nursing homes. Finally, it is estimated that approximately one-third of homeless people have chronic mental illness, mainly schizophrenia. Although the concept of community care for patients with schizophrenia is a noble one, it requires the creation and constant evaluation of appropriate systems of support. In the absence of this, states may save money but patients clearly suffer massively adverse outcomes.

There are a number of efforts underway to redress these problems. It must be recognized that the care of people with schizophrenia rests mainly with families and government at the present time. Third-party insurance coverage is rarely sufficient to provide medical care, especially the newer and expensive medications, for patients with schizophrenia given the chronic nature of the illness. A number of novel approaches, including "assertive community care," the use of case managers, half-way houses, and day programs have been attempted. Each of these is in limited use, but there are promising data that such methods of service delivery, advocacy for patients with chronic mental illness, and community care can work to improve the lives of patients and reduce hospital admission recidivism. There is urgent need for experimentally-driven services research in schizophrenia to develop and evaluate methods of service delivery that will neither require chronic institutionalization nor result in homelessness or imprisonment.

Another emerging area of research need is the evaluation of the cost-benefit ratio of atypical antipsychotic medications. Most of the typical medications are now available in generic preparations and therefore are relatively inexpensive. The newer drugs, clozapine, risperidone, and soon olanzapine and sertindole, are protected by patent and are
vastly more expensive. It will fall largely on the shoulders of state mental health systems to pay for these new drugs. There is a wide consensus among patient advocates, patients and physicians that the new medications are more effective and safer. A few studies seem to indicate that, by virtue of their enhanced efficacy and therefore ability to help patients return to work and stay out of the hospital, atypical antipsychotic use actually reduces the cost of treating schizophrenia. These studies are controversial and small in scale, however. While it would be unthinkable to deny patients with any illness truly effective and safer treatment, it will be important to document the extent to which more expensive medications do in fact produce improved long-term outcome and to calculate the cost to taxpayers.

VIII. Centers of research excellence

Until about a decade ago, research in schizophrenia was seen as lower in priority to research in mood and anxiety disorders. Clearly, vastly more people suffer from depression and the anxiety disorders (approximately 30% of the population) than from schizophrenia (approximately one percent). However, the devastating and chronic nature of schizophrenia along with new research promise has led to a shift in research priorities to the point that schizophrenia research is now seen as one of the most important areas of investigation. Most of the funding for research in schizophrenia, as in all of mental illness, comes from the National Institutes of Health, primarily the National Institute of Mental Health (NIMH). There is also funding from the pharmaceutical industry, which funds mainly clinical trials of investigational drugs but occasionally also other types of research. Finally, there is a growing source of research funding from private philanthropy. The largest private organization now funding research in mental illness, including schizophrenia, is the National Association for Research of Schizophrenia and Depression (NARSAD). Several other foundations, including the Scottish Rite Foundation, Mental Illness Foundation, and Stanley Foundation are also active and there has been some funding of schizophrenia projects recently from the March of Dimes. However, private support of psychiatric research is still a much smaller fraction of total research funding, compared to that seen with other medical disorders, such as heart disease and cancer.

Because schizophrenia research involves expensive technology, experts from diverse areas of specialization, inpatient units, and a large population of available patients it has tended to cluster in about a dozen centers in the United States. These include: 1) University of Michigan, 2) the New York State Psychiatric Institute/Columbia University program, 3) Mount Sinai/New York University Medical Center, 4) Long Island Jewish/Hillside Medical Center, 5) McLean/Massachusetts Mental Health/Harvard program, 6) the intramural division of the National Institute of Mental Health, 7) the University of Pennsylvania, 8) University of Maryland/Maryland Psychiatric Center, 9)
University of Iowa, and 10) UCLA. This is not meant to be an exhaustive list but rather suggest that the centers are fairly well distributed geographically. Most of the centers have sophisticated brain imaging programs and also conduct clinical trials of investigational drugs. Some are further involved in genetics, molecular biology, and epidemiology. These centers have been relatively stable over the past 10 to 15 years, enabling them to train and nurture young scientists and to follow patients for longitudinal observations, which are critical for a number of research questions. Unfortunately, there is incessant discussion of the cost of research centers by government officials that promotes uneasiness and disrupts scientific work.

IX. Future directions

Throughout this report the need for research in several discrete areas has been emphasized. These will be briefly summarized.

1. Biological research

Understanding exactly what part(s) of the brain is affected by schizophrenia is a critical research priority. To do this, sophisticated brain imaging, neurophysiological, and neuropathological studies must continue to be conducted. This research will go hand in hand with advances in technology, so that improvements in the temporal and spatial resolution capacities of brain imaging techniques, new activation methods, and new methods of studying brain structures in post mortem samples will be needed to advance schizophrenia research. It will be best to fund several neuroimaging centers that will include experts in diverse areas including physics, chemistry, cognitive neuroscience, nuclear medicine, neuroradiology, and psychiatry rather than to spread limited neuroimaging technologies at multiple sites. Several brain banks are needed to advance neuropathology research.

There is reasonable hope that genetic markers and abnormal genes involves in schizophrenia will be found. This is very complex research involving clinicians, epidemiologists, statistical geneticists, molecular geneticists, and computer experts. Again, several large centers are preferred. At the same time, research into the non-genetic causes of schizophrenia centering around prenatal events such as infection, autoimmunity, and nutritional deprivation must continue. These will be enhanced by the development of animal models.

Finally, molecular biology research of the structure and function of brain systems believed to underlie schizophrenia must be funded. This work should be done in many
laboratories so that a wide range of candidate systems, including those involved with neuropeptides such as neurotensin, dopamine, glutamate, serotonin, and GABA can be conducted.

2. Treatment research

Research centers must continue to collaborate with the pharmaceutical industry to develop new atypical medications. Once these drugs are found, we need research centers with experience in clinical trials to conduct standard phase II, III, and IV studies and to investigate the neurobiology of the new agents. There is also a need to continue to work on therapies for negative symptoms and for antidotes to side effects of antipsychotic medication such as TD, weight gain, and bone marrow suppression, all of which lead to patient discontinuation of therapy.

Development of useful psychosocial treatments must also be encouraged. It is important that these non-medication treatments be evaluated scientifically and that they be created in such a way that they can be transported to clinical settings. The impact of these therapies on symptoms, function, and long-term outcome must be evaluated rigorously.

3. Service delivery

Methods of delivering care to outpatients must be improved. It is clear that hospitalization wastes resources and prevents patients from assuming functional roles, but it is also clear that patients cannot be dumped into the community without systems in place to insure that they will be properly housed, have access to services, and receive the full range of medical care. Studies of the cost-benefit ratio of atypical antipsychotic drugs and of better ways of delivering them to patients must also be conducted. If more expensive medications are to be widely provided, it is imperative that data be generated proving that they are superior to older, cheaper medications.

Although the care of patients with schizophrenia is expensive, it is important that emphasis be placed on finding causes and improving care rather than saving money. There is currently a tremendous opportunity to make major breakthroughs in understanding and treating schizophrenia. We must be aggressive in maintaining this unprecedented momentum.
X. Bibliography


Andreasen NC. Negative symptoms in schizophrenia: Definition and reliability. *Arch Gen Psychiatr* 1982; 39:784-788.


Janssen PAJ, Niemegeers CJE, Awouters F, Schellekens KHL, Megens AAHP, Meert TF. Pharmacology of risperidone (R 64 766), a new antipsychotic with serotonin-S₂ and dopamine-D₂ antagonistic properties. J Pharmacol Exp Ther 1988; 244:685-693.


The mood disorders refer to a large group of psychiatric disorders associated with pathological moods (such as depression, dysthymia, mania, or hypomania), with characteristic somatic signs and symptoms, and dysfunctional ways of thinking. They are usually defined by clusters of typical symptoms which commonly are sustained for relatively long periods of time. These syndromes are usually distinctly different from the person's usual functioning and are commonly but not always associated with impaired functioning in daily activities, such as work, interpersonal relations, and home life. The mood disorders are prevalent in the general population, tend to be recurrent, and often vary in severity in the individual over time, for example, from euthymia to subsyndromal states with mild to moderate symptomatology.

The introduction of new treatments during the past two decades, particularly antidepressant and mood stabilizing medications, has stimulated considerable interest in the mood disorders from clinicians, scientists, the pharmaceutical industry, and the general public. These developments have helped destigmatize these disorders and the patients who suffer from them. The American public appears to be more open than previously to recognizing the signs and symptoms associated with mood disorders and more ready to seek treatment. In turn, the federal government appears more inclined to require coverage of mental disorders by the health insurance industry. In part, the mood disorders are increasingly seen as 'real' (i.e., medical) disorders, with a biological etiology and treatment response, rather than shameful character disorders.

Nevertheless, stigmatization and misinformation remain major impediments to the understanding and treatment of psychiatric disorders. Public surveys reveal that 71% of respondents still believe that mental illness is due to emotional weakness, 65% believe it is caused by bad parenting, 45% say that it is the fault of the patient, and 35% say it is the consequence of sinful behavior. Only 10% say that it has a biological basis or involves the brain. Many individuals with mood disorders never seek professional evaluation or treatment. Many who want help never obtain it from health care providers. And, unfortunately, many who find help are misdiagnosed, mistreated, or undertreated. From the scientific perspective, much remains to be learned about the etiology, pathophysiology, and optimal treatment of these disorders. A recent review predicted that depression will be among the most common cause of morbidity and mortality during the next quarter of a century.
I. Clinical description

The syndromes of depression and mania, for example, must be distinguished from the normal moods of sadness and elation. On the one hand, sadness, grief, feeling blue, or disappointment, and, on the other hand, joy, exuberance, optimism, and self-pride are normal human emotional responses to everyday experiences, probably deeply embedded in our evolutionary history. Furthermore, the mood disorders should be distinguished from individual temperaments, characterized by, for example, life-long depressive, hyperthymic, or cycloid variations in normal emotional expressiveness. The boundaries between normal and pathological mood states continue to be matters of dispute, research, and clinical judgement, but the dividing lines are usually defined in terms of duration and degree impairment associated with symptoms.

The two major mood diagnoses are the depressive disorders and bipolar disorders (formerly known as manic-depressive disorders). The exact diagnostic criteria are still evolving but, in practice, have been most recently codified in the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Ed. 4, published by the American Psychiatric Association, 1994). The specific diagnosis is made on the basis of characteristic symptoms during specific episodes of the disorder as well as the longitudinal history of the disorders. The diagnostic criteria for a Major Depressive Episode and a Manic Episode are shown in Tables 1 and 4, respectively. Both depression and mania are defined by clusters of symptoms, including cognitive or psychological characteristics (mood, concentration, speed of thinking, future outlook, attention span), vegetative (sleep, appetite, libido), impulse control (suicide, poor judgement), physical (motor activity, fatigue), and behavioral (motivation, interests).

Table 1. Abbreviated DSM IV Diagnostic criteria for Major Depressive Episode (MDE)

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Five or more symptoms for at least two weeks; must include either depressed mood or loss of interest or pleasure:</td>
</tr>
<tr>
<td>• Depressed mood most of the day every day</td>
</tr>
<tr>
<td>• Markedly diminished interest or pleasure in all or nearly all activities</td>
</tr>
<tr>
<td>• Significant weight gain or loss when not dieting or change in appetite</td>
</tr>
<tr>
<td>• Insomnia or hypersomnia nearly every day</td>
</tr>
<tr>
<td>• Psychomotor agitation or retardation</td>
</tr>
<tr>
<td>• Fatigue or loss of energy</td>
</tr>
<tr>
<td>• Feelings of worthlessness or excessive and inappropriate guilt</td>
</tr>
<tr>
<td>• Diminished ability to think or concentrate nearly every day</td>
</tr>
<tr>
<td>• Recurrent thoughts of death or suicide, a suicide attempt, or suicidal plans</td>
</tr>
<tr>
<td>b. Marked impairment in occupation, social activities, relationships, or need to hospitalize</td>
</tr>
<tr>
<td>c. Not directly due to a substance or medical disorder or preavention</td>
</tr>
</tbody>
</table>
Table 2: Subtypes of major depression disorder (MDE)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Features</th>
<th>Treatment</th>
<th>Prognosis/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotic</td>
<td>Hallucinations</td>
<td>Antipsychotic + Antidepressant</td>
<td>Recurrent usual psychotic</td>
</tr>
<tr>
<td></td>
<td>Delusions</td>
<td>ECT</td>
<td>Runs in families</td>
</tr>
<tr>
<td></td>
<td>Anhedonia</td>
<td>Antidepressants</td>
<td>Consider maintenance Rx</td>
</tr>
<tr>
<td>Melancholic</td>
<td>Unreactive</td>
<td>ECT</td>
<td>Older patients</td>
</tr>
<tr>
<td></td>
<td>Diurnal mood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical</td>
<td>Reactive</td>
<td>MAOIs may be better than TCA</td>
<td>More common in younger</td>
</tr>
<tr>
<td></td>
<td>Overeating</td>
<td>SSRIs ??best</td>
<td>Often considered “lazy”</td>
</tr>
<tr>
<td></td>
<td>Oversleeping</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rejection sensit.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leaden limbs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winter</td>
<td>Fall- onset</td>
<td>Bright light Rx</td>
<td>Recurrent</td>
</tr>
<tr>
<td></td>
<td>Spring-offset</td>
<td>? Antidepressants</td>
<td>Both UP &amp; BP forms</td>
</tr>
<tr>
<td></td>
<td>Annual, recurrent</td>
<td></td>
<td>Same time every year</td>
</tr>
<tr>
<td></td>
<td>Non-equatorial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-Partum</td>
<td>Acute onset</td>
<td>Hospitalize</td>
<td>50% recurrence</td>
</tr>
<tr>
<td></td>
<td>Severe, labile mood</td>
<td></td>
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</tbody>
</table>

Episodes of major depression disorder can be further characterized, for example, as (a) Psychotic or delusional, (b) Melancholic, (c) atypical, (d) seasonal or seasonal affective disorder (SAD), typically a depression occurring during the fall and winter, and (e) postpartum depression (PDD) (Table 2). Without going into a detailed description of all the subtypes of mood disorders, Seasonal Affective Disorder (SAD), occurs at the higher latitudes in both hemispheres, usually in the late fall or early winter. It is usually an atypical depression, with hypersomnia, hyperphagia, psychomotor retardation, and social withdrawal; in the spring it typically remits spontaneously, often with a period of mania or hypomania. Interestingly, the winter depressions can be prevented or treated with exposure to bright lights.

Several other possible mood disorders have been identified in the DSM-IV classification as Depressive Disorder Not Otherwise Specified (NOS). These include: (a) Premenstrual. Several other possible mood disorders have been identified in the DSM-IV classification as Depressive Disorder Not Otherwise Specified (NOS). These include: (a) Premenstrual Dysphoric Disorder, characterized by depressed mood, anxiety, affective lability, and marked disability occurring during the week or two
before the onset of
menses, (b) Minor
Depressive Disorder,
characterized by one or
more periods of
Depression lasting at least
two weeks with fewer
symptoms (more than
2 but less than 5) and less
psychosocial impairment
than MDD, (c) Recurrent
Brief Depressive
Disorder, characterized
by brief episodes lasting
between 2 to 14 days at a
time, monthly for 12
months, of full MDD
symptoms (except for
duration); it is not associated
with menstrual cycles and is found equally in men and
women, and (d)
Postpsychotic Depressive
Disorder of Schizophrenia,
an episode of MDD
occurring during the
residual phase of
schizophrenia.

Dysthymia is
essentially a chronic, mild
depressive disorder. (Table
3) Mild in this context,
however, means that the
patient does not meet the full
diagnostic criteria of MDD.
It does not mean that
dysthymia is less severe
than MDD. In reality, many
patients with dysthymia

### Table 3. Abbreviated DSM-IV Criteria for Dysthymia

a. Depressed mood most of the day, for more days than not, for at
least 2 years. In children or adolescents, mood can be irritable and at
least 1 year.

b. Two or more symptoms:
   - poor appetite or overeating
   - insomnia or hypersomnia
   - low energy or fatigue
   - low self esteem
   - poor concentration, indecisiveness
   - hopelessness

c. Never without symptoms for 2 years (1 year in children or
adolescents)

d. No MDD during the 1st 2 years of the disorder

e. No history of mania, hypomania, cyclothymia, chronic psychosis

f. Not due to a medical disorder or substance

### Table 4. Abbreviated DSM IV Diagnostic Criteria for Manic Episode

a. A distinct period of abnormally and persistently elevated, or elevated
mood for at least a week

b. At least 3 of the following (or 4 if only irritable mood):
   - Inflated self-esteem or grandiosity
   - Decreased need for sleep
   - More talkative than normal or increased pressure to talk
   - Flight of ideas or racing thoughts
   - Distractibility
   - Increased goal directed behavior (socially, work, school, sexual) or
psychomotor agitation
   - Excessive involvement in pleasurable activities which have high
potential for painful consequences

c. Marked impairment in occupational functioning, usual social
activities, relationships or need for hospitalization
have more impairment in social, occupational, emotional, and physical areas than do patients with MDD. In addition, many patients eventually develop MDD or co-morbid alcohol, substance abuse, or personality disorders. For example, if MDD develops, it is called double-depression. If dysthymia begins during childhood or adolescence, the long-term effect on psychosocial development can be severe. The lifetime prevalence of Dysthymia is estimated to be about 6%.

Many clinical features of mania are opposite those of major depression (Table 4). It is characterized by an elevated and expansive mood, grandiosity, rushing thoughts, rapid speech, increased physical activity, and decreased need for sleep.

A less severe form of mania is distinguished and called hypomania. It is characterized by a distinctly elevated mood and other manic-like signs, but is not severe enough to cause marked impairment or require hospitalization. Hypomania may contribute to productivity and creativity in the arts, politics, business, and other activities.

Mania and hypomania rarely occur in individuals without a lifetime history of an episode of major depression; isolated mania or hypomania is very rare if patients are followed over time. Thus, patients who experience MDEs with no history of mania have Unipolar Disorder (or Major Depressive Disorder [MDD]) while patients who experience both MDEs and manic or hypomanic episodes suffer from Bipolar Disorder. Based upon the differences between mania and hypomania, two forms of severe cycling mood disorder are defined, Bipolar I (manic episodes) and Bipolar II (hypomanic episodes). In recent years, two other subgroups of bipolar disorder have been recognized as particularly difficult to treat: mixed states, characterized by simultaneous mixture of depressive and manic (or hypomanic) signs and symptoms, and rapid cycling bipolar disorder, defined as at least four episodes of mood disorder in a 12 month period of time.

Unipolar and bipolar disorders differ from each other in many clinical, demographic, and treatment characteristics (Table 5). Bipolar disorder is less common but, in general, more severe than unipolar disorder. It is estimated that the average woman with Bipolar Disorder spends 12 years in florid episodes, loses 14 years of a productive career, and dies 9 years earlier than expected. It has been estimated that about 15-20% of patients with a history of major depression or bipolar disorder will eventually commit suicide.

Cyclothymia, like Dysthymia, is a chronic mood disorder, a form of recurrent, cycling mood disorder characterized by a two year history with numerous episodes of hypomania depressive symptoms which do not meet diagnostic criteria for MDD. Both
can be continuous or intermittent and relatively incapacitating. The lifetime prevalence of Cyclothymia is about 0.4-1.0%.

While not yet a formal psychiatric diagnosis, Subsyndromal Depression has been proposed and has tentatively been defined by at least 2 or more symptoms lasting at least 2 weeks without meeting diagnostic criteria for minor depression, dysthymia, or MDD. The arguments for formally recognizing, studying, and treating these minor disorders are that they are associated with significant impairment, dysfunction, and dysphoria, that these patients over utilize general medical services, that they are probably at high risk for developing more serious episodes of mood disorder, and that they may respond to treatment.

II. Epidemiology

The incidence of new cases of depression are estimated to be about 1.6% per year in the general population. This estimate includes both recurrent episodes and first time cases in individuals who were not affected at the beginning of the year. In individuals who have never had depression before, the annual incidence is estimated to be about 0.43% in men and 0.76% in women. The public health importance of depression is reflected in the lifetime probability of an episode of depression, which is approximately 27% in men and 45% in women. Whether or not the incidence or prevalence of mood disorders has changed over time is a matter of current controversy. Some research has suggested that the risk of major depression in Western

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Bipolar (BP)</th>
<th>Unipolar (UP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Typical Characteristics</td>
<td>M=F</td>
<td>F&gt;M</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Teens-30s</td>
<td>30s-50s</td>
</tr>
<tr>
<td>Race</td>
<td>Blacks=Whites</td>
<td>Blacks&lt;Whites</td>
</tr>
<tr>
<td>Lifetime Prevalence</td>
<td>BPI 0.5-1.8%</td>
<td>BPII 0.5%</td>
</tr>
<tr>
<td>Socioeconomic Status</td>
<td>Higher</td>
<td>Men 5-12%</td>
</tr>
<tr>
<td>Family History</td>
<td>1BP, 1UP</td>
<td>Females 10-25%</td>
</tr>
<tr>
<td>Stressful life events</td>
<td>? Normal rates</td>
<td>Lower</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics of Depressive Episodes</th>
<th>Bipolar (BP)</th>
<th>? Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-partum disorders</td>
<td>Higher</td>
<td>Fewer</td>
</tr>
<tr>
<td>Number of Episodes</td>
<td>Higher</td>
<td>3-12 months</td>
</tr>
<tr>
<td>Duration of episodes</td>
<td>3-6 months</td>
<td>Agitation</td>
</tr>
<tr>
<td>Psychomotor activity</td>
<td>Retardation</td>
<td>?&gt;1 Duration</td>
</tr>
<tr>
<td>Sleep</td>
<td>?&gt;1 Duration</td>
<td>Antidepressant</td>
</tr>
<tr>
<td>Antidepressants (ADs)</td>
<td>Can induce mania</td>
<td>Ineffective alone</td>
</tr>
<tr>
<td>Lithium carbonate</td>
<td>Antidepressant</td>
<td>Potentiates</td>
</tr>
<tr>
<td>ADs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Europe, New Zealand, Canada, and the United States has increased in individuals born after World War II compared with older individuals born before the war. This phenomena is called the age-cohort effect. Among the factors supporting this claim are (a) progressively younger age of onset of depressive disorders in epidemiological studies, (b) increased rates of suicide in younger populations but decreased rates of suicide in older populations compared with 30 years ago.

As mentioned earlier, Major Depressive Disorder is more common in women than men. Although the gender ratio is even in patients with bipolar disorder, affected women experience more depressive episodes while affected men experience more manic episodes. Epidemiological surveys in children and adolescents show that depressive symptoms increase among young women around the ages of 12-13 but remain constant or even decrease slightly among young men during the prepubertal and adolescent period.

Mood disorders may also arise and may even result from medical disorders, alcoholism, and substance abuse. Symptoms of depression occur in 12-36% of patients with general medical conditions. Depressive symptoms, for example, are common among patients suffering from diabetes, stroke, coronary artery disease, Parkinson’s disease, Huntington’s Chorea, or pancreatic cancer. It is also prevalent in persons receiving steroids, drugs which interfere with certain brain neurotransmitters (norepinephrine or serotonin), in alcoholics during and after alcoholic binges, and in substance abusers during

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### Table 6. Medical and medicinal confounds of psychiatric disorders

<table>
<thead>
<tr>
<th>1. Concurrent medications may:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause depression (i.e., reserpine)</td>
</tr>
<tr>
<td>Change blood levels of drugs</td>
</tr>
<tr>
<td>Increase side effects of psychotrophic drugs</td>
</tr>
<tr>
<td>Block effects of antidepressant drugs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Concurrent illnesses may:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause depression (i.e., CA of pancreas, hypothyroidism, early Alzheimer’s, strokes)</td>
</tr>
<tr>
<td>Alter efficacy of psychiatric medications</td>
</tr>
<tr>
<td>Change metabolism of antidepressants (i.e., renal or hepatic disease)</td>
</tr>
<tr>
<td>Impair ability to comply with treatment (i.e., no insurance, income, physical activity, etc)</td>
</tr>
<tr>
<td>Increase demoralization, chronicity, disability</td>
</tr>
<tr>
<td>Require simplified medication dosing schedules</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Concurrent non-mood psychiatric disorders may:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase risk of depression (i.e., alcoholism, cocaine, schizophrenia, borderline disorder, OCD, etc)</td>
</tr>
<tr>
<td>Change medications (i.e., avoid BZs in alcoholism)</td>
</tr>
<tr>
<td>Impaired ability to comply with treatment</td>
</tr>
<tr>
<td>Worsen prognosis</td>
</tr>
<tr>
<td>Alter treatment plan</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Other issues associated with other physical conditions, medications, or other disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging may slow metabolism of drugs (i.e., long-half life Benzodiazepines)</td>
</tr>
<tr>
<td>Reduce resources (i.e., transportation, support of spouse, money, etc)</td>
</tr>
</tbody>
</table>
withdrawal from cocaine or amphetamine. The Depressive Guideline Panel suggested four possible relationships between depression and medical conditions. (Table 6)

Finally, many patients with mood disorders also suffer from other psychiatric (comorbid) diagnoses, such as anxiety disorders (panic disorder, generalized anxiety disorders, post traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), somatization disorder, eating disorders, alcoholism and substance abuse, Borderline Personality Disorder, and Adjustment Disorders. Comorbidity is very common. For example, formal diagnostic criteria for substance or alcohol abuse are met in about one-third of patients with major depressive disorder and about three-fifths of patients with mania. Many unanswered questions remain about the reasons contributing to comorbidity. Are these independent disorders with separate genetic and etiological mechanisms? Do the different disorders, if that is what they are, share common pathophysiological mechanisms? How does comorbidity affect natural course and optimal treatment?

III. Natural course

Several prospective epidemiological studies suggest that one or more prodromal symptoms of depression are risk factors for the later onset of an episode of major depression. Sleep disturbances, such as two weeks or more of insomnia or hypersomnia or both, are particularly robust risk factors. The report of insomnia increased the risk of depression within 3.5 years by twofold in young individuals who had never previously met diagnostic criteria for depression. Other prospective risk factors for later onset of a major depressive disorder include psychomotor retardation or suicidal ideation.

Depression is a chronic, relapsing, debilitating disorder with many unrecognized costs. (Table 7) It is thought that untreated episodes last between 6 and 24 months. Many patients never fully recover but develop dysthymia. Even in patients who are successfully treated, many patients experience a remission (euthymia

<table>
<thead>
<tr>
<th>Morbidity &amp; Mortality of mood disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Suicidality (depression)</td>
</tr>
<tr>
<td>- Marital &amp; interpersonal difficulties</td>
</tr>
<tr>
<td>- Educational &amp; professional failure</td>
</tr>
<tr>
<td>- Substance abuse</td>
</tr>
<tr>
<td>- Accidents</td>
</tr>
<tr>
<td>- Secondary medical problems</td>
</tr>
<tr>
<td>- Recurrence, relapse, chronicity</td>
</tr>
<tr>
<td>- ~ 50% recurrence after 1 MDE</td>
</tr>
<tr>
<td>- Shortened life expectancy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effects on society</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Dysfunctional families</td>
</tr>
<tr>
<td>- Medical &amp; welfare costs</td>
</tr>
<tr>
<td>- Decreased productivity at work</td>
</tr>
<tr>
<td>- Absenteeism</td>
</tr>
<tr>
<td>- Job-related accidents</td>
</tr>
</tbody>
</table>
relapse (loss of euthymia during remission), and recurrence (depression occurring during recovery).

With adequate pharmacological treatment, about two-thirds of depressed patients respond, usually defined as a 50% or greater improvement in mood ratings, such as the Hamilton Rating Scale for Depression (HRSD). Nevertheless, about one third of patients treated with placebo in double-blind clinical trials also recover. In current practice guidelines, patients should be continued on antidepressant treatment for about a year after recovery if it is their first episode of depression. For patients who have experienced several episodes of depression, the practice guidelines are still evolving. In patients with recurrent major depressive disorder who have been successfully treated, rates of recurrence appear to be high in patients who are switched to placebo compared with those who remain on active medication. The morbidity associated with subsyndromal depressive symptoms has also been shown in individuals in primary care settings. Even when controlling statistically for physical health status in primary care settings, patients with depressive symptoms, whether or not they met full diagnostic criteria for depression, perceived their current health to be worse and their levels of pain to be greater than those without depressive symptoms. Furthermore, poor functioning was worse or comparable in those with depressive symptoms than in patients with any one of eight major medical disorders. For example, the number of bed days per month was greater in patients with depression than in patients with hypertension, diabetes, or arthritis. Other studies suggest that depression is a negative prognostic risk factor in a variety of medical disorders, for example, poor recovery from a myocardial infarction.

Despite the greater prevalence of depression in women compared with men, the rates of completed suicide are higher in men than in women. (Table 8) Women, however,
do make more suicide attempts than men. The typical risk factors for suicide include middle-aged or elderly white males, unemployed, single or divorced, a family history of suicide, and a history of prior suicide ideation or attempts, mood disorders, schizophrenia, substance abuse and alcoholism, or chronic physical illness. Low concentrations of a metabolite of serotonin in cerebral spinal fluid (CSF) has been shown in several studies to be associated with increased risk of a completed suicide in longitudinal studies in depressed patients.

IV. Suspected causes

I. Genetic factors

Genetic factors of mood disorders has been mentioned from at least the time of Hippocrates. Many studies during the 20th century have confirmed and extended the earlier impression that genetic factors, rather than purely family factors, increase the risk of mood disorder in the offspring and first-degree relatives of a proband with mood disorder. Moreover, the findings suggest that the genetic factors are different and stronger in bipolar disorder than in unipolar disorder.

Controlled family studies of bipolar probands indicate that the risk of bipolar disorder in their first degree relatives was increased by about sevenfold (with a range of 3.7-17.7 times) compared with control subjects. The absolute rates of bipolar disorder were between 3.8 to 6.8% in the relatives of the probands, which is considerably higher than that of the general population of controls (about 1%). The rates of unipolar disorder were also increased among the relatives of bipolar probands by about twofold compared with the relatives of controls, which is consistent with epidemiological evidence that unipolar disorder is more prevalent than bipolar disorder. The data support the familial nature of bipolar disorder but do not prove that it is genetic. These studies do not distinguish between nature or nurture.

In controlled family studies of probands with major depressive disorder, the relative risk of major depressive disorder was increased by about twofold, while the rates of bipolar disorder are minimally increased if at all, in the first degree relatives of probands compared with relatives of non-affected controls.

Twin studies have also suggested that mood disorders are strongly heritable, more so in bipolar disorder than in major depressive disorder. For example, in a review of five twin studies of bipolar disorders, the average concordance rate was 60% for monozygotic twins and 12% for dizygotic twins, a fivefold increased relative risk. In contrast, in two
twin studies of major depressive disorder, the comparable relative increased risk was 1.9 and 1.2 fold. Furthermore, twin studies also suggest that bipolar and unipolar mood disorders breed pure, that is, bipolar index twins are more likely to have an affected twin with bipolar compared with unipolar disorder and vice versa.

Finally, adoption studies, while few in number, suggest that genetic factors are involved in the causation of mood disorders, although they also suggest a contribution from common environmental factors in the expression of mood disorders.

With the advent of modern molecular genetic methods, investigators have applied a whole new, powerful tool to identify genetic markers and, hopefully, specific genes which are involved in the etiology and treatment of mood disorders. Some of the early results, while exciting, proved to be premature. One of the first of these disappointments, for example, came with the dramatic report of a linkage between bipolar disorder and the Harvey-ras oncogene on the short arm of Chromosome 11. With the addition of other extensions of the family, the finding was subsequently not replicated. Another sobering example of non-replication concerns reports of a genetic marker on chromosome X. Bipolar disorder has been linked in the past with classical markers on the X-chromosome, for example, with color blindness, the Xg blood group, and glucose-6-phosphate dehydrogenase deficiency (G6PD). One of the most convincing reports linked bipolar disorder to color blindness and G6PD in several large Israel families, but later studies in North America failed to confirm these findings. As in the Amish study, genetic heterogeneity could be blamed for the failure to replicate.

Attempts to map genes for psychiatric disorders to specific chromosome locations have been exceedingly frustrating, even using the tools of modern molecular genetics. As of April, 1996, Risch and Botstein identified 19 published studies reporting positive evidence for linkage of bipolar disorder with 14 defined chromosomal locations. None of the specific regions has been convincingly replicated. They concluded that the genetic mechanisms underlying bipolar disorder are more complicated that previously thought. As they and others have repeatedly stated, many factors increase the complexity of the genetics of mood disorders. Among these factors are reduced penetrance, which occurs when the gene is present but the disorder is not. A second factor is the presence of phenocopies, when the disease is present but the gene is not, that is, a non-genetic form of the disorder. Another problem is variable expressivity, in which the same gene expresses itself differently in different individuals, for example, the possibility that a single gene produces bipolar disorder in one person and unipolar disorder in his sister. A very difficult problem is genetic heterogeneity, in which multiple genes are involved. For example, several different genes could exist which cause the same phenotypical clinical
disorder. Alternatively, in *polygenic models*, several genes must be expressed simultaneously in the same individual to produce the disorder.

Nevertheless, the news is not hopeless. It is much too early to be totally pessimistic about the ultimate utility of the current genetic approaches. Chromosome 18 has now been linked by at least three groups to bipolar disorder; the locations of the genetic markers, however, are not universally identical. Other promising sites are located on Chromosomes 5p, 6, 11p, 13, 15, 21q, 22, and even the X chromosome.

Further research is clearly needed. The difficulties to convincingly establish a specific genetic mechanism for mood disorders should not be minimized. The diagnostic validity of specific mood disorders and their subtypes is still evolving with clinical and scientific experience, especially in light of the variability of symptoms, of the natural history of the disorder, of treatment response, and of comorbid conditions.

2. Biochemical pathophysiological mechanisms in mood disorders

Several key pharmacological treatments were discovered by the late 1950s: lithium for bipolar disorder, phenothiazines for psychosis, and tricyclic compounds and monoamine oxidase inhibitors for depression. These observations had at least three major impacts on psychiatry in general, and mood disorders in particular. First, medications became the major form of treatment for serious mood disorders. Secondly, these discoveries stimulated clinicians to become more scientifically sophisticated. This has lead to more scientifically credible methods of diagnosis, ratings, and clinical trials. It also stimulated the development of the field of biological psychiatry, with its interest in the role of biological factors in the etiology, pathophysiology, and treatment of psychiatric disorders. Thirdly, it stimulated basic scientists and pharmacologists to study the brain, how it works, and how drugs affect it. For example, Axelrod and others established many of the current principles about chemical neurotransmission in uncovering how antidepressants and lithium work in the brain.

Since the mid-1960s, study of biogenic amines has been a major focus of research on the pathophysiology and treatment of mood disorders. Based on the early observations that many antidepressants potentiated the effects of a specific class of neurotransmitters, the biogenic amines (in particular, norepinephrine, serotonin, and possibly, dopamine), the aminergic theory of mood disorders was formulated. It basically postulated two related but necessarily connected hypotheses: (a) depression was associated with a relative deficiency of monoaminergic neurotransmission and (b) the mechanism of action of antidepressants involves the potentiation biogenic amine neurotransmission.
Consistent with the monoamine hypothesis of mood disorders, early studies suggested that the tricyclic antidepressants (TCAs) potentiated neurotransmission by inhibiting reuptake of the neurotransmitter into the presynaptic neuron, thereby maintaining an elevated presence in the synaptic cleft between the pre- and post-synaptic neurons. Examples of the TCAs included amitriptyline, imipramine, and nortriptyline. (Table 9) In addition, another class of antidepressants, the monoamine oxidase inhibitors (MAOIs), worked by inhibiting the enzyme which metabolized the monoamine neurotransmitters. Examples of MAOIs included phenelzine and tranylcypromine. In later years, new classes of antidepressants have been discovered, including the selective serotonin reuptake inhibitors or serotonin specific reuptake inhibitors (SSRIs), which have become very popular in recent years. Fluoxetine, for example, now has annual sales of over $2 billion. Sertraline is not that far behind. Other newer drugs include bupropion; the mechanisms of action are largely unknown but it may inhibit reuptake of both dopamine and norepinephrine. Nefazodone, which shares some common mechanisms of action with trazadone, is both a 5HT-2 inhibitor and a SSRI. Venlafaxine appears to be a mixed serotonin-norepinephrine reuptake inhibitor.

Although many antidepressant medications probably affect monoamines in some way, the original monoamine hypothesis for the pathophysiology of mood disorders was clearly too simplistic and apparently wrong in many important respects. No convincing or diagnostically specific abnormality of monoamines has yet been established in patients with mood disorders. (Table 10) For example, as mentioned earlier, levels of 5-hydroxyindoleacetic acid (5-HIAA) are low in a subgroup of depressed patients who are

**Table 9. Examples of Common Antidepressants**

<table>
<thead>
<tr>
<th>Tricyclic Antidepressants (TCAs)</th>
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</thead>
<tbody>
<tr>
<td>Amitriptyline (Elavil)</td>
</tr>
<tr>
<td>Imipramine (Tofranil)</td>
</tr>
<tr>
<td>Nortriptyline (Pamelar)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monoamine Oxidase Inhibitors (MAOIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenelzine (Nardil)</td>
</tr>
<tr>
<td>Tranylcypromine (Parnate)</td>
</tr>
<tr>
<td>Deprenyl (Eldepryl)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serotonin Specific Reuptake Inhibitors (SSRIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine (Prozac)</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Types of Antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine (Effexor)</td>
</tr>
<tr>
<td>Bupropion (Wellbutrin)</td>
</tr>
<tr>
<td>Trazadone (Desyrel)</td>
</tr>
<tr>
<td>Nefazodone (Serzone)</td>
</tr>
<tr>
<td>Clomipramine (Anafranil)</td>
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</tbody>
</table>

**Table 10. Biochemical Abnormalities Reported in Depression**

<table>
<thead>
<tr>
<th>Norepinephrine System</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1-adrenergic binding in platelets</td>
</tr>
<tr>
<td>Blunted GH response to clonidine</td>
</tr>
<tr>
<td>β-Adrenergic receptors in postmortem brain of suicide victims</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serotonin System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma tryptophan</td>
</tr>
<tr>
<td>5-HIAA in CSF</td>
</tr>
<tr>
<td>5HT transporter binding in brain &amp; platelets</td>
</tr>
<tr>
<td>Prolactin response to fenfluramine</td>
</tr>
</tbody>
</table>

particularly prone to attempt suicide by violent methods, such as guns or jumping from high places. At the same time, however, low CSF 5HIAA has also been implicated in other psychiatric disorders, such as non-depressed individuals with poor impulse control or outbursts of violence, for example, antisocial personality disorders, arsonists, and borderline personality with self-destructive behavior. In addition, some potent monoamine reuptake inhibitors are not good antidepressants. For example, cocaine. Some antidepressants are not potent monoamine reuptake inhibitors, for example, iprindole and mianserin. Finally, although the classic antidepressants affect monoamine activity immediately, the antidepressant benefits are delayed for the first 1-6 weeks of treatment.

Because of the limitations of the early monoamine hypothesis, many investigators now hypothesize that depression results from or is associated with abnormal function of the receptors on which monamines act. They postulate, as one example, that postsynaptic serotonin receptors are upregulated in depression, possibly as a result of insufficient serotonin release from presynaptic stores into the synaptic cleft. According to this theory, since the postsynaptic neurons receive abnormally low amounts of neurotransmitter, the postsynaptic neuron increases the number or affinity of postsynaptic receptors. While evidence for this hypothesis is sparse, several studies have reported upregulated 5HT receptors in frontal cortex collected during autopsies from suicide victims. Studies in animals also suggest that receptors downregulate after several weeks of administration of antidepressants. According to this theory, a reuptake inhibitor or a MAOI increases and prolongs the presence of the neurotransmitter in the synaptic cleft; this, in turn, leads to downregulation of the post-synaptic receptors.

Because of the intense interest in how drugs affect receptors, a great deal has been learned recently about receptors. Using both traditional pharmacological strategies and modern molecular techniques, basic neuropharmacologists have identified families of receptors for each neurotransmitter. At last count, for example, about 15 receptors subtypes for serotonin had been identified. Numerous subclasses of receptors have been found for noradrenergic alpha and beta receptors, for the classical muscarinic and nicotinic cholinergic receptors, and for dopamine receptors. Understanding how receptors operate is fundamental to current concepts about pharmacodynamics and the pathophysiology of psychiatric disorders. Receptors are located not only at postsynaptic but at presynaptic sites in the many different areas of the brain which receive monoaminergic terminals originating in the brainstem. Furthermore, different receptors are found on the dendrites of the monaminergic neurons in the brainstem and on other neurons which are in feedback relationships with these neurons. Since receptors can be either inhibitory or excitatory, a neurotransmitter can either inhibit or excite a cell depending upon the type of receptor. If we think of the neurotransmitter as a master key, it can act on a whole family of locks,
opening some, closing others, and perhaps either opening or closing a specific lock depending upon the circumstances.

Receptors are now classified according to two different schemes, first, the specific neurotransmitter to which they respond, secondly, the two superfamilies of receptors to which they belong. One superfamily of receptors is called the G-protein linked receptor superfamily. All the receptors in this family contain a seven transmembrane region (the protein components of the receptor cross the membrane between the inside and outside of the cell seven times) and are linked to a G-protein and use a second messenger to transmit the message to the cell machinery within the cell which does the work. The second superfamily of receptors are called the ligand-gated ion channel receptors. The receptors contain five transmembrane regions, which act as molecular gatekeepers regulating the passage of ions (for example, sodium, potassium, chlorine) affecting the excitability of the cell. Unlike the first superfamily, the second superfamily is influenced by many different neurotransmitters or drugs, which act upon the multiple receptor subtypes affecting the ion channel at the core of the receptor. The G-protein-linked receptors appear to mediate "slow" responses, while the ligand-link receptors appear to mediate "fast" responses.

Not only has the emphasis on receptors helped to explain and predict the therapeutic effects of antidepressants but they have opened up new ways of understanding and preventing side effects. Few if any drugs affect only one receptor. For example, many of the tricyclic antidepressants block alpha-1 adrenergic receptors, thereby causing orthostatic hypotension and dizziness. Likewise, they block cholinergic, muscarinic receptors, which are associated with dry mouth, urinary retention, constipation, and blurry vision, and H1 histamine receptors, which cause weight gain and sedation.

The discovery of the SSRIs was, therefore, not only a therapeutic advance but a conceptual advance. The drugs were largely devoid of the noradrenergic, adrenergic, muscarinic, and histaminergic side effects associated with the tricyclic antidepressants. Because side effects were reduced, compliance by patients was increased and dosing decisions by doctors was decreased. Furthermore, these drugs had clinically significant antidepressant effects although they were devoid of noradrenergic reuptake properties. Moreover, they were found to be more potent in treating obsessive-compulsive disorder, panic disorder, and social phobia than the tricyclic antidepressants. None of the newer drugs, however, are clearly better antidepressants than the TCAs or the MAOIs, but they have fewer side effects, at least those associated with the older drugs, such as weight gain, orthostatic hypotension, sedation, and potential lethality in overdose. SSRIs do, however, have side effects, including GI upset, insomnia, and sexual dysfunction.
Consistent with the key role of serotonin in the mechanisms of the antidepressant effects of SSRIs, the beneficial effect of several serotonergically-active antidepressants have been reversed temporarily by experimental manipulations designed to decrease central serotonin. These interventions include both (a) administration of para-chloro-phenylalanine (pCPA), an inhibitor of tryptophan hydroxylase, and (b) a challenge with a tryptophan-free amino acid drink (TFD) or "cocktail" which has been shown to significantly reduce plasma tryptophan levels in humans and brain serotonin levels in animals. When administered to euthymic patients treated with SSRIs or MAOIs, the TFD induced a clinical relapse in about half of the patients. Relapse lasted about 12-18 hours, ending after subjects started eating a normal, tryptophan containing diet.

In contrast, euthymic patients treated with noradrenergically active drugs such as desipramine or nortriptyline were not affected when challenged with the TFD. Nevertheless, administration of a drug which inhibits synthesis of catecholeamines, alphamethyl-para-tyrosine (AMPT), reversed the antidepressant effects of noradrenergic reuptake inhibitors, such as desipramine and nortriptyline, in euthymic patients with a history of depression.

Rapid reduction of plasma tryptophan levels by administration of the TFD, but not by gradual reduction with a 10-day restricted tryptophan diet, has been reported to induce depressive symptoms in some but not all randomly selected normal controls. Of interest, the TFD challenge did not increase depressive ratings in depressed drug-free patients, as opposed to euthymic drug-treated patients, possibly because the central serotonergic neurotransmission was already decreased. Of considerable interest, the TFD was reported to induce depressive symptoms in nonaffected subjects who came from multigeneration families positive for mood disorders but not in controls with no family history of mood disorder. These preliminary results suggest that the TFD may uncover a genetic predisposition to a mood disorder in unaffected individuals at risk.

Since SSRIs are clinically effective in obsessive-compulsive disorder and panic disorder in addition to depression, it may be that the site of action is specific to diagnosis. SSRIs probably downregulate serotonergic, somatodendritic autoreceptors, thereby disinhibiting serotonergic neurons originating in the raphe nuclei. If this hypothesis is true, it is likely that increased serotonergic input occurs throughout all the projection fields. It may be that the prefrontal cortex or limbic system is important for the antidepressant benefits, the basal ganglia for the OCD benefits, and the hippocampus for the panic disorder benefits.
Another weakness of the original biogenic amine hypotheses of mood disorders was the implication that only one neurotransmitter abnormality was involved in the pathophysiology of these disorders. With their complex cluster of symptoms, the mood disorders must involve many neural systems in the brain involved in the regulation of mood, thinking, and vegetative functions. One early theoretical alternative hypothesis, the cholinergic-aminergic imbalance hypothesis, suggested that depression was associated with an increased ratio of cholinergic neurotransmission, compared to that of catecholamine and serotonergic systems. This hypothesis was supported by reports of (a) antimanic effects of cholinomimetic drugs; (b) intensification of depressive-like states by cholinomimetic drugs in both normals and depressed patients; (c) cholinergic mediation of biological markers of depression, such as short REM latency and hypothalamic-pituitary-adrenal hyperactivity (HPA axis) in depression (see below); (e) More recently, the possible role of cholinergic mechanisms in depression has been broadened to include central nicotinic in addition to muscarinic receptor mechanisms, largely because smoking is so prominent in depressed patients and so difficult to quit.

In addition to the antidepressants, another very important class of drugs has been developed over the past 40 some years, the so-called mood stabilizers. (Table 11) These drugs are particularly useful in long-term prevention of recurrent episodes of depression, mania, or hypomania in patients with bipolar disorders, although they also have antimanic effects. Lithium has mild-to-moderate antidepressant effects in patients with bipolar disorder and, unlike the standard antidepressant medications, does not induce a switch from depression to mania. By itself alone, lithium probably has no inherent antidepressant effect on major depressive disorder, although it does potentiate the antidepressant effects of antidepressants when given concomitantly. Little is currently known about the mechanisms of action of the mood stabilizers. One theory is that repeated episodes of mania and, perhaps depression, "kindle" the limbic system, that is, sensitize the neural circuits involved in episodes of mood disorder. Each episode thereby increases the likelihood and reduces the latency to the next episode. Anticonvulsant medications may prevent or reduce "kindling" in recurrent mood disorders.

In view of the kindling model and the use of anticonvulsant medications in mood disorders, it may seem curious the electro-convulsive therapy (ECT) remains the "gold standard" for the treatment of mood disorders, especially for depression but, at times, for severe unresponsive mania. In severe depression, ECT is usually better than antidepressant drugs, with about 90% versus 70% success rates. Nevertheless, ECT is

<table>
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<th>Table 11. The Mood Stabilizers</th>
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<tbody>
<tr>
<td>Lithium (Eskalith)</td>
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<tr>
<td>Carbamazepine (Tegretol)</td>
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<tr>
<td>Valproate (Depakene, Depakote)</td>
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generally reserved for patients with severe or suicidal depression which has failed to respond to adequate trials of antidepressant medications. The mechanisms of ECT remain basically unknown.

While this brief review has stressed the role of the biogenic amines, particularly serotonin, in the pathophysiology and pharmacological treatment of mood disorders, many other neurotransmitters have also been implicated in the mood disorders, including GABA, aspartate, glycine, and histamine. No reader should forget how little we know about the nervous system. About 40-50,000 genes are estimated to be specifically expressed in the brain. We only know of about a handful at this time. With the rapid advances promised by modern molecular neurobiology, we are at the threshold of major advances in neurobiology, which will revolutionize how we think about brain and behavior, mind and mental disorders, and pharmacology and psyche.

V. Biological mechanisms and correlates

1. Neuroendocrine and neuroimmune abnormalities in depression

Relationships between endocrinology and mood disorders have been suspected for a long time for several reasons. First, many patients with endocrine disorders experience psychiatric symptoms, for example, Cushing’s disease (associated with oversecretion of cortisol) has long been associated with changes in mood. Secondly, individuals receiving specific hormones may also experience mood disorders, for example, exogenously administered glucocorticoids and depression or mania. Thirdly, the limbic system in the brain apparently modulates both the emotions and the hypothalamus, which plays an important role in the regulation of hypothalamic-pituitary activity.

Table 12. Endocrine Abnormalities in Mood Disorders

<table>
<thead>
<tr>
<th>Increased Hypothalamic-Pituitary-Axis Activity</th>
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<tbody>
<tr>
<td>• Cortisol secretion (24 h urine, blood)</td>
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<tr>
<td>• CRH concentrations in CSF</td>
</tr>
<tr>
<td>• DST nonsuppression</td>
</tr>
<tr>
<td>• Enlarged pituitary and adrenal gland</td>
</tr>
<tr>
<td>• Blunted CRH challenge test</td>
</tr>
<tr>
<td>• CRH receptors in frontal cortex in suicide victims</td>
</tr>
<tr>
<td>• 5-HTP &amp; ACTH induced cortisol secretion</td>
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<table>
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<tr>
<th>Subclinical Hypothyroidism</th>
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</thead>
<tbody>
<tr>
<td>• Decreased plasma TSH &amp; thyroid hormone concentrations</td>
</tr>
<tr>
<td>• Blunted TRH challenge test</td>
</tr>
<tr>
<td>• Blunted ΔΔ TRH challenge test</td>
</tr>
<tr>
<td>• TRH in CSF</td>
</tr>
<tr>
<td>• Nocturnal TSH</td>
</tr>
<tr>
<td>• Antimicrosomal thyroid antibodies</td>
</tr>
<tr>
<td>• Antithyroid globulin antibodies</td>
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<table>
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<tr>
<th>Decreased Growth Hormone Secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Daytime GH secretion</td>
</tr>
<tr>
<td>• Blunted sleep related GH secretion</td>
</tr>
<tr>
<td>• GH response to GH-RH</td>
</tr>
<tr>
<td>• SRIF in CSF, apomorphine, clonidine</td>
</tr>
</tbody>
</table>
Some of the more endocrine abnormalities associated with mood disorders are briefly summarized (Table 12). Many clinical studies during the past 30 years have demonstrated hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis in patients with moderate to severe depression. This has been documented by measuring adrenal cortical steroids in 24-hour urine samples and round-the-clock blood samples for cortisol. Cortisol has long been regarded as a stress hormone, but it is hypersecreted in about half of patients with moderate to severe depression whether or not they are overtly stressed. It is secreted from the adrenal cortex in response to adreno-corticotropin hormone (ACTH), which is released by the pituitary. As would be expected, corticotropin-releasing-hormone (CRH)- which is liberated by the hypothalamus and acts on the pituitary to release ACTH- is elevated in the spinal fluid in patients with depression compared with normal controls. In addition to its trophic effects on hormone, CRH has receptors scattered throughout the limbic system and brainstem, especially near the locus ceruleus, the origin of the norepinephrine containing neurons in the brain. Thus, CRH probably acts as a neuromodulator in addition to stimulating release of pituitary ACTH.

Another method of assessing HPA hyperactivity is the dexamethasone suppression test (DST). Dexamethasone is a synthetic glucocorticoid. When it is given to normal subjects it exerts a negative feedback effect on the HPA axis, shutting down secretion of CRH, ACTH, and cortisol. When given to depressed patients, however, it suppresses cortisol secretion in only about half of the subjects, especially in older, melancholic, or psychotic patients. Like other biological markers which have been studied to date, the DST is not diagnostically specific.

Consistent with HPA hyperactivity, many patients with depression have enlarged pituitaries and adrenal glands on radiological imaging studies compared with normal controls. While depressed patients hypersecrete cortisol when challenged with exogenously administered ACTH, they hyposecrete ACTH when challenged with exogenously administered CRH. These later results suggest that CRH receptors in the pituitary are downregulated as a result of chronic hypersecretion of CRH by the hypothalamus.

Turning to the role of the hypothalamic-pituitary-thyroid (HPT) axis in mood disorders, clinicians have long observed abnormal changes in mood in patients suffering from either hypothyroidism or hyperthyroidism. Furthermore, small doses of triiodothyronine (Cytomel or $T_3$) potentiate the antidepressant effects of TCAs. Some studies, but not all, have shown that depressed patients have lower than normal levels of circulating thyroid hormones or thyroid stimulating hormone (TSH), which is released by the pituitary to stimulate release of thyroid hormones by the thyroid gland. Mild or
subclinical hypothyroidism is particularly common in bipolar patients, particularly rapid cycling bipolar patients.

As with the DST and the HPA in depression, the thyroid releasing hormone (TRH) test has been used to study thyroid function in depression. TRH is released by the hypothalamus and stimulates the release of TSH by the pituitary. When groups of depressed patients are compared with normal controls, they generally show diminished TSH release when challenged by exogenously administered TRH, or a blunted TRH test. Blunting has been reported in 20-70% of depressed patients, depending upon the specific methodologies and patient groups studied. Since TSH secretion is normally higher before bedtime (i.e. 11 pm) than after sleep (i.e. 8 am), some investigators have compared the TRH test at these two time points in depressed and normal control groups. The difference between the two tests in the same individual, called the ΔΔ TSH test, has generally been reported to be lower in the patients, suggesting an abnormality of the circadian system in depression. Nevertheless, the clinical and pathophysiological significance of the TSH test remains undetermined at this time. Again, it is not diagnostically specific. More research is still needed.

Although less well characterized in depressed patients, abnormalities of the hypothalamic-pituitary-growth hormone (HPGH) axis have been reported. Twenty-four hour total growth hormone secretion has been reported to be low in depression, apparently because sleep-related growth hormone secretion is blunted. While some studies have reported decreased concentrations of the hypothalamic trophic hormone, somatostatin (GHRIF), in CSF of depressed patients, other studies have not replicated this finding. Provocative challenge studies with drugs to release growth hormone, such as GHRIF, L-DOPA, desipramine, clonidine, and amphetamine, have also had mixed results.

While not as well studied as yet, neuroimmune abnormalities may be present in depressed patients. This supposition is suggested by studies in bereaved widows, who show low Natural Killer cell activity and reduced in vitro response to mitogen stimulation in bereavement. Similar findings have now been reported in depressed individuals. While the clinical significance of these immune abnormalities remains unknown, life expectancy in depressed patients is apparently reduced, even when controlling for the effects of suicide.

2. Sleep and chronobiological abnormalities

As mentioned earlier, complaints about sleep are common, if not the most common symptoms of depressed patients. Most patients complain of insomnia, with difficulties
falling asleep, maintaining sleep, and, especially, early morning awakenings. Coupled with the common complaint of worse mood in the morning than in the evening, the early morning awakening may indicate an abnormality of circadian regulation in depression. In addition, some patients report hypersomnia during depression, for example, patients with winter depression, "atypical" depression, and bipolar depression.

Objective sleep measures, including all-night polygraphic recordings of brain waves, eye movements, and muscle tone, as well as other physiological measures, show a constellation of sleep-related abnormalities in many, if not the majority of moderately to severely depressed patients. (Table 13) Consistent with their subjective complaints, depressed patients often have difficulty initiating and maintaining sleep. Perhaps of more interest, they show loss of the "deeper" stages of sleep, Stages 3&4 (Delta or high amplitude, low frequency EEG patterns), as well as a redistribution of REM sleep towards the beginning of sleep. The REM latency, the duration of time between the onset of sleep and the first REM period, has been reported to be short in dozens of studies around the world. The first REM period of the night is typically longer and has more ocular activity per minute of REM sleep (increased REM Density) in depressed patients compared with normal controls. In addition to abnormalities of sleep stage and architecture, these include "microarchitecture" sleep EEG anomalies, increased core body temperature, abnormal neuroendocrine secretion (increased cortisol and decreased testosterone, growth hormone, prolactin, and, possibly, melatonin secretion). In addition, whole brain and local cerebral glucose metabolic rate (LCGMR), as assessed by positron emission tomography (PET) with \(^{18}\)F-deoxyglucose (FDG), is increased during the first NonREM period in mildly-to-moderately depressed patients compared with normal controls. Loss of NonREM sleep and Stage 4 sleep are correlated with reduced natural killer cell activity in normal controls and depressed patients.

The objective sleep abnormalities generally tend to ameliorate with clinical improvement in depression. Nevertheless, certain abnormalities may persist, for example, loss of Delta sleep and short REM latency. Whether the persistence of these sleep

<table>
<thead>
<tr>
<th>Table 13. Sleep Related Abnormalities in Depression</th>
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<tbody>
<tr>
<td>$\text{Sleep Latency}$</td>
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<tr>
<td>$\text{REM Sleep Latency}$</td>
</tr>
<tr>
<td>$\text{Slow Wave Sleep (Stages 3&amp;4)}$</td>
</tr>
<tr>
<td>$\text{Low Frequency EEG}$</td>
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<tr>
<td>$\text{Delta sleep ratio}$</td>
</tr>
<tr>
<td>$\text{Fast frequency EEG in REM sleep}$</td>
</tr>
<tr>
<td>$\text{Intrahemispheric EEG coherence}$</td>
</tr>
<tr>
<td>$\text{Duration of first REM period}$</td>
</tr>
<tr>
<td>$\text{REM Density of first REM period}$</td>
</tr>
<tr>
<td>$\text{Blunted TSH, growth hormone}$</td>
</tr>
<tr>
<td>$\text{Blunted melatonin secretion}$</td>
</tr>
<tr>
<td>$\text{Testosterone secretion}$</td>
</tr>
<tr>
<td>$\text{Core body temperature}$</td>
</tr>
<tr>
<td>$\text{Cerebral glucose metabolism (NREM)}$</td>
</tr>
<tr>
<td>$\text{Cholinergic REM sleep induction}$</td>
</tr>
<tr>
<td>$\text{Clonidine induced REM suppression}$</td>
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abnormalities reflects subsyndromal disorders, dysthymia, minor depression, "scars," or state independent traits, remains to be determined.

The theoretical importance of sleep to the pathophysiology of depression is emphasized by the puzzling and paradoxical observations that Total Sleep Deprivation (TSD) and Partial Sleep Deprivation (PSD), selective REM sleep deprivation, or phase advance of bedtime (i.e., retiring and arising 6 hours earlier than normal) have antidepressant effects. For example, about half the patients with a moderately severe depression improve significantly in the morning after being kept awake starting at 3 am. Unfortunately, when they go to sleep, even for very short periods of time, they usually awaken depressed again. Although sleep deprivation has not found its way into the clinical armamentarium, it remains a powerful research tool. Sleep deprivation and recovery sleep are the only experimental manipulations which consistently turn depression "off and on", respectfully. The mechanisms involved in the antidepressant effects of sleep deprivation remain elusive, but one of the most promising leads comes from functional brain imaging studies. Patients who improve with sleep deprivation apparently have increased localized cerebral metabolism in cingulate and other limbic regions at baseline prior to Total Sleep Deprivation (TSD), as assessed by positron emission tomography (PET) with fluorodeoxyglucose (¹⁸F-DG), or single photon emission computerized tomography (SPECT) with technetium-⁹⁹-d,1-hexamethyl propyleneamine oxime (Tc⁹⁹m-HMPAO). After sleep deprivation, localized cerebral metabolism normalizes, possibly closely correlated with the degree of clinical improvement induced by sleep deprivation.

The pathophysiology of these sleep-related abnormalities remains poorly understood at this time. Based upon both basic science concepts about the neurobiology of sleep and clinical studies of patients, considerable evidence indirectly implicates the following factors in the pathophysiology of sleep disturbance in depression: (a) neurochemical factors, such as an increased ratio of cholinergic to aminergic (serotonergic, noradrenergic, and possibly dopaminergic) neurotransmission. As described below, REM sleep appears to be promoted by cholinergic and inhibited by aminergic neurotransmission. (b) neuropeptide factors, such as increased corticotropin releasing hormone (CRH) and decreased growth hormone releasing factor (GHRIF) (c) immunomodulatory factors, such as decreased activity of interleukins, tumor necrosis factor, or other immune processes, which apparently promote slow-wave sleep, (d) abnormal homeostatic regulation of sleep-wakefulness, for example, decreased strength of Process S (wake dependent "pressure" to sleep) in the Two Process Model of Sleep Regulation, (e) dysregulation of the circadian system, for example, a phase-advance of the circadian clock or decrease in the amplitude of circadian rhythms, (f) structural brain abnormalities, such as enlarged ventricles which have been associated with diminished Delta sleep in schizophrenics and some patients with mood disorders (see
below), (g) genetic determinants, such as reports that short REM latency is genetically influenced within families and that unaffected first degree relatives of patients with mood disorders are at increased risk for the later development of depression.

Of particular relevance to understanding the pathophysiology of depression and its sleep abnormalities, normal REM sleep and Delta sleep are modulated by the reciprocal interaction between cholinergic-aminergic neurotransmission. REM sleep is promoted by cholinergic neurons and is inhibited by noradrenergic and serotonergic neurons in the brainstem. In contrast, when cholinergic neurons in the brainstem and forebrain are inhibited, Stages 3&4 (Delta) sleep are facilitated, largely through thalamic-cortical interactions. In particular, serotonergic neurons from the dorsal raphe inhibit cholinergic neurons in the parabrachial region of the brainstem. Consistent with this hypothesis, administration of the tryptophan-free amino acid drink (TFD), which depletes brain serotonin, shortens REM latency in normal volunteers and reverses the prolonged REM latency found in euthymic patients receiving SSRIs.

Several groups have now reported that administration of muscarinic agonists, such as arecoline or RS 86, induces REM sleep more rapidly in depressed patients than in controls. Moreover, some studies have found supersensitive, cholinergic induction of REM sleep in unaffected, first-degree relatives of patients with mood disorders. In addition, one group has shown that depressed patients have a blunted delay in REM sleep following intravenous administration of clonidine, an alpha-2 noradrenergic agonist, during NonREM period. These pharmacological challenge studies further implicate the interaction between cholinergic and aminergic mechanisms in mood disorders.

3. Structural and functional brain imaging in mood disorders

It has long been argued whether or not psychiatric disorders are associated with structural or functional brain abnormalities or both. Even Freud wrote a draft of a project for a scientific psychology, in which he sought to understand mental phenomena and pathology in terms of neural circuitry and mechanisms. The quest reflected the zeitgeist which spawned the great neuroscientists of the late 19th century, Wernicke, Broca, Broadmann, Golgi, and Nissl, who laid the grounds of modern neuroscience and neurology. Psychiatry, however, took a different turn, towards psychodynamic theories, after Freud abandoned his project, perhaps because he realized that neurosciences of his time were still incapable of understanding the higher cognitive processes and psychopathologies.
A century later, however, much has been learned about the basic circuitry and processes of the brain. Moreover, new imaging methodologies have become available to measure the inner structure and functions of the living brain. For example, magnetic resonance imaging (MRI), which provides exquisite anatomic maps of the brain, can be co-registered with positron emission tomography (PET) or single photon emission computerized tomography (SPECT), to carefully localize changes in glucose metabolism, oxygen consumption, blood flow, or uptake of appropriately labeled ligands. Other methodologies include functional MRI, magnetic resonance spectroscopy, magnetoencephalography, and typographical EEG mapping.

During the past 20 years or so, many studies have revealed subtle structural brain abnormalities in patients with mood disorders compared with normal controls. (Table 14) These abnormalities, however, are not found in all patients and are not diagnostically specific. For example, several studies, but not all, have reported that subcortical focal white matter abnormalities are more prevalent in bipolar disorder than in either normal controls or unipolar disorder. The focal abnormalities are found predominately in frontal regions of the brain and may be associated with increased cognitive impairment, increased rates of psychiatric illness in relatives, later age of onset of the disorder, and poor treatment response. In addition, patients with mood disorders as a group have been reported to have statistically enlarged ventricles and more sulcal prominence than normal controls, although the differences were generally small. Compared with mood disorder patients, however, schizophrenics appear to have even larger ventricles.

**Table 14. Structural & Functional Brain Imaging Findings in Mood Disorders**

<table>
<thead>
<tr>
<th>Magnetic Resonance Imaging</th>
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<tbody>
<tr>
<td>• Ventricular volume (geriatric depression)</td>
</tr>
<tr>
<td>• White matter hyperintensities</td>
</tr>
<tr>
<td>• Cerebellar volume</td>
</tr>
<tr>
<td>• Temporal lobe, putamen, &amp; caudate volume</td>
</tr>
<tr>
<td>• Pituitary gland volume</td>
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<tr>
<th>Positron Emission Tomography</th>
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<tr>
<td>• Cerebral glucose metabolic rate (CGMR) in cortex &amp; basal ganglia during depression</td>
</tr>
<tr>
<td>• CGMR in hypomania (BP disorder)</td>
</tr>
<tr>
<td>• CGMR during NonREM sleep (UP disorder)</td>
</tr>
<tr>
<td>• Blunted CGMR after fenfluramine</td>
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Functional studies of localized glucose metabolism, blood flow, or oxygen consumption, are beginning to be used to identify neural structures associated with emotion in normal controls. For example, when normal female controls were asked to simulate sadness, cerebral blood flow increased in the medial prefrontal cortex, left lateral prefrontal cortex, bilateral anterior cingulate, fornix, insula, thalamus, and bilateral putamen and caudate compared with a neural emotional state. The happy condition, however, was associated with decreased blood flow in the bilateral midtemporal cortex,
right prefrontal cortex, and right superior temporal cortex. Interestingly, some preliminary data suggests that males show different patterns of cerebral blood flow than women when asked to simulate the same emotional states. The finding of a close association between local blood flow and a specific emotional state should not be interpreted as a cause and effect relationship. Many more studies will be needed to exploit these methodologies and to develop new circuitry models for the neural basis of normal emotions.

Functional brain imaging of depression has again shown relatively nonspecific differences compared with normal controls or other psychiatric disorders, such as hypofrontality (decreased ratio of metabolic activity in frontal as compared with occipital lobes) and mildly decreased activity within caudate nucleus, parietal cortex, temporal lobe.

In a recent preliminary study using PET scanning with $^{18}$F-deoxyglucose, Mann and his colleagues reported that fenfluramine, a pharmacological agent which releases serotonin, increased local glucose metabolism in the left prefrontal and temporoparietal cortex and reduced it in right prefrontal cortex in normal controls. In contrast, depressed patients showed no change at all. These results are consistent with the biogenic amine hypothesis that serotonin neurotransmission is impaired in depression.

If the newer brain imaging methods have not fulfilled the early hopes that they would reveal the underlying pathophysiology of mood disorders, it should again be remembered that the field is young, the pathophysiology is complex, and the methodological problems of brain imaging are formidable.

VI. Treatment

The primary goals of therapy are to prevent and reduce morbidity and mortality and to increase the quality of life and well being of individuals with mood disorders.

Unfortunately, no specific documented measures are now known which can prevent the onset of mood disorders in individuals who have never experienced a mood disorder. As mentioned earlier, however, with the increasing recognition that mood disorders are recurrent, chronic, and subsyndromal, there is renewed attention to eliminate all symptoms and to prevent recurrence and relapse. Patients with both recurrent unipolar and bipolar disorders are now frequently maintained on long term drug therapy. Several well controlled, double-blind studies have shown that long term treatment with antidepressants or mood stabilizers reduce the rates of relapse compared with placebo in recurrent unipolar and bipolar disorders, respectively. Whether or not psychotherapy prevents relapse is less
clearly documented, but many experienced clinicians advocate either supportive or specific forms of psychotherapy in the long term treatment.

Antidepressant medications and mood stabilizers are the mainline form of treatment for depression and mania in most cases. Unfortunately, many patients with depression never seek treatment. Many who do remain underdiagnosed and undertreated. As reviewed in Table 2, other forms of somatic therapy are also appropriate in specific subtypes of major depression, including antipsychotic medications for delusional depression, bright lights for winter depression, and ECT for severe, unresponsive depression.

VII. Service delivery

Psychiatric services have traditionally been delivered in public and private sectors. Although many long term publicly-supported mental hospitals have been phased out, they still play a role in long term protection and treatment of severely ill, unresponsive patients. Acute hospitalization, whether public or private, is still necessary for many patients who are suicidal, manic, psychotic, incapacitated, or need ancillary or specialized services. Because the health care dollar is currently shrinking, the need for hospitalization is under increasing scrutiny. More and more patients are now routinely treated in outpatient settings, public and private. The number of direct controls between the patient and his or her clinician is falling and shorter.

Because the cost of psychiatrists is perceived to be higher than nonphysicians, patients are probably more likely to be managed by teams, typically a psychiatrist, or perhaps a primary doctor who managed medical issues and medicine, and nurses, social workers, or psychologists who see the patients regularly.

In this topsy-turvy world of changing delivery of medical care, a current challenge is to determine how to best treat acute and chronic disorders within the current fiscal, administrative, and ethical boundaries. For example, does fee for service offer better treatment for depression than managed care? Are specialists better than general clinicians for subsets of patients? Are labor intensive therapies, such as psychotherapy, worth the cost compared with medications? Are the newer SSRI’s, which cost more per pill, cheaper in the long run than TCA’s, which are cheaper but likely to have significant side effects?
VIII. Centers of excellence

Centers of excellence include:

Harvard University
Southwestern Medical School, Dallas
Massachusetts General Hospital

University of Texas Medical School
University of Richmond
McLean Hospital

Yale University
Columbia University
University of Minnesota
University of Pittsburgh
University of Pennsylvania

Washington University, St. Louis
University of Michigan
University of Wisconsin
University of California, San Diego
University of California, San Francisco

Stanford University
University of North Carolina
University of Cincinnati
Rush Institute, Chicago

Other sources of expertise include the MacArthur Foundation and some of the pharmaceutical companies.

IX. Future directions

There is little doubt that modern psychiatry and clinical psychology now have more to offer patients with mood disorders than they did thirty years ago. Diagnosis, ratings, and clinical description are more creditable. The clinical efficacy of drug treatment of depression and mania has been validated again and again in clinical trials. The new drugs we now have are probably better than the old drugs in many situations, and our understanding of how they work has improved. The importance of genetics in the etiology of mood disorders has been strengthened; this thrust has not eliminated and may quantify the role of other factors, many of which remain unknown. Importantly, we have an increasingly sophisticated cadre of clinical, social, and basic scientists who devote their professional careers to these disorders. The future of neuroscience in psychiatry is established, but it does not exclude other perspectives.

Nevertheless, this is no time to gloat about our success. Too much is unknown. The diagnosis of psychiatric disorders is still based primarily upon descriptive methods of mood, behavior, cognition, and vegetative functions. Despite advances in the
neurosciences and the decades of careful research on neurochemistry, neuroendocrinology, sleep and chronobiology, brain imaging, neuropsychology, and genetics, we still have no sensitive or specific marker or validator for any psychiatric disorder. Although we honor the biogenic hypothesis of depression, especially the serotonergic version, we still lack the data to believe it completely. We can achieve good diagnostic reliability but we have not established diagnostic validity. Specialists still argue whether mood disorders and schizophrenia are separate disorders or a continuum. The clinical effectiveness of antidepressants in panic disorder, OCD, PTSD, enuresis, narcolepsy, and sleep apnea argue against diagnostic specificity. So does the prevalence of the so-called biological markers in both mood disorders and other psychiatric disorders, such as DST nonsuppression, blunted TSH response, short REM latency, focal white matter hyperintensities on MRI, or hypofrontality on functional brain images.

We may applaud the value and safety of our pharmacological treatments for major depression and bipolar disorders, but we cannot deny that the long-term prognosis of many, if not most, patients remains problematic. Whether measured by rates of relapse and recurrence or by the poor quality of life they experience, too many patients suffer enduring, pervasive psychosocial difficulties for years after treatment, despite good compliance with treatment. Despite sustained resolution of major clinical symptoms, income, employment, social status, and interpersonal relationships often decline. It is estimated that only about 40% of bipolar patients sustain a full recovery despite reasonable adherence to lithium. There is also little evidence that modern psychopharmacology has reduced the suicide rates in the general population. While the new SSRIs are better tolerated than the older TCAs and MAOIs, they may be less effective in severe depression. We still have no good data on how long patients should be maintained on antidepressants or mood stabilizers after their first episode or after their nth episode; the rule of thumb seems to be a long time or life after the third episode of depression but no one knows how effective or safe this guideline is. Despite 50 years of intensive work, ECT remains the gold standard even though its antidepressant effects were discovered more than a decade before the MAOIs were recognized serendipitously in the early 1950's. And, by the way, does psychotherapy have a role in the management of mood disorders as we enter the new century, a hundred years after Freud developed psychoanalysis? So-called prescription psychotherapies, such as cognitive behavioral treatment and interpersonal psychotherapy, have shown their worth in too many studies to be dismissed out of hand. But again, with psychotherapy as with pharmacotherapy, the unanswered questions remain: For whom? How long? What type? And, probably the most important questions in this revolutionary age of managed health care are, who will deliver it and how will we pay for it? How will our patients obtain access to quality health care in the future?
X. Bibliography


ANXIETY DISORDERS

I. Clinical description

PANIC DISORDER

Panic disorder is an anxiety disorder characterized by recurrent, spontaneous, and unexpected panic attacks with or without agoraphobia. Panic attacks are defined as a sudden onset of intense fear or discomfort involving somatic and cognitive symptoms of distress. The symptoms are accompanied by a sense of danger and an impulse to escape the situation. To meet the clinical criteria for a panic attack, 4 of 13 symptoms must be present including: 1) palpitations; 2) sweating; 3) trembling or shaking; 4) shortness of breath or a sensation of smothering; 5) choking; 6) chest pain or discomfort; 7) nausea or abdominal distress; 8) dizziness or lightheadedness; 9) derealization or depersonalization (a feeling of being outside or detached from oneself); 10) fear of losing control or going crazy; 11) fear of dying; 12) paresthesias; and 13) chills or hot flashes. Dyspnea is particularly characteristic of the panic attacks in panic disorder.

In order to meet the criteria for panic disorder, there must be multiple, unexpected panic attacks and at least one of these episodes must be followed by at least one month of concern about having additional attacks, anxiety about the implications or consequences of an attack, and a significant change in behavior or functioning. In addition, organic causes (i.e. a medical disorder or substance abuse) must be ruled out.

Agoraphobia may or may not be present in conjunction with panic disorder. Agoraphobia is defined as anxiety about being in a place where escape or assistance would be difficult in the event of a panic attack. Some of these places include: crowds or lines, bridges, or public transportation. It can also more broadly include any place outside of the home in the absence of a companion. In agoraphobia, these situations are avoided. If encountered, they provoke significant apprehension that may or may not be punctuated by a panic. Agoraphobia can also occur in the absence of panic attacks, but this condition is not given the diagnosis of panic disorder.

II. Epidemiology

The lifetime prevalence of panic disorder is estimated to be 1.5-3.5%. The one year prevalence is 1-2%. Epidemiological surveys done by the Epidemiological Catchment Area Study (ECA) indicate that panic disorder without agoraphobia is twice as common as panic disorder with agoraphobia. It is diagnosed three times more often in women than in men and cases have been documented worldwide. It has been suggested that there may
be a lower lifetime prevalence in African-Americans and Hispanics, but otherwise there do not appear to be significant ethnic differences. Amongst the age groups, prevalence is highest in the thirties and early forties. It is not as common in younger adults or individuals over the age of 65.

These data, however, are suspect since direct comparisons with clinical interviews have not been done except with agoraphobia without panic disorder; this condition appears to be specific phobia.

Regarding socioeconomic status, no differences were found in terms of educational attainment in the ECA survey. However, higher occupational status was related to a lower incidence of panic disorder in men and a higher incidence in women. Analyzing public assistance records, panic disorder was correlated with financial dependence. Married men had lower rates of panic disorder, but no relationship to marital status was found for women.

III. Natural course

The onset of panic disorder tends to occur between adolescence and mid-thirties. The course of the illness varies and can be intermittent or continuous. Some individuals have long remissions and the symptoms can reappear at different stages in life. The onset can be acute or insidious. The typical course tends to be lifelong but intermittent, with periods that are more severe followed by a decrease in the number of symptoms or complete remissions.

There is substantial comorbidity in panic disorder, with 50-65% of individuals also having major depression (MDD). In one third of the cases, MDD precedes the development of panic disorder. Substance abuse or dependence in the form of self medication is also observed. It occurs frequently with other anxiety disorders with 15-30% of patients having social phobia; 8-10% having obsessive compulsive disorder (OCD); and 10-20% having generalized anxiety disorder.

The impairment from panic disorder can be substantial, but it is highly variable. In severe cases, individuals with agoraphobia can be isolated in their homes. Due to the frightening and acute physical symptoms that are experienced, individuals with panic disorder often find it difficult to believe that they are not suffering from a physical illness and a large amount of money can be spent on medical consultation. Job loss and impairment of relationships can also result from the condition.
Service utilization amongst individuals with panic disorder is high. In the ECA study, 25% of subjects with recurrent panic attacks consulted mental health services and 14% of subjects with agoraphobia sought help. In a follow-up of patients 6 to 10 years after treatment in a tertiary care setting, it was found that 30% had recovered, 40-50% had improved and 20-30% showed no improvement or had deteriorated.

IV. Suspected causes

There is evidence that there is a genetic component in the development of panic disorder. First degree relatives of patients have a 4 to 7 times greater chance of developing panic disorder. Twin studies have been very important in providing preliminary evidence that is heritable, but additional twin and pedigree studies are needed to fully investigate the genetics of panic disorder.

Panic disorder may also be related to separation anxiety. It is estimated that 25% of patients have suffered from a clinically defined syndrome termed separation anxiety during childhood.

V. Biologic mechanisms and correlates

The biological correlates of panic disorder have interested researchers since it is one of the few disorders in which it is possible to physiologically induce symptoms. Panic attacks can be triggered by sodium lactate infusion and carbon dioxide inhalation in laboratory settings. The ability to induce attacks is promising for future biological research.

It has been found that panic attacks are associated with compensated respiratory alkalosis (decreased levels of carbon dioxide and bicarbonate with nearly normal levels of pH). Elevated systolic blood pressure has also been found during attacks. Some studies have shown that there is an increased incidence of mitral valve prolapse and thyroid disease in individuals with panic disorder. However, mitral valve prolapse is present in a high percentage of the population and this has made studies difficult. Other mechanisms that have been investigated include adrenergic dysfunction, brain perfusion abnormalities, increased levels of serotonin antibody, endorphinergic deficits, respiratory diseases, and a hypersensitive suffocation alarm mechanism.
VI. Treatment

Psychopharmacology and psychotherapy have been used in the treatment of panic disorder. Imipramine has been the most well demonstrated pharmacological agent for use with panic disorder. Alprazolam is also commonly used as well as clonazepam, SSRI’s, phenelzine, and reversible monoamine oxidase A inhibitors. Imipramine has been found to be effective in treating panic attacks with symptoms of respiratory distress. This symptom is typical of panic attacks associated with the diagnosis of panic disorder.

Alprazolam and clonazepam have a fast onset (one week) as opposed to tricyclics and SSRI’s which can take three to six weeks to have noticeable therapeutic effects. Clonazepam is long-acting but it is sedating and, along with alprazolam, should be started at low doses.

A significant placebo effect has been found in several pharmacological studies of panic disorder. In one study, 50% of subjects on placebo were panic free at follow-up. However, the intermittent course of panic disorder makes it difficult to assume recovery and control for the episodic nature of the disorder.

The most comprehensive treatment studies include placebo and medication groups to assure medication responsiveness. A number of psychotherapy studies have included medication but rarely include placebo control groups or combinations of therapy. Various cognitive therapies have been employed including: computer assisted biblio therapy, panic control therapy, exposure therapy, sequential therapy, and relaxation therapy. In several studies cognitive therapy was effective; however, in some studies there was no difference between psychotherapies and this questions psychotherapeutic specificity. In spite of conflicting findings, the therapeutic alliance and support characteristic of psychotherapy may benefit individuals with panic disorder, especially if there is a history of separation anxiety.

VII. Service delivery

There is little comparative data. The utility of nurse practitioners, biblio therapy and even computer driven therapeutic programs have been discussed in the literature. However, all of this work has not been independently replicated. It seems clear that much of the behavioral approaches can be carried out by trained nonprofessionals (paraprofessionals).
VIII. Centers of research excellence

Anxiety Disorders Clinic, New York State Psychiatric Institute, Unit 13, 722 West 168 Street, New York, NY 10032.

Biological Studies Unit, New York State Psychiatric Institute, Unit 24, 722 West 168 Street, New York, NY 10032.

Alexander Bystritsky, M.D., Suite 2340, 300 UCLA Medical Plaza, Los Angeles, CA 90024-6968.

Dennis S. Charney, M.D., Psychiatry Service 116A, VA Connecticut Healthcare System, 950 Campbell Avenue, West Haven, CT 16516.

Clinical Pharmacokinetics Unit, Upjohn Company, Kalamazoo, Michigan 49007.

College of Pharmacy, University of Michigan, Ann Arbor, Michigan 48109-1065.

Department of Psychiatry, University of Michigan, Ann Arbor.

Department of Psychiatry, Wayne State University School of Medicine, Detroit, MI 48207.


Abby Fyer, M.D., Director, Anxiety Genetic Study Family Unit, New York State Psychiatric Institute, Unit 82, 722 West 168 Street, New York, NY 10032.

Jack M. Gorman, M.D., Deputy Director, New York State Psychiatric Institute, Chief, Department of Clinical Psychobiology, New York State Psychiatric Institute, Unit 121, 722 West 168 Street, New York, NY 10032.

Rachel G. Klein, Ph.D., Director, Psychology, New York State Psychiatric Institute, Unit 80, 722 West 168 Street, New York, NY 10032.

R. Bruce Lydiard, M.D., Ph.D., Department of Psychiatry, Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425.

Donna Moreau, M.D., Director, Children’s Anxiety and Depression Clinic, Babies Hospital, Columbia Presbyterian Medical Center, Unit 60, 722 West 168 Street, New York, NY 10032.

Daniel Pine, M.D., Post Doctoral Fellow in the Center to Study Youth Anxiety, Depression and Suicide, New York State Psychiatric Institute, Unit 78, 722 West 168 Street, New York, NY 10032.

Jerrold F. Rosenbaum, M.D., Chief, Clinical psychopharmacology Unit, Behavior Therapy Unit, Harvard Medical School, Massachusetts General Hospital, 15 Parkman Street -- WACC 815, Boston, MA 02114.

Murray B. Stein, M.D., Anxiety & Traumatic Stress Disorders Research Program, Department of Psychiatry, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0603.
IX. Future directions

In general, the epidemiological data would be made more solid if there were independent checks of subsamples of the patients. This could be done using structured interviews while allowing clinical elaborations as well.

Genetic studies, including twin studies, are needed to further investigate the genetic component of panic disorder. This research could have an impact on our understanding of biological correlates and environmental factors. In addition, viable new treatments could be developed.

Panic disorder is an extremely promising area of study since it is one of the few psychopathological phenomena that can be brought within the laboratory. We can both turn it on and turn it off. Recent emphasis upon respiratory derangements as related to panic disorder in the form of false suffocation alarm has stirred wide interest. The ability to objectively monitor spontaneous panic attacks via ambulatory respiratory monitoring brings some objectivity to the field. Recent hypotheses with regard to periodic endorphinergic deficits tying panic disorder, separation anxiety, suffocation sensitivity, and premenstrual syndrome together provide a unique base for further clinical work. Recent developments in the area of behaviorally inhibited children provides a developmental framework similar to the one proposed with regard to separation anxiety. Challenge studies in the area of anti-endorphin and the possibility of carbon monoxide being an antianxiety agent via its action as a neurotransmitter in the carotid body furnish yet more promising leads.

Other possibilities are to modify the activity of the heme oxygenase system which synthesizes carbon monoxide. Inhibiting the heme oxygenase system in tin mesoporphyrn should lead to increased respiratory sensitivity and perhaps a panicogenic agent. Similarly, enhancing the effects of heme oxygenase by agents such as cobalt which occurs in vitamin B 12, may increase the endogenous production of carbon monoxide and therefore act as an anti-panic agent.

Currently the collaborative study of cognitive therapy, imipramine and its combination is undergoing data review and this may provide leads for future investigations.
X. Bibliography


OBSESSIVE COMPULSIVE DISORDER (OCD)

I. Clinical description

Obsessive compulsive disorder (OCD) is an anxiety disorder characterized by obsessions or compulsions. Obsessions are defined as intrusive thoughts or impulses that are distressing to the individual. They are experienced as uncontrollable and inappropriate. The content of the obsessions is often unrelated to everyday concerns and problems. An attempt is made to suppress these thoughts or images with either another thought or an action. In spite of experiencing the thoughts as strange and disturbing, the person knows that the obsessions are created by his/her own mind. The patient is surprised and puzzled by these thoughts.

Compulsions are repetitive, ritualized behaviors such as hand washing, persistent checking, or counting that are performed following the occurrence of an obsession. There is a strong drive to perform the compulsion rigidly following a self-imposed set of rules. The purpose of the compulsion is to avoid a negative event or reduce the distress that results from the content of the obsession. Some compulsions occur without evident obsessions. However, they are not rationally directed to prevent the event and can be likened to the performance of a superstition or ritual.

In order to meet the criteria for OCD, the person must, at some point during the course of the illness, recognize the irrational nature of the obsessions or compulsions in order to differentiate the condition from the delusional symptomatology characteristic of psychotic disorders. In children, this condition is not necessary. The symptoms must also cause significant distress, interfere with normal functioning, or consume a large amount of time.

II. Epidemiology

The lifetime prevalence of OCD in psychiatric populations is 0.9 to 4%. In the general population it was once considered to be rare with a prevalence of 0.05%; however, recent community estimates suggest that it may be as high as 2.6%. The one-year prevalence is between 1.5-2.1%.

It is not necessary that obsessions and compulsions occur together and there is some evidence that the majority of cases may involve either one or the other. The most severe
cases may exhibit both symptoms. In one sample, 55% of the subjects reporting OCD had obsessions and 53% had compulsions. Only 8% of the subjects had both at some point during the course of the disorder. In institutional settings this rate was found to be 22%. A number of studies report that OCD occurs slightly more often in women (53% women). An epidemiological survey (ECA) found no differences between the sexes when controlling for marital status, unemployment, job, ethnicity, and age.

In terms of ethnicity, the highest rate is among white women under the age of 45. The lowest rates are in Hispanic men over the age of 45.

Other studies have suggested that there is an increased risk for OCD with increasing educational attainment. However, there are also findings to the contrary. Unemployment was not related to incidence of OCD; however, there was a correlation with underemployment. Underemployment is defined as being unemployed for a total of six months in the previous five years. This group had the highest rate of OCD. Subjects on welfare were twice as likely to have OCD as those that were not financially dependent. OCD was unrelated to marital status. Epidemiological surveys require validation by clinical cross-checking.

III. Natural course

The onset of OCD usually occurs in childhood or late adolescence. It has been reported that an onset before the age of 25 occurs in 64% of cases, and 74% exhibit symptoms before the age of 30. There occasionally is an older age of onset. The age of onset may differ for men and women. The onset for men has been reported to be the highest between the ages of six and fifteen. In women, the predominant age of onset is between 20 and 29 years of age.

The duration of the illness is typically long. In the ECA survey, of the subjects who reported OCD during their lifetime but not in the past year, 20% reported a duration of more than 10 years. The mean duration in this sample was 7 years. Two-thirds of the subjects sampled had symptoms in the past year and one half had symptoms as recently as the past 30 days. This strongly suggests that the course is chronic with a low remission rate. The disorder can be severe and a large number of individuals with OCD are hospitalized.
Overall, the typical course involves waxing and waning symptoms that appear to be exacerbated during times of stress. There is a deteriorating course in 15% of patients and only 5% have an episodic course with full remissions.

Three-quarters of patients with OCD were found to have a comorbid condition. The conditions that tend to precede the development of OCD are panic disorder and phobias. Phobia was the most common comorbid disorder. Approximately 12% of OCD patients also have schizophrenia. Psychoactive substance dependence is often a comorbid condition and it usually develops after the onset of OCD. It may be significant etiologically that 35-50% of Tourette patients also have OCD.

The use of mental health services falls in the middle of the spectrum of anxiety disorders. As previously noted, there is a large proportion of patients who are hospitalized for OCD. Within the community, 18% of individuals reporting OCD have consulted a specialist in the field of mental health and 11% have consulted a general practitioner. It is believed that the low estimates of OCD that were in the literature prior to the publication of DSM-IV may have resulted from the high numbers of individuals who do not have a severe form of the disorder and have successfully concealed the condition. However, it is also possible that the threshold for diagnosis was low.

IV. Suspected causes

Twin studies suggest that OCD is heritable. There may also be a genetic relationship between Tourette Disorder and OCD based upon the fact that there is a higher incidence of OCD in first degree relatives of Tourette patients and 20-30% of individuals with OCD report current or past tics.

V. Biologic mechanisms and correlates

Relevant laboratory findings include decreased physiological reactivity in individuals with OCD following the completion of a compulsion. Research settings that prompt an obsession have also found high autonomic activity. In addition, it has been reported that serotonin agonists, particularly MCPP, heighten the symptoms in some patients.

VI. Treatment

OCD has been fairly resistant to ordinary psychotherapy, but pharmacological treatments and behavioral response prevention techniques have been shown to be effective.
Sertaline, fluvoxamine, fluoxetine, and clomipramine (SSRI's) have led to improvement in many patients. Fluvoxamine in conjunction with exposure therapy has been found to be effective. The primary difficulty in treating OCD is the high drop out rate. Approximately 50% of patients withdraw from behavioral and pharmacological treatments.

VII. Service delivery

All forms of known treatment require highly skilled professional personnel. Comparative and combined studies are just under way.

VIII. Centers of research excellence

Brian Fallon, M.D., Anxiety Disorders Clinic, New York State Psychiatric Institute, Unit 13, 722 West 168 Street, New York, NY 10032.

Edna Foa, Ph.D., The Medical College of Pennsylvania, 3200 Henry Avenue, Philadelphia, PA 19129.

John Greist, M.D., Suite 302, 8000 Excelsior Drive, Madison, WI 53717.

Michael A. Jenicke, M.D., Director, OCD Clinic and Research Unit, Massachusetts General Hospital-East, Bldg. 149 - 13th Street, Charlestown, MA 02129.

Michael R. Liebowitz, M.D., Director, Anxiety Disorders Clinic, New York State Psychiatric Institute, Unit 120, 722 West 168 Street, New York, NY 10032.

Franklin R. Schneier, M.D., Anxiety Disorders Clinic, New York State Psychiatric Institute, Unit 13, 722 West 168 Street, New York, NY 10032.

University of Michigan Medical Center, Department of Neurosurgery, Ann Arbor 48109-0338.

IX. Future directions

Since 50% of the patients drop out of both psychotherapy and pharmacotherapy, it is evident that studies of how to maintain patients in treatment would be of great interest. There is no detailed information concerning whether patients who drop out of response prevention behavioral treatment would be accepting of psychopharmacology or vice versa.

Genetic studies, including additional twin studies, are also needed if the etiology of OCD is to be fully understood.

It has been suggested that there is a match-mismatch comparator in the central nervous system that compares the inferences that we make about ourselves and the
environment with the incoming data. When the inferences and the data match, we feel certain; but when they do not match we feel doubtful. The outstanding feature of OCD is the very high level of doubt. After washing their hands 30 times, the patients may still doubt whether their hands are clean although they can state objectively that they know that their hands are clean; however, the feeling persists.

It is possible that there is a waxing and waning of the defect in the match-mismatch apparatus so that acute doubfulness resulting in obsessional thoughts may come and go. However, the compulsions may maintain functional autonomy even when the inciting obsessions are in remission.

It has generally been thought that response prevention therapy is the most useful for patients dominated by compulsions, but of little use for those who are purely obsessional. Documentation of this belief is needed. Conversely, medication may be most useful for those patients who are in an actively obsessional state characterized by horrific thoughts.

It has also been suggested that many of the cleansing rituals in OCD are characteristic of disorders of a grooming instinct. This idea is not antithetical to the match-mismatch hypothesis because it is possible that there are a variety of match-mismatch devices associated with important biological activities.

There is considerable interest in the possibility that streptococcal infections may produce auto antibodies to the cordate nucleus and that damage to this structure may incite OCD. Recent work by Swedo confirms this point of view. Further, there have been studies of plasma pheresis in young patients with OCD that seem positive.

There are recent studies involving brain scanning of the basal ganglia in patients with OCD that appear to reveal abnormalities, affording yet another approach to this difficult problem.

X. Bibliography


POST-TRAUMATIC STRESS DISORDER

I. Clinical description

Research on Post-traumatic stress disorder (PTSD) has focused primarily on Vietnam veterans; however, PTSD can result from a wide range of traumatic events, including rape, physical assault, child abuse, torture, imprisonment, and witnessing violence. Rescue workers who are involved in accidents and natural disasters are also at risk for PTSD.

PTSD is defined by a syndrome, i.e. a constellation of symptoms, that occur following a severely traumatic experience. The definition of the event states that the individual must have witnessed or been confronted with a life-threatening or severely dangerous situation in which there was a threat to self or others and that this event must have been experienced with profound helplessness, fear, or horror.

The syndrome’s cardinal symptom is re-experiencing the traumatic event, in intrusive memories or nightmares. The person could also feel as if it is recurring (i.e. flashbacks) or have distress when cues or reminders are present. Another clinically significant symptom is physiological reactivity. In addition to re-experiencing, there must be indications of persistent avoidance or a decrease in responsiveness (numbing). At least three of the following symptoms must be present: 1) avoidance of thoughts, feelings, or conversations related to the trauma; 2) avoidance of activities, people or places related to or reminiscent of the event; 3) the inability to recall certain details of the incident; 4) decreased interest or participation in normal activities; 5) detachment or estrangement from friends and family; 6) restricted range of affect (emotion); or 7) a sense of a foreshortened future.

PTSD also involves an increase in arousal as evident by the presence of at least 2 of the following: 1) sleep difficulty; 2) irritability or anger; 3) concentration difficulties; 4) hypervigilance; 5) exaggerated startle response (the individual may seem jumpy).

II. Epidemiology

The lifetime prevalence of PTSD in the general population is estimated to be between 5-6% in men and 10-12% in women. There are also prevalence estimates based upon studies of individual subgroups; almost 50% of rape victims have PTSD. Among
Vietnam veterans, over one quarter of the women and nearly one third of the men met the criteria in one study.

III. Natural course

PTSD can occur at any age and the symptoms typically develop within days or weeks following the trauma. There are cases, however, in which the development of symptoms is greatly delayed. There is evidence to suggest that cumulative trauma is present in many cases of PTSD. One half of individuals with PTSD recover within one year; however, in some persons the disorder persists for many years.

The comorbidity of PTSD with other disorders is high. It is often seen in conjunction with other anxiety disorders, major depression, substance dependence, somatization, and dissociative disorders. In one study, 76% of patients with PTSD also had major depression and 38% had alcohol abuse or dependence.

In comparison to the other anxiety disorders, impairment is high in individuals with PTSD. In one study of overall functioning, it was found that 30% of individuals with PTSD had attempted suicide and half required psychiatric hospitalization. A high percentage were on work disability as well (25%).

IV. Suspected causes

Risk factors can be understood in terms of the risk of experiencing a traumatic event as well as the risk of developing PTSD following the event. An increased risk of experiencing such an event is related to lower SES, male sex, urban environment, and familial mental illness or substance abuse.

Once a traumatic event has occurred, there are certain variables that may make an individual more vulnerable to PTSD. Females are more likely to develop PTSD after exposure. Younger age may also be a risk factor for PTSD. Prior psychiatric history is an important risk factor, including preexisting depression or anxiety disorders. Family history of psychiatric disorder, in particular anxiety disorder, is correlated with the development of PTSD. The severity of trauma is often predictive of the development of PTSD. The symptoms of arousal, avoidance, and reexperience have been related to genetic factors.
V. Biologic mechanisms and correlates

Psychophysiological findings and theories may provide clues to the etiology of PTSD and the biological changes that may occur following its onset.

There are a number of physiological mechanisms that may be involved in the symptomatology of PTSD. The septohippocampal region is believed to respond to unpleasant stimuli and lead to increased arousal. The Locus Ceruleus of the sympathetic nervous system also responds to threatening circumstances. In addition, perceived threat is related to cortisol and opioid release. It is possible that the symptoms of PTSD can be understood on the basis of elevated fear response. It has been reported that PTSD subjects have chronically low cortisol.

In addition to theories related to physiological mechanisms, researchers have also proposed cognitive processes that may aid in the understanding of PTSD. There are theories of cognitive reprocessing in which the traumatic event is integrated into existing schemas of the self and the environment. This is then used as a context for explaining the change in arousal, behavior, and emotional responses. Learned helplessness has also been used as a model for the development of PTSD. Learned helplessness is a classic theory that was used to explain the decrease in responsiveness and escape attempts of dogs subjected to unpredictable electric shock. It has been used as a model for human responses to uncontrollable stressors in which apathy and depression result.

Information has been obtained (personal communications, Basogln, Silove, Bouwer) from Turkey, Australia, and South Africa indicating that torture by suffocation is particularly prone to elicit PTSD. Such PTSD patients are sensitive to lactate infusion.

VI. Treatment

There are a variety of treatment modalities in PTSD including supportive- psychodynamic therapy, cognitive-behavioral desensitization, family/group therapy, hypnosis, stress inoculation training, and psychopharmacology.

In one study of psychotherapy, supportive-psychodynamic therapy was compared to hypnotherapy and traumatic desensitization. A control group with no therapy was also used. All of the therapies were more effective than no therapy, but all were equally effective. In another study, certain symptoms were found to respond better to different therapies. Desensitization and hypnotherapy were the most effective in decreasing
intrusive symptoms. Psychodynamic therapy had the most success in decreasing avoidance. These differences diminished at follow-up. Posttraumatic therapy, which includes psychodynamic and cognitive elements, was the most effective overall.

In the realm of pharmacologic treatment, some medications have been found to decrease the comorbid symptoms of depression whereas others have resulted in an improvement in the core PTSD symptoms. Imipramine and amitriptyline have been found to be effective in treating core symptoms in an 8 week trial. There are conflicting results in trials of phenelzine (MAOI).

Desipramine was found to be effective in reducing comorbid symptoms of depression, but the PTSD symptoms remained. Alprazolam has been found to be somewhat effective, although there is the risk of dependence on benzodiazepines. Fluoxetine (SSRI) was effective in reducing core symptoms in a civilian population and associated depression in a sample of veterans. Many studies suggest that the various populations with PTSD may be very different and respond to different modes of treatment.

VII. Service delivery

Treatment programs in Veterans Administration Medical Centers have employed a variety of type of professionals, including psychiatrists, psychologists and counselors. Both individual and group psychotherapy have been used. There are no comparative data on the efficacy of these approaches. Community Mental Health Centers in major West Coast cities have developed a crisis intervention model, called Debriefing, designed to prevent the development of psychiatric symptoms and PTSD in persons exposed to earthquake devastation and other civilian catastrophes. There are no systematic data on these interventions.

VIII. Centers of research excellence

Naomi Breslau, Ph.D., Director of Research, Department of Psychiatry, Henry Ford Health Sciences Center, Detroit, Michigan 48202-3450.
National Center for Post-Traumatic Stress Disorder, VA Medical Centers, White River Jct, VT; Boston, MA; Palo Alto, CA; West Haven, CT; Honolulu, HI.
Department of Psychology, Central Michigan University, Mount Pleasant 48859.
School of Social Work, University of Michigan.
VA Medical Center, Battle Creek, Michigan 49016.
Wayne State University Law School, Detroit, Michigan.
IX. Future directions

There are several aspects of PTSD that complicate the clinical picture and deserve further study. PTSD is an extremely heterogenous diagnosis. It often involves comorbidity, particularly major depression and psychoactive substance use. Some patients with PTSD have panic attacks, while others do not. These aspects of the disorder demand carefully controlled research studies, perhaps in different populations of subjects.

Epidemiologically it is important to study the course of the illness more closely as well as the functional impairment. In terms of treatment, many patients are refractory to both drug treatment and psychotherapy. Many individuals with the disorder are financially dependent and this suggests a high level of functional impairment.

Biological correlates indicate that some individuals with PTSD have sleep disturbance. It would be useful to delineate the nature of sleep disturbances associated with PTSD.

The current understanding of PTSD could also be augmented by studies conducted on the function of the amygdala and hippocampal volume. The amygdala is believed to be the emotional moderator of stress, and few studies have been conducted on laboratory animals in this specific area. There is a hypothesis that stress can have an impact on hippocampal neurons, and this effect may be reversible.

Certain neurotransmitters may also play an important role in PTSD including: oxytocin, CRH, neuropeptide Y, and the GABA-benzodiazepine system.

In terms of clinical interventions, studies that identify and provide professional consultation immediately following a traumatic experience could enable researchers to design an early treatment and detect the precursors of the disorder before it becomes chronic. It may be possible to develop pharmacologic interventions immediately following a traumatic experience that could have preventive functions in terms of autonomic instability.

There are a number of somatic symptoms that accompany PTSD and there need to be studies that investigate these symptoms as well as the overall health outcomes of individuals subjected to chronic stress.
PTSD is still poorly understood; therefore, research is needed in a number of areas. Most of the biologic research on PTSD has been conducted in VA medical centers with Vietnam veterans. The need for studies on sleep and biological systems involved in stress in persons with PTSD in the community cannot be over-emphasized.

X. Bibliography


SOCIAL PHOBIA

I. Clinical description

An individual with social phobia has a fear of social or performance situations in a setting with unfamiliar people. The primary fear is that the person will experience public embarrassment or humiliation (SSRIs), which miliation.. The anxiety that results from encountering the feared situation may or may not result in a panic attack. The panics of social phobia are not marked by dyspnea, but rather by palpitations, sweating and trembling.

The individual has insight and recognizes that the fear is unreasonable or excessive but nonetheless the feared situations are avoided or provoke intense distress. This avoidance or distress must interfere with functioning in either social or occupational contexts. In order to warrant the diagnosis under the age of 18, the duration must be at least six months.

In clinical practice, two subtypes of social phobia are often recognized. Generalized social phobia is defined as a fear of most social situations, whereas nongeneralized social phobia is considered to be a fear of less than most social situations. In addition to the difference in the number of feared situations, individuals with generalized social phobia have been found to have a greater number of fears of interpersonal interactions than individuals with the nongeneralized subtype. There is additional evidence to suggest that these are two distinct subtypes. The generalized subtype has been associated, in some studies, with an increased prevalence of comorbid atypical depression and alcoholism. Individuals with generalized social phobia have an earlier age of onset and are less likely to marry than individuals with nongeneralized social phobia. Generalized social phobia may prove to be the familial subtype, since individuals with generalized social phobia are more likely to have a relative with social phobia than individuals with nongeneralized social phobia. Lending further support for this hypothesis, individuals with nongeneralized social phobia have been found to have the same familial rate of social phobia as controls.

There is some variation in the presentation of symptoms. A common fear centers on public speaking. Since many people in the general population have a fear of public speaking, the diagnosis of social phobia must be given only if this interferes directly with functioning. About one-half of patients have a fear of talking to strangers or meeting new people. Difficulty in public performances, dating, and relation to authorities are salient features. Blushing and mind going blank are highly specific for social phobia.
II. Epidemiology

The lifetime prevalence of social phobia is estimated to be between 3 and 13%. In the ECA report, only 2.7% of the community sample had social phobia at some point during their lifetime. In clinical outpatient settings, social phobia constitutes approximately 10-20% of the cases of anxiety disorders.

Community samples have a higher proportion of women than men; however, this sex difference is not found in clinical settings. In clinical samples the ratio of men to women is equal or there is a higher percentage of men with the disorder. Epidemiological surveys suggest that African-Americans have a higher rate of social phobia than Whites or Hispanics. The lifetime prevalence for African-American women was found to be approximately 5%.

There may also be cultural factors that play a role in the symptomatology of social phobia.

III. Natural course

The onset of social phobia is typically in the mid-teens but it can also occur in childhood. It has been suggested that behaviorally inhibited children are prone to social phobia. Social phobia can have an acute onset or it may be gradual. In children who were believed to be merely shy and withdrawn in childhood, the adult may exhibit social phobia. It is frequently lifelong, although it may decrease in severity in adulthood. Comorbidity is substantial in social phobia and it may precede a number of other anxiety disorders, mood disorders, psychoactive substance use disorders, and somatization disorder. In the most severe forms of social phobia, the individual may have no social contact and never marry. The disorder is often associated with job and academic difficulties, including test anxiety.

Individuals with social phobia or symptoms of the disorder have a moderate rate of medical consultation, either from their general practitioner or a mental health specialist. Approximately 10% seek help from a specialist, and 8% present in other medical settings. An even higher percentage of subjects seek help for specific symptoms of social phobia. Services are utilized by approximately 20% of subjects with a fear of eating in public, by 18% of subjects with a fear of public speaking, and by 22% of subjects with a fear of speaking to new acquaintances.
IV. Suspected causes

Family studies have demonstrated an increased rate (threefold) of social phobia in first degree relatives of diagnosed individuals. This increased risk does not generalize to other anxiety disorders and this supports the classification of social phobia as a distinct clinical entity. Twin studies have found higher concordance rates in monozygotic than dizygotic twins on relevant dimensions including shyness, but the specific symptoms of social phobia have not been directly assessed.

Patients with social phobia often report retrospectively extremely harsh, demanding and perfectionistic families.

V. Biologic mechanisms and correlates

Little is known.

VI. Treatment

Social phobia can be treated with medications or with psychotherapy. A combination of both treatments may be the most effective. There is evidence that social phobia can be successfully treated with phenelzine and high potency benzodiazepines. However, tricyclics are generally not effective. For patients with pure performance anxiety, the use of beta blockers on an ad hoc basis is extremely effective, especially for public speaking and public performance.

Cognitive behavioral group therapy has been shown to be particularly effective.

VII. Service delivery

There is little comparative data. At the moment, both forms of demonstratively effective treatment require professional personnel. However, the possibility exists of developing patient self help groups utilizing trained patients as group leaders.

VIII. Centers of research excellence

Department of Psychiatry, Wayne State University School of Medicine, Detroit, MI 48207.
IX. Future directions

The pathophysiology of social phobia is quite obscure. Attempts to describe this are just beginning. The comparison and integration of pharmacological and psychological forms of treatment has recently been initiated. The utility of the MAO inhibitors is established; however, the utility of the more patient acceptable reversible MAO inhibitors requires further work. Of particular interest would be the combination of the reversible MAO inhibitor with a pure non-toxic B inhibitor such as deprenyl.

The genetics of social phobia are also not understood. As is the case with all of the anxiety disorders, comprehensive twin and pedigree studies would be valuable.

Since social phobia often presents in childhood and early adolescence, it is possible that treatment at a young age would have prophylactic value. Research on this strategy could have important clinical ramifications. Case finding in elementary school could prove useful for social phobia as well as for a number of other anxiety disorders.
X. Bibliography


ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

I. Clinical description

As the name implies, Attention-deficit/hyperactivity disorder (ADHD) is characterized by attentional deficiencies and excessive motor activity. Another key dysfunction, not reflected in the disorder's name, consists of impaired impulse control. Therefore, the hallmarks of the disorder include inattention, hyperactivity and impulsivity. The impact of these symptoms varies with the child's age, and consideration of developmental level is an important component of the diagnostic process. In addition, when present, the features of ADHD cause difficulty and incur disadvantage in multiple functional domains.

1. Symptom picture

a. Inattention. Broadly speaking, there are two main aspects of attention. One consists of turning one's attention to an activity, the other of maintaining focus on an activity once attention has been engaged. Either or both aspects may be impaired. In ADHD, it is the second, the maintenance of attention which is abnormal. There is no difficulty in capturing the attention of children with ADHD. They are responsive to their environment, and do not display indifference to external stimulation. However, they have difficulty sustaining their attention and a central feature of the disorder is a limited persistence in tasks for periods of time appropriate to the child's developmental level. The typical consequence of this symptom is that children with ADHD engage in multiple activities but fail to complete them. Even enjoyable activities may be done in fits and starts. This lack of self-application, which often results from the failure to attend, may also lead to careless errors, messy or disorganized work, and creates the impression that the children are not invested or motivated to perform.

b. Hyperactivity. Excessive activity manifests itself by excessive climbing, running, and, importantly, difficulty remaining still when doing so is expected, such as during reading and sedentary games. Children with ADHD may appear as if they are "driven by a motor." There is also excessive talking, noisiness, and general havoc associated with hyperactivity. This symptom changes as children mature.

c. Impulsivity. Impulsivity is manifested by impatience, and difficulty in situations that require waiting. Children with ADHD interrupt others excessively, jump
into things, call out inappropriately, grab or touch objects when such behavior is inappropriate. Impulsivity can create major difficulty during shopping trips, visiting others' homes, and during cooperative play where regulation of one's behavior is the norm.

2. Age-related features

The overt manifestations of ADHD are inversely related to age: the younger the child, the more obvious they are.

a. Preschool. Toddlers with ADHD are very difficult to manage. They dart from activity to activity, are into everything, comply only briefly with limit-setting. Hyperactivity is prominent. However, children are rarely brought to attention in preschool years, due to the fact that families usually accommodate to the child's erratic behavior, and although parents may experience the child as incorrigible or exhausting, they usually interpret the behavior as reflective of a high energy level rather than as a disorder.

b. Early and mid-childhood. It typically is in mid-childhood that ADHD is recognized because of its deleterious effects on children's ability to apply themselves in school, and their disruptive influence in the classroom provoke teacher complaints. Typically, teachers report that the children lack attention, have poor work habits and fail to complete homework, that they disturb other children, do not sit still, and require excessive attention. These complaints are the usual trigger for parents to seek professional attention. At this stage, hyperactivity is not as blatant as in earlier years, and usually takes the form of squirming, or fiddling with objects. Poor impulse control leads to marked behavioral difficulties in school due to calling out, interrupting teachers, clowning during instructional periods, etc.

c. Adolescence. In early to mid adolescence, the symptoms of ADHD become more subtle. Hyperactivity is rarely obvious. Rather, individuals report subjective feelings of restlessness. As a result, sedentary activities requiring long periods of inactivity are typically experienced as unpleasant. Inattention continues to affect school performance. Usually, by the time children with ADHD reach adolescence, they have developed negative attitudes toward school work, whose demands they have great difficulty meeting. As a result, conflicts with disappointed, frustrated parents ensue.

Impulsivity often leads to ill-conceived, spur of the moment, risk-taking activities that cause considerable problems, such as spontaneously taking a car for a joy ride, riding the back of buses, getting into fights.
3. Impairment

The characteristics of ADHD, inattention, hyperactivity and impulsivity occur in most children at some time. What distinguishes ordinary extremes of these features and the symptoms of ADHD is the persistence of the behaviors, and the impact they have on the individuals' lives. Children and adolescents with ADHD have difficulty fulfilling ordinary age appropriate demands due to a pattern of inattention and disinhibition. They fail to meet their own goals because of regularly occurring disruptions in self-regulation. The impairment caused by ADHD affects children's well-being in all or almost all important life circumstances, and across a variety of developmental processes.

a. Home. At home there is conflict because the child is judged as not listening, not doing what the parent demands, not following through on tasks, as being irresponsible, intrusive and disruptive. Interpersonal problems with adults and peers are typical, and children with ADHD are unpopular.

b. School. In school, in addition to being disruptive, children with ADHD fail to note and complete assignments. They are disorganized, and do not perform up to their intellectual ability. As a result, academic performance is compromised.

c. Intellectual and cognitive (mental) development. A large literature documents that the cognitive development of children with ADHD is deficient. Their IQ is lower than expected. Although the decrement is not large (i.e., about five to eight IQ points on average), its magnitude is sufficient to suggest some interference with mental development. This intellectual decrement does not appear to be wholly due to poor school performance since findings of relatively lower IQ have been obtained in preschool age ADHD children.

A great deal of research has been directed to the detection of specific deficits in mental processing in ADHD. A number of discrete cognitive functions have been found to be relatively impaired in children with ADHD. These include the failure to inhibit motor response during cognitive tasks, elevated rates of impulsive errors on vigilance tasks (i.e., continuous performance tasks), planning and forethought (i.e., Wisconsin Card Sort Test) as well as inflexible problem solving strategies as manifested by persistence of inadequate task responses, lowered ability to ignore or suppress irrelevant task cues (i.e., Stroop Word-Color Association Test), limited ability to apply previously acquired problem-solving strategies to new tasks, poor sense of time, impaired narrative skills (i.e., organizing story lines), and reduced persistence at tasks.
It is important to note that the disadvantages of ADHD children in multiple developmental cognitive functions reflect group differences. In all instances, ADHD and normal groups overlap considerably; this overlap indicates that in any single function many children with ADHD do not differ from their normal peers. As a result, none of the cognitive measures has sufficient discriminatory value to serve as a diagnostic procedure. Nevertheless, the differences in mental function are meaningful, and should not be dismissed. They have been interpreted as signifying impairment in frontal lobe function, since the latter is associated with planning, forethought, self-regulation and inhibition.

II. Epidemiology

Several population surveys have documented that ADHD is relatively common among elementary school children. In general, 3% to 5% are affected, although several studies report much higher rates. For example, a recent study diagnosed ADHD in 12.9% of 10 to 13 year olds. In adolescence, the rate of ADHD drops relative to childhood (in one instance, from 4% at age 11 to 1.2% at age 15 and in another from 12.9% to 7.5%). These divergent rates reflect differences in methods for establishing the diagnosis. The lower rates originate from clinical interview by child psychiatrists, and the elevated rates from interviews by non-professionals. No information is available regarding the frequency of ADHD in pre-school children. The reduction of diagnosable cases between childhood and adolescence suggests that there is spontaneous remission of the disorder as children mature.

ADHD is much more common in boys than girls. Depending on the diagnostic approach used, and the population of children studied, the boy to girl ratio ranges from 2:1 to 9:1. The highest ratio characterizes referred cases, whereas the lowest has been found in the general population.

Although results are not unanimous, several studies have reported higher prevalence of ADHD in lower socio-economic groups. It is not clear whether socio-economic disadvantage has a direct effect on risk for the disorder, or whether it is through other factors typically associated with social disadvantage that risk is increased (e.g., parental psychopathology, lesser parental supervision, poorer prenatal care, low birthweight, etc.). Differences between social classes have been found in all racial and ethnic groups. Different rates of ADHD have been reported across ethnic or racial groups, but studies have not applied consistent strategies for establishing the diagnosis, and rate differences may be a function of dissimilar standards. Importantly, the range in prevalence across various national, ethnic or racial groups are similar to the range reported across studies in
the U.S. in Caucasian groups. Therefore, no clear or even suggestive evidence exists for a relationship between ADHD and ethnicity or race.

III. Natural course

1. Comorbidity

Other psychiatric disorders have a relatively elevated prevalence in ADHD children. The most frequent is Oppositional Defiant Disorder, which consists of a pattern of negativism, non-compliance, and defiance. It may legitimately be considered a complication of severe ADHD, since children who are inattentive and impulsive find it difficult to conform to ordinary demands, and become negative and resistant to adult expectations.

In addition to a pattern of oppositional behavior, a relatively high rate of Conduct Disorder is well documented. The latter entails more serious rule breaking than Oppositional Defiant Disorder. It includes the failure to conform to major societal standards, and is manifested by repeated truanting, stealing, lying, aggression, cruelty to others and animals, and generally irresponsible behavior. There is now good evidence documenting that ADHD promotes the development of Conduct Disorder.

Comorbidity with childhood anxiety disorders has also been reported, although the evidence is contradictory, in part because longitudinal studies of children with ADHD have not identified anxiety disorders as a feature of course. Similarly, some investigators have indicated that mood disorders, especially depression, are frequent in children with ADHD. A currently controversial issue is the relationship between ADHD and bipolar disorder (also known as manic-depressive disorder). Some systematic diagnostic studies have reported a high rate of manic-depression in children with ADHD. This observation, if correct, is potentially important since the management of bipolar disorder, requires treatment strategies that diverge markedly from those appropriate to ADHD.

ADHD is common among children treated for Tourette's disorder, which consists of persistent motor and vocal tics. It is not clear whether this comorbidity is a genuine phenomenon, or whether it occurs mostly in children who have come to professional attention in clinics that specialize in the treatment of Tourette's disorder. In any case, Tourette's disorder is a very rare condition, and is not usually seen among children referred because of ADHD.
Finally, specific learning disorders, such as impaired skill acquisition in reading or arithmetic, are associated with ADHD.

2. Longitudinal course

Because of the high prevalence of ADHD and the serious nature of its associated impairment, its longitudinal course takes on special importance. The vast majority of children are referred during elementary school years, and it is during this developmental period that impairment is most clearly evident. Therefore, we follow the evolution of childhood ADHD through adolescence into adulthood.

The information on longitudinal course is restricted to prospective controlled studies, since their diagnosis of ADHD in childhood is not in question, and permit comparisons with "normal" controls. A number of studies have described the adolescent outcome of boys with ADHD, but only three investigations of adult status have been conducted. Because of the scarcity of affected girls in clinical samples, very little information is available on their eventual fate.

3. Adolescent outcome

There is agreement across studies that considerable dysfunction characterizes the adolescent adjustment of male children who were diagnosed with ADHD in childhood.

a. School functioning. As adolescents, ADHD boys who were diagnosed with ADHD have poorer school performance than their peers and limited data suggest that they continue to have impaired cognitive functioning. A large proportion have behavioral problems, and exhibit provocative, rule breaking behaviors in school. Consequently, they are relatively more often suspended, and are much more likely than other adolescents to drop-out of school.

b. Social adjustment. The social adjustment of adolescent males is especially poor in the school setting, where conforming to others' expectations is most problematic. In the community, where the youngsters can select their social settings, the evidence for impaired social relationships is not so clear.

c. Psychiatric disorders. A large proportion of adolescents continue to have the full complement of ADHD symptoms (about 70%). The continued presence of ADHD is likely to account for their characteristically marked academic disadvantage. In addition, ADHD children, if they did not already have a Conduct disorder in childhood, are at risk
for developing the disorder. Furthermore, in adolescence, ADHD children have elevated rates of Substance use disorders (i.e., significant functional interference due to substance use). A clear clinical pattern emerges as the boys reach adolescence: about 30% remit from ADHD and have relatively good academic, social and psychiatric outcomes (i.e., free of Conduct and Substance use disorders). In those whose ADHD symptoms do not remit during early adolescence, the likelihood of developing a Conduct disorder is sizeable (about 50% in the persistent cases vs. 10% in remitted individuals and controls); and, in turn, drug use disorders will occur in about two-thirds of those in whom a Conduct disorder has set in (vs. 4% in the rest of subjects). Thus, a sequential unfolding characterizes the course of ADHD into adolescence: 1) the persistence of ADHD; 2) the development of Conduct disorder in those who retain their ADHD; 3) substance use disorders in those with a Conduct disorder.

Further functional disadvantage in adolescence is evidenced for ADHD boys by more arrests, more serious criminal offenses, and more incarcerations. A history of criminality and contact with the police is completely due to the development of Conduct disorders. If these do not arise, there is little risk for this very negative outcome.

4. Adult outcome

Given the bleak picture of the adolescent adjustment of a large subgroup of ADHD boys, there has been major concern about outcome in adulthood. Three investigations have followed up ADHD boys into adulthood.

a. Socioeconomic outcome. In terms of broad demographic status, which includes marital status, and living circumstances, adults who had a diagnosis of ADHD in childhood do not differ from their peers. However, other disadvantages occur. The educational attainment of children with ADHD is seriously compromised. In non-disadvantaged Caucasian ADHD children, about one third do not complete high school, as compared to only 2% of controls. As adults, ADHD children are not more likely than peers to be unemployed or on public assistance. However, in keeping with their relatively limited schooling, they have lower occupational levels. Their childhood disorder has put them at a significant economic disadvantage. Childhood ADHD does not appear to cause a downward drift toward the lower classes, relative to their family of origin. Characteristically, ADHD children maintain their parents' socio-economic status, but do not go up the educational and economic ladder, whereas their normal counterparts surpass their families' attainment.
b. Psychiatric disorders. A relatively elevated rate of psychiatric disorders continues to characterize ADHD children as they reach adulthood. However, ADHD which was still highly prevalent during adolescence drops dramatically. Two studies find an ADHD rate of about 10% for the disorder in adulthood, but another reports that a third of the adult ADHD children still have an ADHD symptom. In spite of a reduction in ADHD, Conduct disorders (called Antisocial Personality Disorders in adulthood) and Substance use disorders continue to be relatively elevated. A substantial minority have chronic criminal histories and some are incarcerated. In addition, death at an early age, due to accidents or murder, has been reported in 3% of ADHD cases compared to none in controls. No other psychiatric complications have been identified. Thus, so far, no excess of mood, anxiety or psychotic disorders has been reported.

5. Outcome of girls with ADHD

The data on the fate of girls are limited, but the little evidence there is suggests that their outcome does not differ from that of boys'. The girls also experience a tumultuous adolescence with an elevation of Conduct disorder. In adulthood, like boys, there is a relatively lower educational attainment, but a marked diminution of psychopathology.

In summary, over time, ADHD remits in a substantial proportion of affected boys, but adolescence is characterized by considerable dysfunction related to antisocial behavior and substance abuse. The latter are entirely a function of the maintenance of ADHD during adolescence. Many of these dysfunctions continue in adulthood in a substantial proportion, but not in the majority. In general, the course of childhood ADHD is characterized by educational and occupational disadvantage. Girls with ADHD appear to follow similar courses but the information is too limited to draw conclusions.

IV. Suspected causes


Several lines of investigation suggest that ADHD is, in part, transmitted genetically. For example, greater concordance for the disorder has been reported in identical than fraternal twins, and in full than half siblings. Unfortunately, these studies are limited by their small size, the lack of independent assessment, as well as other methodological limitations. Other studies have evaluated the rate of psychiatric disorders in parents of clinic children with ADHD. These studies have found a higher rate of ADHD in the relatives of ADHD children and therefore document familial aggregation for ADHD. Interpretation of transmission is less clear in these reports than in the case of twin or
sibling studies, since they confound environmental and genetic transmission. Thus, it is not clear whether the disorder is conferred to the child via the family's behavioral or biological characteristics, or both. In spite of the limitations of the family studies, their findings suggest genetic transmission since, whenever familial concordance has been found with the family method, genetic transmission has been documented via rigorous investigative approaches. Therefore, it is likely that genetic transmission influences the development of childhood ADHD. Why boys should be differentially affected is unclear. However, a gender difference in hereditary conditions is not unusual and, in itself does not argue against heritability.

The most informative strategy for studying genetic transmission is the cross-fostering method which compares the rate of disorder in adopted away offspring of affected and unaffected parents. No adequate study of the children of well diagnosed ADHD individuals has been conducted, whether adoptees or natural offspring. One study examined the adopted away offspring of parents with a pattern of antisocial behavior or criminal conviction and found an elevated rate of ADHD among their children. In view of the relationship between ADHD and antisocial disorders found in follow-up studies of children with ADHD, these results support a genetic factor in ADHD.

The increased concordance for ratings of ADHD (not the diagnosis) obtained among biologically related adoptees compared to non-related adoptees also supports genetic transmission of features of ADHD. Similarly, studies of twins have yielded evidence for concordance of scale ratings of inattention and hyperactivity, with genetic rather than environmental factors accounting for the concordance.

In addition to ADHD, relatives of affected children have been found to have elevated rates of depression and anxiety, but the evidence is not consistent.

Results of the family research have prompted a search for a specific gene abnormality. Thus far, one study has reported that a dopamine transporter gene is affected. If so, the finding is extremely important. However, it requires replication since reports of gene abnormality often fail the test of verification. Unfortunately, such an attempt, recently published, failed to corroborate this finding.

The research on the genetics of ADHD should not mislead one into the belief that most children with ADHD have affected parents. In fact, most do not. A family history of ADHD is neither a necessary nor sufficient antecedent to the childhood disorder; other factors must influence its occurrence.
2. Environmental factors

Environmental factors include a broad variety of influences, ranging from home environment and parental behavior to nutrition or intrauterine events or exposure to toxins. All these have been implicated as causal mechanisms in ADHD.

a. Parental behavior. Much weight has been given to the role of parental behavior in the origin of ADHD. In this context, ADHD children were viewed as having been deprived of the normal pattern of reward for appropriate social and self-regulatory behaviors, leading to an excess of maladaptive behavior characteristic of ADHD. Indeed, mothers of ADHD children, compared to mothers of normal children, are more controlling, demanding, more intrusive and negative. However, if children are treated successfully, mothers’ behavior toward the ADHD children normalizes and becomes indistinguishable from the behavior of other parents. Therefore, the deviant parenting experienced by ADHD children are the result of their disorder, not their cause.

b. Nutritional factors. Two main food constituents have been hypothesized to provoke symptoms of ADHD: sugar and artificial food coloring. Attempts to link these nutritional factors and ADHD have failed, and it must be concluded that they do not appear to influence the expression of ADHD.

c. Paranatal factors. Birth and pregnancy complications have been reported to be associated with relatively higher levels of activity in children, but no elevation of paranatal complications obtained from hospital records has been found in children with ADHD. Investigative strategies have limited the ability to rule out these events altogether since no systematic prospective study has been conducted.

A recent prospective study of infants found that low birthweight (<2,500gm) coupled with social disadvantage was an antecedent of ADHD in early elementary school age children. This report represents the first demonstration of the influence of paranatal factors on ADHD. The effect of birthweight on ADHD is not large, and does not account for a large proportion of cases. Nevertheless, it represents an important finding that should be pursued to identify the ultimate nature of the risks conferred by low birthweight, and the exact nature of the disadvantage incurred by the children over time.

d. Toxins. Children’s exposure to lead has been found to be related to elevated ratings of activity (not specifically ADHD), and mildly elevated lead levels have been found in ADHD children. However, the magnitude of the contribution of lead to the emergence of ADHD is very small. Therefore, even if all lead exposure were eliminated,
rates of ADHD would not be affected to any meaningful degree. At the same time, the research points to the importance of efforts to eliminate exposure to lead.

In summary, no single factor alone accounts for ADHD. The most important influence identified so far is parental history of ADHD. Other correlates with weaker contributions consist of low birthweight and lead exposure. The notion that parental behavior is a causal influence in ADHD has been refuted.

V. Biological mechanisms and correlates

Empirical findings give strong support to a biological basis for ADHD; therefore, a search for brain function abnormality has been an active endeavor that has relied on several approaches.

1. Neurochemistry

A common strategy for inferring brain activity is to measure neurotransmitter metabolites in the blood, the urine, and the spinal fluid. Mainly, the neurotransmitters dopamine and norepinephrine have been viewed as important to the biology of ADHD. The multiple studies that have examined metabolites in blood and urine have yielded contradictory findings. Some, but not all studies of spinal fluid dopamine metabolites have supported a hypothesized reduction of dopaminergic activity in ADHD. There is also preliminary evidence that dopamine activity may predict response to stimulants in children with ADHD and that the same may be true in adults.

The biological models that have been tested are crude. Relationships between neurotransmitter activity and ADHD are likely to be very complex, and unlikely to be reflected in simple quantitative differences. More sophisticated models of brain function will be required to enable informative investigations of brain chemistry in ADHD.

2. Brain imaging

Brain imaging is the most recent investigative approach to the study of brain anatomy and function. It is a highly technical field with built-in obsolescence as new measurement and analytic techniques rapidly evolve. Therefore, it is difficult to integrate results of early and recent investigations since they utilize different methodologies. In addition, brain imaging is very costly; consequently, small samples are the rule. The situation is changing with the recent contributions by NIMH researchers who have conducted the largest studies to date. Some studies have reported differences in overall
brain metabolic rates and in cerebral blood flow in ADHD, but these findings have not held up when various controls were introduced, and have not been replicated. Therefore, the focus of research has shifted from the documentation of diffuse, non-specific global brain abnormality to the identification of specific abnormal brain regions in ADHD.

Reduced brain asymmetry in ADHD children has been regularly observed, but its exact nature varies. Anterior brain structures appear especially deviant in ADHD. Of interest is that abnormalities found in other diagnostic groups, such as enlarged brain ventricles in schizophrenia, do not occur in ADHD, and the specific regions found to deviate from the norm may be specific to ADHD. Therefore, the search for brain abnormality via neuroimaging techniques appears promising. At this stage, the lack of consensus across studies precludes establishing a clear pattern of brain abnormality in ADHD. The NIMH study which has the largest sample to date reports two main findings: 1) that ADHD children display normal left-right brain asymmetry, but its magnitude is reduced. This abnormality, presumed to reflect abnormal fetal development, occurred regardless of age; 2) reduced volume of the right anterior frontal brain region. On the whole, results point to abnormal development of the right hemisphere in ADHD. Findings of frontal lobe abnormality are especially important, since many of the cognitive and behavioral deficits of ADHD children are consistent with frontal lobe dysfunction. Brain imaging research in childhood ADHD is relatively new, and a clearly articulated model of brain abnormality awaits further investigation. What is important is that ADHD has been shown to be associated with deviant brain development, and that the abnormalities appear different from those found in childhood schizophrenia, and therefore may be specific to ADHD.

3. Electrophysiology

Prior to the advent of neuroimaging, electroencephalographs (EEG) were the standard tools for assessing brain function. Although the technique has been supplanted for some purposes, it still remains a legitimate means of assessing brain function. Studies have not always reported differences in EEG responses to specific sensory stimulation (i.e., auditory or visual evoked potentials), however, the positive findings fit an overall model of what is called hypor arousal, revealed by diminished amplitude of EEG tracings that reflect arousal. These findings have led to the argument that ADHD children suffer from a lack of brain responsivity, and therefore seek greater stimulation than their normal counterparts. This model is appealing since it fits nicely with the sensation seeking behavior observed in these children.
In summary, methods that have relied on peripheral measures (blood or urine) of brain metabolism have not provided documentation of specific dopamine or norepinephrine abnormality in ADHD. However, some studies report that central (spinal fluid) dopamine levels are deviant in ADHD and predict stimulant efficacy. Brain imaging studies have identified abnormal development of anterior right hemisphere regions.

VI. Treatment

The treatment of children with ADHD includes medication as well as psychotherapeutic approaches.

I. Psychopharmacology

The stimulants are the most widely used and best studied compounds for the treatment of ADHD. Antidepressants also are employed, but represent second line treatments.

a. Stimulants. Stimulant efficacy was discovered accidentally in the mid-1930's and has been researched extensively over the past three decades (for methylphenidate [Ritalin], dextroamphetamine [Dexedrine] and pemoline [Cylert]). They all have relatively short periods of efficacy and require multiple daily administration. There is overwhelming evidence of their efficacy in ADHD. The symptoms of inattention, hyperactivity and impulsivity are markedly improved by treatment. In addition, social behavior with peers, parents, and teachers is also enhanced, leading to more positive behavior toward the child by others. Academic performance, which is regularly problematic in ADHD children, has been found to be ameliorated by stimulant treatment. The stimulants have broad, clinically meaningful impact with efficacy demonstrated for symptomatic status, cognitive performance and interpersonal relationships. The compounds have been shown to be efficacious throughout the age range (from childhood through adulthood).

b. Antidepressants. The antidepressant compounds used in ADHD are not used for their effect on mood. Rather, they substitute for stimulants when these are not tolerated or are ineffective. Their use has implications for the biology of ADHD, since they are viewed as affecting noradrenergic regulation (one of the functions hypothesized as deviant in ADHD). The antidepressants are not as effective as stimulants and represent a second line treatment. Their effect on the noradrenergic system has not been found to predict behavioral response.
c. Other compounds. Other medications have been used and reported useful (i.e., clonidine, bupropion), but they do not approach the efficacy of stimulants and do not play a primary role in the therapeutics of ADHD.

2. Psychotherapeutic treatments

The psychotherapeutic approaches applied to ADHD do not include traditional individual psychotherapy, which is not felt to be relevant to the amelioration of ADHD symptoms. Rather, they have been developed from putative models of the disorder.

a. Behavior modification therapy. Behavior modification consists of developing a program of negative consequences for problematic behaviors and rewards for appropriate behaviors. This treatment rests on the theory that ADHD symptoms are the result of faulty early parental training. By correcting the latter, children are given the opportunity to acquire and maintain skills they never were taught. The evidence indicates that the behavior of ADHD children is ameliorated by behavior modification, but only while the dispensing of rewards and punishment is ongoing. When it ceases, the symptoms return. Therefore, the hope that the treatment would alter children's ability for self-control has not been met.

b. Cognitive training. The view has been advanced that the underlying deficit in ADHD consists of impaired ability to organize and process experience (mental as well as social), and aims at enhancing self-regulation through training of specific strategies, and ultimately at altering the way the individual experiences the world. This ambitious approach has failed to induce behavioral, academic, or other gains in several well-executed studies.

3. Combined pharmacotherapy and psychotherapy

The greatest expectation for optimal treatment efficacy has been placed on the combination of medication and psychotherapy. This approach has been applied for short and long intervals (up to 2 years). The studies have combined medication with single as well as multiple psychotherapeutic interventions. So far, the results have not provided documentation for the superiority of combining stimulant and psychosocial treatments, even when their application is extended for two years.

In summary, the clinical efficacy of stimulants is very well-established. Other medications offer less satisfactory alternatives. Psychosocial interventions alone are not
viable competitors to stimulant treatment; when combined with stimulants, they have not been shown to provide significant incremental advantage over the use of stimulants alone.

VII. Service delivery

The vast majority of children with ADHD are identified by teachers. However, many children go unrecognized and it is mostly those who are disruptive who are referred for treatment. Those whose ADHD symptoms incur serious disadvantage for their academic progress with mild behavioral disruption typically are missed. The diagnosis is often made by pediatricians, or child mental health clinics. Only a minority of children are seen by child psychiatrists. The diagnosis has a good measure of consistency across practitioners because of the availability of standardized rating scales that have established validity for the diagnosis. Pediatricians are the exception since their practice does not typically rely on consultation with school personnel. Diagnostic and therapeutic practices are closely linked and usually occur in the same setting. Although ADHD is a disorder with prolonged duration, most treatment centers do not have treatment models that anticipate long-term care with the goal of minimizing the complications known to have high frequency in ADHD.

VIII. Centers of research excellence

*Columbia University, NY
   Clinical Research:  
   i. Treatment evaluation  
   ii. Longitudinal studies

*Duke University, NC
   Clinical Research:  
   i. Treatment evaluation  
   ii. Assessment  
   iii. Cognitive function  
   iv. Longitudinal studies

*Long Island Jewish Medical Center, New Hyde Park, NY
   Clinical Research:  
   i. Treatment evaluation  
   ii. Longitudinal studies

National Institute of Mental Health, Washington D.C.
   Basic Research:  
   i. Neuropsychology  
   ii. Brain imaging
University of Buffalo, Buffalo, NY
Clinical Research:
i. Treatment evaluation
   ii. Longitudinal studies

University of California at Berkeley, CA
Clinical Research:
i. Treatment evaluation
   ii. Longitudinal studies

University of California at Irvine, CA
Clinical Research:
i. Treatment evaluation
   ii. Longitudinal studies
Basic Research:
i. Genetic research (gene identification)

University of California at Los Angeles, CA
Clinical Research:
i. Family studies

University of Massachusetts, Worcester, MA
Clinical Research:
i. Early intervention
   ii. Parent-child interaction
   iii. Longitudinal studies

Massachusetts General Hospital, Boston, MA
Clinical Research:
i. Family studies
   ii. Comorbidity
   iii. Treatment evaluation

Henry Ford Health System
Perinatal antecedents:
i. Low birthweight
   ii. Maternal smoking

The Henry Ford Health System has an outstanding record of research in psychiatric epidemiology, which has included recently a program of research on low birthweight children and maternal smoking which has focused on ADHD.

*The starred centers are part of a multi-site research program which is completing a study of medication and multiple psychosocial treatments in about 300 children with ADHD. The cohort is slated for follow-up starting in 1997.
IX. Future Directions

1. Treatment development

   a. Medication. In spite of very well documented efficacy for stimulant treatment, the latter is not a panacea, and the development of other effective compounds that can be used instead of, or in conjunction with, stimulants is clearly a desideratum.

   Some of the limitations of stimulants include: short span of action, requiring multiple daily dosing, intolerance of the medication by some, severe symptom recurrence while medication wears off in some children, delay of sleep-onset which preclude drug administration late in the day and therefore prevents therapeutic coverage for the entire waking hours, potential for abuse in older individuals. Therefore, research for new compounds is to be encouraged and supported.

   b. Psychosocial treatment. At this juncture, plans for innovative psychosocial treatments await results from an ongoing large scale, multi-site study conducted under the aegis of NIMH that compares four treatments delivered for 14 months: intensive psychosocial treatment with parents, families and teachers, stimulant treatment alone and combined with the psychosocial intervention, and treatment obtained in the community. The outcome of the study will guide future development of non-medical interventions in ADHD.

2. Secondary Prevention Strategies

   The follow-up studies of ADHD children have been important in delineating specific disadvantages in the ultimate adjustment of these children. As summarized above, conduct disorder, criminality and substance use disorders are elevated. In addition, educational attainment is compromised with ultimate occupational disadvantage. Attempts to design educational settings that would facilitate the retention of ADHD adolescents appears worthwhile. At the same time, the development of standardized means for identifying children who are just beginning to develop antisocial behavior and the development of strategies for reversing these would represent a major public health contribution.

3. Biological research

   The evidence for the influence of biological factors is considerable but still insufficient for clear identification of specific brain abnormality. Brain imaging is the most promising approach. At this time, only one center in the US is conducting research with
adequate samples to generate meaningful data. A single center is insufficient, since it is critical that results be reported from multiple independent sources to become fully established. Therefore, support in this area is called for. In addition, the identification of an abnormal gene is most encouraging, but requires further proof. Such research also lacks support.

4. Family and twin studies

The family studies conducted to date have been limited in scope. There is a lack of twin studies, one of the most informative strategies for dissecting genetic and environmental influences, as well as their interaction. Due to limited access to twins, this model has been neglected. Research that specifically targets studies of twins would make a major contribution in furthering our knowledge of ADHD.

X. Bibliography


CONDUCT DISORDER

I. Clinical description

In broad terms, Conduct disorder is defined as a pattern of serious disregard for the social rules of one's cultural subgroup in such a way that the well-being and rights of others are damaged. The concept does not refer to eccentric comportment that is at odds with the group, but to deliberate action that inflicts pain or loss to others. The behavioral characteristics of Conduct disorder are perhaps the most easily understood of all psychiatric conditions since they encompass ordinary, familiar but problematic antisocial behaviors, such as lying, physical fighting, stealing, vandalism, physical cruelty to others, and general disregard for rules, for example truanting or violating curfews.

It is not unreasonable to question why these features form the basis of a psychiatric disorder since they appear to reflect mundane, even if objectionable, childish behaviors and to indicate bad attitudes rather than dysfunction. However, several features distinguish Conduct disorder from simple naughty activity or mean tendencies. For one, there is a pattern of such behaviors. The latter are not occasional, isolated acts, but form the fabric of the child's interactions. Therefore, most relationships (home, school, social) are affected deleteriously. In addition to the specific symptom picture which is bad enough in itself, the functioning of children with Conduct disorders is compromised in other ways. They typically do poorly in school, fail to develop meaningful friendships, are in serious conflict with parents and siblings. In some instances, the youngsters are institutionalized. In fact, conduct disorders form the bulk of the inpatient child population.

The disorder has been recognized for a very long time, and was one of the first to attract professional attention. The first child psychiatric clinics were formed to treat children with antisocial behavior in response to the needs of juvenile courts, in the first quarter of this century. As a result, relatively greater knowledge has been accumulated concerning its manifestations, treatment and natural history.

To provide a full appreciation of the diagnostic standards for Conduct disorder, its official diagnostic definition is presented below.

I. A repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated, as manifested by the presence of three (or more) of the following criteria in the past 12 months, with at least one criterion present in the past 6 months:
Aggression to people and animals
(a) often bullies, threatens, or intimidates others
(b) often initiates physical fights
(c) has used a weapon that causes serious physical harm to others (e.g., a bat, brick, broken bottle, knife, gun)
(d) has been physically cruel to people
(e) has been physically cruel to animals
(f) has stolen while confronting a victim (e.g., mugging, purse snatching, extortion, armed robbery)
(g) has forced someone into sexual activity

Destruction of property
(a) has deliberately engaged in fire setting with the intention of causing serious damage
(b) has deliberately destroyed others’ property (other than by fire setting)

Deceitfulness or theft
(a) has broken into someone else’s house, building, or car
(b) often lies to obtain goods or favors or to avoid obligations (i.e., "cons" others)
(c) has stolen items of nontrivial value without confronting a victim (e.g., shoplifting, but without breaking and entering; forgery)

Serious violations of rules
(a) often stays out at night despite parental prohibitions, beginning before age 13 years
(b) has run away from home overnight at least twice while living in parental or parental surrogate home (or once without returning for a lengthy period)
(c) is often truant from school, beginning before age 13 years

2. The disturbance in behavior causes clinically significant impairment in social, academic, or occupational functioning.

It is apparent that the symptoms reflect a failure to adhere to society's values. Does this mean that the children are budding social activists, and that are we mistakenly diagnosing potential political rebels? Unfortunately, that is not the case. The youngsters with Conduct disorders do not pursue a cause, or violate rules because they aspire to different ideals. They disregard the welfare of others insofar as it brings advantage or satisfaction to themselves only. This distinction is important, since some concerned
citizens fail to distinguish deviations from the norm that rest on rational principled rejection of societal standards and those that come from a selfish disregard for others' welfare. As a result, some controversy has occurred concerning the legitimacy of this diagnosis, especially when it is applied to disadvantaged minority groups. It is important to stress that although Conduct disorder has a negative impact on others, it also occasions multiple disadvantages to the affected individual himself. Some of these are noted in the section on course. Nevertheless, there is controversy concerning the legitimacy of considering this pattern of behavior as definitional of a disorder. Is it simply society's failure to instill moral values in children? This argument is weakened by the observation that there is a well established pattern to the disorder, that its features aggregate in reliable fashion, and that it has a predictable natural history. However, regardless of the origin of Conduct disorder, or its status as a disorder, families with affected children are in desperate need of assistance. From this vantage point alone, it behooves the mental health professions to dedicate themselves to the better understanding and treatment of Conduct disorder.

Conduct disorder must be distinguished from delinquency. Although the two concepts overlap, they are not identical. Delinquency is not a psychiatric term; rather, it is the legal definition of a minor who violates the law, or is in trouble with the law. It is possible to have a Conduct disorder without involvement in illegal activities (for example, by the combination of lying, bullying, and being cruel to animals). It is also possible for youngsters to break the law and become known to the legal system without their having a chronic pattern of antisocial behaviors. In spite of these exceptions, delinquents generally encompass the most extreme Conduct disorders, but the two terms are not synonymous and the distinction between Conduct disorder and delinquency is not a mere semantic argument.

The bulk of the research has focused on delinquents. This strategy is understandable since identification of children who have had police contact is simple, and does not require specialized assessments. However, the fact that many children with Conduct disorder are not included in populations of delinquents, and since delinquents are almost entirely adolescents, the information generated on them may not be relevant to the whole range of children with Conduct disorder. The point is illustrated by finding that, in a population of women with the adult form of Conduct disorder, only 17% had ever been arrested at least twice, or had ever been convicted of a felony.

There is also overlap between aggressive behavior and Conduct disorder. However, many children considered aggressive do not display a pervasive versatility of antisocial
behaviors and therefore do not have a Conduct disorder. Because of potentially important distinctions between Conduct disorders and delinquency, as well as aggressivity, the summary of research is restricted to data pertaining specifically to the diagnosis of Conduct disorder, except for a few instances.

Impairment. Even in its mild form, Conduct disorder may pose serious problems because, often underlying the behaviors is an uncaring, even callous attitude toward others. Impairment becomes accentuated with age. Early on, in preschool and early school age, children are typically rejected by peers, and are the butt of more punishment at home. The disadvantages do not so much change, as accrue over time. As they mature, in addition to being ostracized and to receiving more punishment than other children, children with Conduct disorder fail to perform up to their academic ability, are more often suspended and left back in school, and may become known to the judicial system, a process which may lead to separation from the family through mandated placement in residential treatment centers at early ages, and in the equivalent of jail in late adolescence.

Conduct disorder exacts a high cost to the child, as well as to the family since theft, rule breaking, and property destruction often occur in the home. Society is burdened due to the disorder’s disproportionate capture of school and treatment resources, and its unique burden on the judicial system.

II. Epidemiology

The frequency of Conduct disorder is related to gender. No matter what diagnostic standards are applied, where cases are identified, or at what point in history the studies have been conducted, boys are over-represented. This gender difference parallels well-established observations of greater propensity for aggressive behavior in normal boys compared to girls. The prevalence estimates of Conduct disorder with current diagnostic standards range from 6 to 10% in boys, and 2 to 9% in girls. The relatively large range of prevalence reflects variations in the frequency of Conduct disorder in different populations as a function of the contrasting distributions of factors, other than gender (these are summarized below). Population surveys indicate that the prevalence of Conduct disorder has been rising steadily over the past thirty years.

The excess of boys is much less marked during adolescence than during preadolescence, but it never disappears.

There is a dramatic elevation of antisocial behaviors in adolescence and it appears that the prevalence of Conduct disorder escalates during this period. In addition, there is
a relationship between gender and age at onset. The over-representation of males is very marked in childhood, with relatively few girls having Conduct disorder as preadolescent. Although a predominance of males continues through all ages, the gender difference is lessened during adolescence. This change is due to a characteristic adolescent onset in girls, whereas in boys it spans the entire age range.

Several aspects of socio-economic adversity have been linked to antisocial behavior in children. They include inner-city residence, high crime neighborhoods, poverty, family crowding, and disadvantaged school environments. Obviously, these are interrelated, and exposure to one greatly increases the likelihood of others being present as well. It is suspected that the effect of these social factors is mediated, in part, through parental behavior. The expectation is that positive parental practices may inoculate the child, so to speak, against the negative effects of multiple deleterious aspects of social and economic disadvantage. The view that social factors have an indirect rather than direct effect on children’s antisocial behavior is bolstered by the observation that the majority of children who live in impoverished, crime ridden communities do not have Conduct disorders. Nevertheless, the impact of these broad social conditions cannot be ignored as making an important contribution to the development of Conduct disorders, and as contributing to the relatively higher prevalence of Conduct disorders among disadvantaged children.

The relationship between disadvantage and Conduct disorder is further complicated by the fact that social factors are related to preadolescent, but not adolescent onset of Conduct disorder.

Insofar as race is correlated with disadvantage, Conduct disorders are associated with race. Beyond this relationship, there appears to be no specific relationship between the two. This conclusion certainly pertains to information collected in the United States. However, a British study reported a higher rate of Conduct disorder among blacks than whites in inner city London, matched for social class. Problematical, it is very difficult to match racial groups on social factors, since racial discrimination cannot be equated, and it might constitute an indirect influence, in combination with other disadvantages, in shaping children’s propensity for antisocial behavior.

III. Natural course

1. Comorbidity

There are important implications to establishing patterns of diagnostic comorbidity. For one, it points to the necessity of assessing cases for disorders known to aggregate.
Second, it may have relevance to treatment since different interventions may be necessary to treat the range of clinical dysfunction.

Among children with Conduct disorder identified in a general population study of 11 year olds in New Zealand, 50% of those with Conduct disorder had another psychiatric diagnosis. The most commonly co-occurring disorder is Attention Deficit-Hyperactivity Disorder (ADHD). In fact, in clinical settings, it is exceptional to find young children with Conduct disorder who do not also have ADHD. Consistent with clinical observations, a recent British epidemiological study could not identify a single child with Conduct disorder who did not also have ADHD. Therefore, this diagnostic overlap is not exclusive to children referred for treatment. As we discuss in the treatment section, this pattern of comorbidity has treatment implications for Conduct disorder, since ADHD is successfully treated with medication. ADHD is also important because the severity of Conduct disorder is considerably greater among children with ADHD.

In addition to ADHD, children and adolescents with Conduct disorder, especially girls, identified in clinical as well as population studies, have been reported to be at risk for anxiety and depressive disorders. The clinical consequences of this finding is unclear, since treatment for these is not well established in young people (this is not the case of the management of adults with anxiety or depressive disorders). Unlike ADHD, these disorders have not been found to affect the severity or other important aspects of Conduct disorder.

2. Stability and change during the lifespan

Ordinary childhood aggression has been shown to be stable, especially in boys. Not only is propensity to aggressive behavior the most consistent of all early childhood characteristics, but it also predicts delinquency in adolescence. These findings from developmental psychology foster the expectation that conduct disorders also are stable. Indeed, stability of conduct disorder has been documented in longitudinal studies. As with normal aggression, there is considerable remission over time, with many cases desisting, but a substantial proportion remaining affected. The worst outcome occurs among those with early onsets—the same youngsters who are likely to suffer from a concurrent ADHD. The combination of ADHD and Conduct disorder is especially pernicious with regard to severity and course compared to Conduct disorder alone. Conduct disorder with an onset in adolescence is often limited to this developmental period, without significant sequelae in adulthood.
3. Adult outcome

   a. Adult psychiatric status

   The most common outcome in adulthood is Antisocial personality disorder, an adult condition which represents the continuation of the diagnosis of Conduct disorder in children. To clarify its nature, the diagnostic characteristics of Antisocial Personality Disorder are presented below.

   1. There is a pervasive pattern of disregard for and violation of the rights of others occurring since age 15 years, as indicated by three (or more) of the following:
      (a) failure to conform to social norms with respect to lawful behaviors as indicated by repeatedly performing acts that are grounds for arrest
      (b) deceitfulness, as indicated by repeated lying, use of aliases, or conning others for personal profit or pleasure
      (c) impulsivity or failure to plan ahead
      (d) irritability and aggressiveness, as indicated by repeated physical fights or assaults
      (e) reckless disregard for safety of self or others
      (f) consistent irresponsibility, as indicated by repeated failure to sustain consistent work behavior or honor financial obligations
      (g) lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another

   2. The individual is at least age 18 years.
   3. There is evidence of Conduct Disorder with onset before age 15 years.
   4. The occurrence of antisocial behavior is not exclusively during the course of Schizophrenia or a Manic Episode.

   The individuals who continue into Antisocial personality disorder have relatively higher rates of criminality, multiple arrests and incarceration.

   As adults, youngsters with Conduct disorder also suffer disproportionately from alcoholism, drug abuse and depression. It is difficult to give precise estimates of the rate of children with Conduct disorder who go on to experience the above psychiatric outcomes since they vary depending on the nature of the group. In the largest study, completed in the late 1950's, about 30% of children with Conduct disorder went on to have Antisocial personality disorder as adults. However, if one focuses on cases who maintain the Conduct disorder into adolescence, half display antisocial disorders in adulthood.
This proportion reflects a very high rate of stability, especially if one considers that the likelihood of having an antisocial disorder in adulthood is virtually nil unless Conduct disorder occurred in childhood. Thus, childhood Conduct disorder is a necessary condition for adult Antisocial personality disorder, and the absence of Conduct disorder guarantees its absence in adulthood. However, even among Conduct disorder cases who do not go on to have Antisocial personality disorder, the rate of other psychiatric symptoms and associated dysfunctions is elevated. Therefore, even among remitters, function is impaired in a variety of ways.

For reasons as yet not understood, antisocial symptomatology is self-limited, and a marked fall off occurs between the ages of 30 and 40 years. This developmental pattern explains why criminal behavior is relatively scarce among older individuals. However, this positive trend does not lead to normalization of adjustment, since alcohol and drug abuse continue to exact a toll.

Mortality is another negative outcome of sustained Conduct disorder. It occurs, in part, from consequences of psychiatric illness since alcoholism and drug abuse lead to medical complications that may be lethal, as well as to suicide and homicide.

b. Educational and occupational status

The ultimate educational and occupational attainment of children with Conduct disorder is greatly compromised. In fact, children with chronic Conduct disorder who come from middle and upper class families are very likely spend their lives in the lower stratum of society. The poor work history of children with Conduct disorder is not simply the result of poor educational attainment; a characteristic feckless attitude, irresponsibility, and failure to meet work standards contribute greatly to occupational instability, low status, and unemployment. Individuals with Antisocial personality disorder place a disproportional burden on social agencies and community resources as a result of their frequent failure to sustain themselves and their dependents.

c. Marital\parental function

As adults, children with Conduct disorder are much more likely than others to experience marital conflict, separation and divorce. There is also a pattern of irresponsibility leading to neglect and abandonment of children. In addition, to the degree that drug abuse and alcoholism occur among adults whose childhood Conduct disorder has not remitted, there is additional disadvantage to offspring. They are not only at much higher risk for Conduct disorder themselves, but also for the deleterious impact of prenatal
exposure to alcohol, nicotine, and other substances. In addition, grown Conduct disorder children contribute to the spiraling effects of poor parenting by continuing the pattern of harsh discipline and neglect with their own offspring.

Women with Antisocial personality disorder frequently have similar mates. (The reason that most antisocial men do not marry similar women is that there are not enough women with Antisocial personality disorder to provide mates for the men). Therefore, further damage is likely if a mother has the syndrome, since double liability is conferred through assortative mating.

d. Social outcome

Unstable relationships are relatively frequent in the adult adjustment of children with Conduct disorder. Adults are described as irresponsible, socially unrelated, promiscuous, delinquent in paying their debts, and belligerent.

Given the fact that many children with Conduct disorder do not go on to a life of crime and disability, it is important to identify characteristics that predict their course. As already noted, early onset is a predictor of poor outcome. Second, the versatility of the conduct problems also portends a negative course. The more varied the symptoms, the more likely a negative outcome. Placement in correctional institutions also appears to play a role. However, this relationship may be related to other factors, such as differences in the homes of children who are and are not institutionalized. At the same time, there is a compelling case made for the observation that exposure to similar peers fosters the stability of Conduct disorder. Parental behaviors that place children at risk for Conduct disorder also play a negative role in maintenance of the disorder.

e. Multiplicity of predictors

We noted that the number of risk factors was associated with increased likelihood of developing Conduct disorder. The same pattern applies to prognosis. The greater the number of factors predictive of poor outcome, the worse the prognosis.

IV. Suspected causes

The identification of factors that go along with Conduct disorder is important to an understanding of who is at risk for the disorder. The temptation is to attribute causative origin to the correlates. Problematically, associated factors may not be causal. They may enhance the disorder's likelihood of developing without causing it directly. Even more
problematic, associated factors may be the result, rather than the cause of the disorder. Therefore, observed relationships between events and Conduct disorder must be considered with these possibilities in mind. Are they causing or merely influencing the manifestation of the disorder? Are they antecedents or rather consequences of the disorder?

1. Genetic/familial transmission

The study of cross-generational transmission of antisocial behavior has dealt mostly with adults. Researchers have targeted criminals since their identification, as explained above, is straightforward. The weight of the evidence comes from adoption studies that examine offspring of antisocial and non-antisocial biological mothers who have been adopted by non-antisocial parents or antisocial parents. There is a relatively higher prevalence of criminality in the biological children of antisocial mothers raised by non-antisocial parents. Complementing these findings are those from twin studies that find greater concordance for adult criminal behavior in identical versus fraternal twins. Interestingly, transmission is not for violent behavior per se but for criminal activity. The literature on adults is noted because there are relatively few findings in children. In addition, alcoholism and drug abuse are more frequent in the mothers of criminals. Notwithstanding the limitations of relying on findings obtained from criminal records, the findings lead to an expectation of familial concordance for Conduct disorders in children. Unfortunately, the research is sparse.

Several investigations of the parents of children attending psychiatric clinics have found relatively higher rates of antisocial parents among Conduct disorders. This relationship holds true for blacks as well as whites in the US. Such findings are provocative, but cannot be viewed as altogether convincing since there might be various biases accounting, at least in part, to these relationships. For example, studies have relied on parents reporting their own behaviors, and since fathers are rarely available, mothers are the informants. It may be that in such situations, for a variety of reasons, parents tend to see similarities between themselves and their children. Also, referred children may come from the most problematic households, where parental pathology is relatively common, thereby exaggerating the concordance between parental and offspring dysfunction.

Definitive studies, such as conducted with adult criminals, that examine adopted away children have not been conducted in Conduct disorder. Another very informative line of research is the study of twins. Twin studies of adolescent delinquents have obtained contradictory results with regard to familial concordance. These findings illustrate the dilemmas that arise when focusing on delinquency in adolescence rather than Conduct
disorder. During adolescence, many non-pathological males go through a temporary period of risk-taking behavior that may bring them to the attention of the police (i.e., driving without a license, taking a car on a joy ride, acts of vandalism). In such instances, there may not be a pattern of antisocial activity, and difficulties may be restricted to a specific time period. Although the relationship between Conduct disorder and criminality is incontrovertible, the exclusive focus on delinquents captures adolescents who may not always reflect the types of youngsters who are true Conduct disorders. That this is likely true is supported by findings of twin concordance for antisocial symptoms in reports of preadolescents with Conduct disorder (these cases are too young to have experienced police involvement).

2. Family and parental factors

Without exception, research has implicated family adversity and parental characteristics as important in Conduct disorders. These relationships hold for white as well as black children. Specifically, severe marital discord, lack of structure in the home, children not living with both natural parents, large family size and overcrowding, unstable family environments are all excessively frequent in the families of children with Conduct disorder. Parental factors include behaviors such as poor monitoring, inconsistent, abusive discipline. In addition, parental psychiatric status is a powerful correlate of Conduct disorders in children. Especially relevant are parental histories of alcoholism, drug abuse, and antisocial behavior. There is a dose effect in that two parents with a positive history, rather than one, increase risk to children incrementally. In fact, when one controls for these parental characteristics, the relationship between Conduct disorder and broken homes, as well as other factors, often disappears. Therefore, the reasons for the broken homes are more important than the broken homes themselves. The effects of family and parent features are complicated because they often are the result of each other. For example, alcoholic parents are more likely to be inconsistent and abusive disciplinarians, etc.

The genetic studies indicate that parental antisocial disorders have a direct influence on the development of Conduct disorders. However, the adoptive studies find that adoption into homes with an antisocial parent also increases risk to children. Conduct disorder is the only psychiatric disorder found to have origins in both genetic and home characteristics. There appears to be an interplay between biological and environmental factors in determining the development of Conduct disorders. Depending on the severity of the familial disadvantage, it might be more or less influential.
Family and parental characteristics are especially relevant to early childhood onset of Conduct disorder. This relationship is of great import since, as noted in the discussion of longitudinal course, children with early onsets have a much worse fate.

3. Individual factors

Gender is the only identified individual characteristic that places individuals at risk for Conduct disorder, with an average fourfold excess of males relative to females. The specific reasons for this gender difference are unknown. Some have suggested that a potentially informative approach might be to examine testosterone levels to determine their contribution to the development of Conduct disorder in at-risk populations. This is a highly conjectural notion. In girls, Conduct disorder is increased in those with early menarche combined with mixed sex schools.

Some have attributed a causal role to children's cognitive ability in the development of Conduct disorder. Indeed, children with the disorder tend to have lower mental ability (about 5-8 IQ points on average), and perform more poorly on some tests of mental function. However, it appears that these cognitive test differences are due to the co-occurrence of ADHD in groups of children with Conduct disorder. Therefore, it is not possible to attribute a direct effect of abnormal cognitive development on Conduct disorder.

Abnormal information processing has also been conjectured to contribute to the formation of antisocial behavior. In turn, it is viewed as influencing social cognition. For example, relative to other children, aggressive children have been reported to misinterpret social situations, to be likely to view hostile intent on the part of others, to have limited understanding of adaptive responses to peer provocations, and to anticipate conflict resolution through aggressive strategies. It is unclear to what extent these attitudes underlie aggressive behavior, or develop as its consequences. Further complicating the picture is the report that these distortions in social information-processing may characterize aggressive children with ADHD, rather than Conduct disorder per se.

Temperaments characterized by high negative emotionality and poor impulse control have been associated with delinquency. It has been claimed that irritability may characterize the temperament of children who go on to develop Conduct disorders as early as infancy. However, no systematic information is available on this point.

4. Community factors
As noted above, inner city residence appears as a risk factor for the development of Conduct disorder. In addition, poor living circumstances, poor schools (with high teacher turnover, large immigrant populations) are also influential factors. Clearly, these environmental features are not independent. Indeed, they are heavily associated. In studies that have teased apart the relative effect of children's living circumstances, the influence does not reside in the nature of the neighborhood (i.e., inner city vs. urban or rural), but in the associated characteristics. The experiential features that mediate the influence of inner city residence consist of the familial features described above, i.e., parental criminality, parental discord, poor familial relationships, large family size and overcrowding. Poor quality of schools provides additional liability. Environmental effects do not appear to be uniform across the age range, but are relatively more contributory to the early onset of conduct problems. Conduct problems that appear de novo in adolescence appears relatively unrelated to these environmental factors.

5. Multiplicity of factors

The above factors may occur transiently or consistently, and may occur singly or aggregate. It is when they are experienced consistently that they influence the development of Conduct disorder. Each alone contributes to Conduct disorder, but multiplicity of factors increases the potential for Conduct disorder.

In summary, there is remarkable consistency in pointing to environmental and familial factors common in Conduct disorder. On the whole, broadly defined social disadvantage appears as a breeding ground. Many of these relationships are mediated by negative parental characteristics in which histories of parental antisocial disorders, alcoholism and drug abuse are prominent. The disadvantage conferred by these factors appears to be both genetic and environmental. Moreover, parent behavior toward the child is also contributory, especially neglect, and inconsistent, harsh discipline. The relationships have not been found to differ between racial groups. It is especially on early onset (preadolescent) Conduct disorder that risk factors exert an effect. Sturdy correlates of adolescent onset have not been identified. Early onset of Conduct disorder occurs typically within the context of an ongoing ADHD. Research on risk factors is just beginning to take this clinical observation into consideration. The potential for Conduct disorder increases with the number of risk factors.

V. Biological mechanisms and correlates

The study of biological abnormality in Conduct disorder is controversial. Objections stem from the belief that this approach implicitly devalues the importance of
social and economic deprivation as causes of aggression in disadvantaged populations. Because the majority of inner city, impoverished groups are from minority racial groups, biological research is interpreted to be racist. Ironically, investigative approaches in children originate in large part from findings obtained in studies of Scandinavian criminals. Therefore, the biological investigations of Conduct disorder have not been fueled by attempts to demonstrate racial differences between Caucasian and other groups.

1. Neurochemical findings.

Brain activity in Conduct disorder has been investigated through evaluation of levels of neurotransmitter metabolites in the blood, urine, and spinal fluid. A key issue in relying on peripheral measures (blood and urine) is whether these permit inferences about central brain mechanisms. On the whole, studying neurotransmitter metabolism from peripheral sources is a poor substitute for central nervous system (CNS) measures.

Mainly, serotonin and norepinephrine have been viewed as relevant to the biology of Conduct disorder. Much of the work with adults, as well as children, has assessed aggression, rather than Conduct disorder, although the trend is shifting to the study of the disorder. In adults, aggressive behavior has been associated with relatively low concentrations of the main metabolite of serotonin. Various strategies have been used to investigate this neurochemical feature in children. Childhood aggression retrospectively reported by adults was found to be associated with low serotonin levels, measured through a challenge paradigm in which an agent (fenfluramine) is administered to stimulate serotonin release. In children, results are contradictory. Actually, the opposite relationship has been found in children: aggression correlates with elevated serotonin levels. These findings have provoked the hypothesis that CNS serotonin regulation follows a developmental pathway as yet not understood, and that one cannot assume identical neurobiological findings in children and adults. The lack of studies in normal children impedes full understanding of data obtained in Conduct disorder. However, a provocative study found an association between children's plasma serotonin levels with aggression, as well as with harsh maternal discipline. This work is important in raising the possibility of complex relationships between the child's home experiences, his biological regulation, and his behavior. Is it possible that parental behavior is at the origin of both biology and aggression in the child? Or does serotonin lead to aggressive behavior which in turn evokes harsh parental discipline? The model positing a causal role for serotonin is not likely to be accurate since, in a longitudinal study of non-aggressive children, harsh maternal discipline predicted children's future aggression, which in turn was negatively correlated with serotonin levels. Unfortunately, serotonin levels were not available at the initial assessment, prior to the development of aggression. A full understanding of the
sequential nature of these relationships awaits further research. The study has been limited to maternal behavior, and it is possible that sturdier findings would emerge if fathers were included as well. Adding importance to this line of research is the observation that central serotonin levels in children with Conduct disorder predict severity of aggression two years later, even while controlling for parental diagnosis of Antisocial personality disorder.

In addition to serotonin, catecholamines, notably norepinephrine has been examined, based on animal studies linking it to aggressive behavior. Most studies have used peripheral measures (blood and urine), raising questions about the meaningfulness of the data. Results are confusing in that some find lower norepinephrine levels in only one subtype of Conduct disorder children (undersocialized), and not in others (socialized). Yet both these groups have persistent patterns of antisocial behavior, and the source of the distinction is curious. To compound the dilemma, these findings have been replicated in some, but not all studies.

2. Physiological measures

Other paradigms have been pursued that aim at examining how input is processed by the nervous system. For example, how efficient it is in inhibiting responses, and how responsive it is. The expectation is that children with Conduct disorder resemble antisocial adults in having poor inhibitory processes, and in requiring higher stimulation.

The rationale for physiological investigation is the search for evidence of underarousal. The various strategies have included skin conductance, heart rate, and brain evoked responses (specifically, the amplitude of responses to various stimuli). All have generated findings consistent with the view that aggressive children and those with Conduct disorder display responses that are consistent with a model of CNS underarousal. Signs of lower arousal from the three experimental approaches have been found to be significant features of Conduct disorder. Importantly, in 15 year old school boys, all three measures were found to be predictive of criminality and recidivism in adulthood (at age 24).

The confluence of neurochemical and physiological findings have led to the interpretation, by some, that children with Conduct disorder suffer from a dysregulation of the reward system. Namely, individuals with Conduct disorder are viewed as having overdeveloped pleasure seeking systems which prevent the actualization of behavioral inhibitory processes.
3. Other biological correlates

Cortisol secretion is believed to reflect, in part, stress vulnerability. In general, it is believed that children with Conduct disorder have lowered stress responsivity. Cortisol levels may be obtained from saliva, blood or urine. These various approaches have yielded inconsistent results regarding cortisol secretion in Conduct disorder children. Testosterone has some relationship to aggression in adult males. Therefore, an association has been posited between testosterone levels and Conduct disorder. The data are limited, but a moderate relationship has been obtained for repeated delinquents.

In summary, investigation of the biology of Conduct disorder is controversial because of the misguided belief that it deflects from attending to critical socio-economic influences. Biological investigation of Conduct disorder has been guided by findings in criminal adults. Although the data are not unanimous, they are provocative. They suggest neurochemical deviations, especially in serotonin metabolism, as well as reduced arousal. The latter has also been shown to predict later delinquency. Less impressive are results of cortisol level abnormality in Conduct disorder. The data on testosterone are limited and do not enable a clear understanding of its role in Conduct disorder. On the whole, there is sufficient consistent evidence to suggest that Conduct disorder is associated with specific differences in neurochemistry and psychophysiology. However, the causal direction of this relationship is obscure. This is an area of current activity.

VI. Treatment

The amelioration of Conduct disorder represents a major public health concern since the disorder is common, its frequency is increasing, and it is a long-lived, serious condition. As stated earlier, the child guidance movement was spurred by the need for treating Conduct disorder, and traditionally, treatment focused on the child, and individual psychotherapy, usually of psychoanalytic variety, was the rule. The results from these approaches are more than disappointing since there is some evidence that insight-oriented approaches may actually lead to worse outcomes than the failure to treat. A shift has occurred in the past two decades, with a de-emphasis on exclusive reliance on treating the child. Instead the family has become the focus of treatment, which often extends for one year or more. When the child receives treatment, it is no longer with the goal of resolving unconscious conflict, but of enhancing the child's acquisition of social skills. How well have we fared?
1. Skills training of child (cognitive problem-solving skills training).

The goal of skills training is to remedy deficits in social perception and hostile reaction to social interactions. The hope is to correct distortions in how social situations are viewed, and to instill new means of responding. Only a couple of controlled studies have treated children with Conduct disorder specifically. Results appear promising in showing a reduction of antisocial behavior with detectable advantage for one year after treatment cessation. However, though better, children are still deviant. The information thus far is too scant to allow for a clear appreciation of the potential for skills training. Unfortunately, the very features that place further disadvantage to children with Conduct disorder (e.g., parental psychopathology, family dysfunction) limit the impact of the intervention.

2. Parent training

Attempting to alter parental influence is eminently reasonable in view of the amply demonstrated problems that characterize the home environment of children with Conduct disorder. An understanding of the specific nature of deleterious parental behavior has led to the design of parent training programs tailored to reverse them. The overall goal is to modify the parent child interaction in order to enable to parent to promote appropriate behavior in the child, and to institute rational effective disciplinary rules. Most of the research on this approach has not included clearly diagnosed Conduct disorders. Gains have been demonstrated in groups broadly defined as aggressive or as behavior problems. In some instances, some improvements have remained beyond the period of active intervention. The intervention is very promising, but as is the case for all family-oriented therapy, many families of children with Conduct disorder are uncooperative, and it is often the most impaired that fail to participate.

3. Classroom interventions

The principles instilled in parents, such as setting specific expectations, consistent explicit disciplinary rules, and reward for positive behaviors have been implemented in schools located in neighborhoods where Conduct disorder is common. By directing interventions to the schools, the problem of poor parent compliance is avoided. The impact of this approach on Conduct disorder itself is not clear, since assessments of the children have not taken diagnosis into consideration. However, the finding that vandalism is reduced relative to control schools is encouraging.
4. Combined psychosocial approaches

A very ambitious, proactive treatment has been developed to intervene at all levels of dysfunction in Conduct disorder adolescents: the community, school, home, and the individual. A group headed by Henggeler in Georgia has pioneered this so-called Multisystemic Therapy. Most of the research has focused on delinquents. This is the only treatment thus far that extends outside the family, and takes into account the extra-familial factors that influence the course of delinquency. The treatment has been shown to be superior to standard clinical care in altering family function, and in reducing antisocial behavior. Impressively, treatment advantages can last beyond the treatment delivery period.

5. Medication

As noted, Conduct disorder of early onset often occurs with ADHD. Stimulant treatment is very effective in reducing symptoms of ADHD, and some research has been conducted to examine whether the treatment can be extended successfully to Conduct disorder. Symptoms of Conduct disorder are improved with stimulant treatment regardless of the concurrent presence of ADHD. Methylphenidate (Ritalin) is the only compound that has been studied.

6. Treatment associated problems

Problematical, high rates of non-compliance occur with all interventions, and seem to be more common among families of children with Conduct disorder than those whose children have other psychopathology. Adequate strategies for enlisting recalcitrant families are not identified.

Treatments, when effective, have only moderate impact and most have not been studied long enough to determine their long-term efficacy. Although a one year maintenance is encouraging, it is still insufficient in view of the extended duration of the disorder. A certain amount of concern about long-term efficacy is in order in view of results from a landmark controlled study, which intervened with high-risk boys in inner Boston in the 1940’s. Thirty years later, the youngsters who had participated in the community program had a worse course on a variety of important outcomes, including alcoholism, and mortality.

Finally, stimulant treatment reduces symptoms of Conduct disorder. So far, no study has examined its combination with other therapies.
7. Prevention

If possible and not inordinately costly, there would be great advantage in preventing the development of Conduct disorder or improving its course. This aim does not appear altogether unrealistic since we know what environmental factors foster the development and maintenance of the disorder. Also encouraging is the finding that programs with preschoolers, whose mission was the enhancement of cognitive ability in disadvantaged children, have been found to have an effect mostly on level of adolescent delinquency. Therefore, there may be early programs that deter the development of severely antisocial development in children. Several programs are underway in the US and Canada. Some focus on total school populations who are known to be at high risk for Conduct disorder because of their socioeconomic circumstances. Others identify kindergarten age aggressive children (secondary prevention). Preliminary results are encouraging but not consistently so, with some failing to find effects after cessation of intervention. In these projects, as in treatment studies, poor parental cooperation is often a major hindrance to treatment delivery and to retrieval for follow-up.

Researchers are beginning to consider the possibility that, by the time children reach school age, it may be too late to circumvent the further development of serious conduct problems.

There is evidence that by intervening with pregnant women from areas characterized by poverty and child abuse, mothers are less likely to be punitive and neglectful, two aspects of parental behavior that enhance the development of Conduct disorder. Similarly, better mother-child interactions have been obtained in mothers of infants who received guidance in child care. Therefore, the potential impact of training mothers of at-risk children before childbirth, or soon postpartum, holds promise.

Intervening with young children also promotes future development. Several controlled investigations of the impact of comprehensive services for mothers of preschoolers in disadvantaged areas have found enhancement of children's social functioning and reduction of aggressive behavior which extended over considerable time (i.e., as long as ten years in one instance). So far, no prevention program has targeted pre-school age children who are at high risk for Conduct disorder, before the appearance of destructive behavior. Such research is just beginning, and it is too early to generate impressions about its potential contribution.
VII. Service delivery

Although there is documentation that aggressive children can be identified at ages 2 to 3, there is great reluctance on the part of nursery school teachers to consider children in need of professional attention at these ages. There is the indulgent attitude that children go through phases, and that it would be deleterious to single them out for professional attention. However, if the toddler's aggression occurs in a context which places him at high risk because of the presence of parental and familial features noted above, there is good reason to institute intervention very early on. Doing so would be an advantage, rather than disadvantage to the child and family. At later ages, it is mostly by schools that children get referred for evaluation and treatment. The judicial system is also a major source of identification for children with conduct disorders.

Children with Conduct disorder are usually treated in outpatient child guidance or child psychiatry clinics. Pediatricians and private practice psychiatrists do not play a major role in the identification and diagnosis of children with Conduct disorder. Diagnosis may be implemented by various mental health professionals. Conduct disorder is not a problematic diagnosis, but it is often missed because attention is paid to the disturbed family relationships, and the child's symptomatology as a process deserving of identification is minimized. Therefore, the child may be diagnosed as having a parent child problem, rather than a bona fide disorder. It is unusual for a concomitant ADHD to be recognized, probably because conduct problems are salient, and the possible occurrence of inattention and hyperactivity is overlooked.

Treatment is delivered in outpatient clinics, typically by psychologists and social workers. The emphasis is now on family treatment. Treatment plans in typical clinical settings do not follow established principles, and often there is poor follow-up care in spite of continued behavior problems. In some instances, the court system offers treatment to families. However, these resources typically are overburdened, and cannot meet the demand. Treatment delivery to families of children with Conduct disorder poses major problems because many do not have the financial resources to afford treatment. As a result, many children go unattended, or are only treated during times of crises, for brief periods of time. Although several research therapeutic programs have been community oriented (i.e., outside clinical facilities), they have not been taken up by clinical resources. This failure is inevitable since reimbursement policies cover only clinic visits, and not other types of interventions such as home, school, or community setting visits.
VIII. Centers of research excellence

The study of Conduct disorders is an active endeavor in the United States and Canada. The list is limited to centers in the US. Nationwide (Alphabetically listed)

**Columbia University, New York**

1) **Clinical**
   a) Research on the longitudinal course in boys at high risk for Conduct disorder with a focus on factors that affect the development of Conduct disorder.
   b) Treatment studies combining medication and psychological interventions.
   c) Features of Conduct disorder in girls.
   d) Primary prevention research in pre-school children at high risk for Conduct disorder.

2) **Basic Research**
   a) Cross-sectional and longitudinal research on the biological correlates of Conduct disorder, including studies of serotonin metabolism, heart.
   b) Studies of the relationships between parental behaviors and biological findings in children at risk for Conduct disorder.
   c) Biological features of Conduct disorder in girls

**Oregon Social Learning Center**

1) **Clinical**
   a) Identification of specific parental behaviors that maintain or otherwise influence children's conduct problems
   b) Development and testing of interventions that alter parental behavior of children with conduct symptoms
   c) Design of preventive strategies for Conduct disorder

**University of Chicago**

1) **Basic Research**
   a) Neurochemistry of Conduct disorder, and its relationship to course.

2) **Clinical**
   a) Longitudinal course
University of North Carolina

1) Epidemiology
   a) Longitudinal course of elementary school children to trace the development of Conduct disorder in boys and girls.

University of Pittsburgh

1) Clinical
   a) Detailed study of developmental nature of new cases of Conduct disorder
   b) Relationship of comorbidity to course
   c) Role of age and gender on course

University of Wisconsin

1) Epidemiology
   a) Cognitive correlates of Conduct disorder
   b) Features of delinquency in girls
   c) Comorbidity of Conduct disorder

Vanderbilt University (Tennessee)

1) Clinical
   a) Social perception and response bias in children with Conduct disorder

Washington University

1) Epidemiological
   a) Study of rates and associated risk factors in Conduct disorder.
   b) Study of the influence of retrospectively recalled symptoms of childhood Conduct disorder on adult psychopathology.

Yale University

1) Clinical Research
   a) Study of treatment efficacy in out and inpatients with Conduct disorder.

2) Basic Research
   a) Neurochemical studies of delinquents.

IX. Future directions

1. Treatment development
The most promising approach investigated so far is one that intervenes in all domains of the individual's life. However, it is extremely intensive, requires 24 hour a day staff availability, and is costly. It is unlikely to be widely applicable. Moreover, current mechanisms for reimbursement do not cover these procedures. This policy may be short-sighted since institutionalization, which is very costly, is a reimbursable treatment. The future should focus on what aspects of this very ambitious program is necessary for efficacy, in order to streamline treatment to render it more feasible and affordable.

There is only one ongoing study of combination treatments with medication in the US, and only one medication (methylphenidate) has been evaluated. The psychopharmacology of Conduct disorder should be pursued vigorously, and its contribution to treatment in combination with psychotherapies is a high priority.

All investigators acknowledge that parents of children with Conduct disorder often are psychiatrically impaired. No attempt has been made to integrate treatment of the parent in the interventions applied to the child. This line of research cannot be ignored in view of the poor compliance of families, especially among those with parental psychopathology.

2. Biological studies

Biological studies have generated interesting, and possibly important findings. However, they have been limited in scope, and are limited to very few centers. Examining the interrelationship between parental characteristics and biology has only just begun. This research is critical in furthering our understanding of the mechanisms that trigger and maintain Conduct disorder. A most productive strategy would be the study of twins since 1) environmental factors are controlled within pairs, and 2) many biological measures are influenced by heredity. Therefore, differences between related individuals are more informative than those between unrelated ones.

3. Prevention

Conduct disorder is one instance where prevention is possible, since we can identify children who are relatively likely to acquire the disorder. The need for preventive efforts is critical in view of the high cost of treatment and its relatively poor showing, once the disorder has set in. Therefore, developing means for early case finding represents an important line of research.
In addition, the study of preventive programs, before the development of aggressive behavior, is a high priority. It is not known how early in a child's development intervention is necessary. To elucidate the question, the prospective study of temperament in infants at high risk for Conduct disorder would be informative. In this instance as well, twin studies would be the most meaningful.

Programs, such as Head Start, have been found to have some effect in reducing later antisocial behavior. However, these programs do not integrate the therapies or prevention programs that have been established for parents. Research on the accrued advantage of combining treatment of parents with Head Start programs is clearly desirable since the educational setting provides access to inner city children who are at relative risk for Conduct disorder.

Part of the prevention effort requires education of parents and children. Schools offer the setting in which to reach both. School personnel need to be informed of the relative consequences of ignoring Conduct disorder symptoms, and be alerted to intervene promptly.

X. Bibliography


Hinshaw S, & Anderson CA. Conduct and oppositional defiant disorders. In (Eds,) Child Psychopathology.


CURRENT FUNDING FOR MENTAL HEALTH RESEARCH

I. Methods of Survey

To determine the nature and extent of research funding for mental health, the research portfolio of the National Institute of Mental Health (NIMH) was evaluated. Since the portfolio is so large, we selected the largest funded area (affective disorders) and reviewed the abstracts of all grants funded in 1995. In addition, we reviewed the entire portfolios of the three foundations providing the greatest support for mental health research: the National Alliance for Research on Schizophrenia and Depression (NARSAD), The William T. Grant Foundation and the John D. and Catherine T. MacArthur Foundation.

We were unable to identify any significant funding for mental health research through the State of Michigan. The University of Michigan, Wayne State University and Henry Ford Health System have intramural funds that are used primarily to collect pilot data to apply for external funding.

II. Extent of Funding

By a significant factor, NIMH is the largest supporter of mental health research. In affective disorders, there were approximately 500 grants funded. About 380 grants were made in the area of schizophrenia, the disease funded second most often.

The NIMH has a variety of grant mechanisms, usually committed for 3-5 years. They include: (1) small grants ($50,000 annually), (2) investigator initiated grants (approximately $125-175,000 annually) (3) career scientists and development awards (75% of investigator's salary), and (4) clinical research centers, center grants, program project grants, and training grants. These are grants in the million-dollar range and support a physical facility to carry out research, integrated studies on a common theme, and infrastructure to train mental health scientists. The strength of the NIMH system is the investigator-initiated grants. These are highly competitive (about 15% get funded) and range in amount from $100,000 to $300,000.

In contrast, each foundation funds about 100-150 total grants per year and the size of these grants varies greatly. The foundations primarily fund young investigator fellowships (about $50,000 each) and a few center grants (which can be greater than one million dollars).

The vast majority of funding goes to universities, while the remaining grants go to free standing hospitals (e.g., Brigham and Women's Hospital, Henry Ford Hospital).
In Michigan, the University of Michigan has the largest research program in mental health. It lists more than 100 grants received in support of its various mental health research initiatives.

III. Projects Supported

The majority of research funding (about 75%) is given to carry out specific research projects initiated by the investigator and reviewed by a panel of peers. Remaining funds provide support for infrastructure. They are for research training grants, clinical research, and shared equipment grants.

IV. Areas of Support

About 60% of grants reviewed were judged as supporting clinical research while the remainder support basic science research. A recent trend is the shift in funding from clinical to basic research. Epidemiological research, especially in conjunction with laboratory studies, is being recognized as an area that can enhance our knowledge of mental disorders.

V. Conclusion

The public funding of mental health research is declining and is expected to decline even further in the future. However, public funding continues to be the major source of research grants. The grants go primarily to universities and, increasingly, to support basic science initiatives. In addition, grants more often support specific research programs rather than research infrastructure. Foundations seem to view their role as complementing federal support by funding the types of programs (typically long-term institutional) not funded by NIMH.