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Schizophrenia: An Integrative Study of Biological Liabilities and Neurological Causes

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Schizophrenia: An Integrative Study of Biological Liabilities and Neurological Causes

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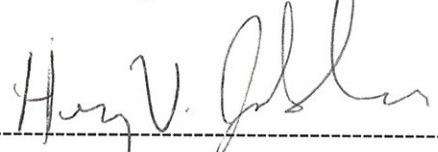

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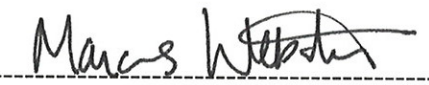

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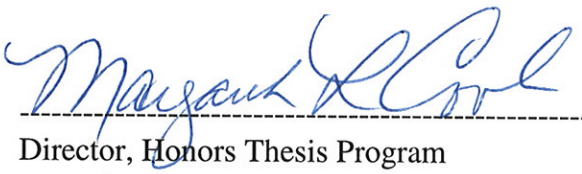

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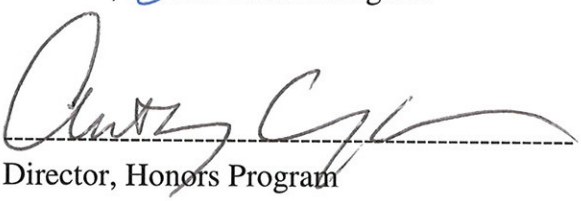

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Contents

Preface

Recently a new frontier in the study of physiology and human behavior has been the intricate mechanisms of the brain. Society has become increasingly aware of the frustrating and confusing disorders that can result when the brain loses control of its intricate mechanisms, such as Alzheimer's disease, autism, and schizophrenia. In addition, the development of neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) has given investigators new sets of tools. With this increasing interest and technology it is no wonder that many studies have been done recently to attempt to explain the environmental and neurochemical causes of such mental illnesses. The number of articles with the word "brain" in their titles has doubled to 100,000 publications in the past five years, and this research has helped to gain an increasing understanding about the nature and nurture of mental illness. In fact, 95 % of what is known about brain function has been acquired in the past 10 years (Gottesman, 1991); certainly the "Decade of the Brian" is upon us. However, although more secrets of the brain are emerging every day, there is a long journey ahead. An adult brain contains some 100 billion neurons with each having about 1500 synapses, across which electrical/chemical signals are constantly being transmitted or blocked. To describe how this "supercomputer" is affected by environmental stress is a daunting assignment. Hooper (1996) summarizes the brain correctly as a " a vast continent, and scientists have barely landed on its shores".

One of the most studied mental illnesses has been schizophrenia. Schizophrenia is known to many as one of the most debilitating human illnesses. It is characterized by a broad spectrum of cognitive and emotional dysfunctions including delusions and hallucinations, disorganized speech and behavior, and inappropriate emotions. The disorder can disrupt a

person's perception of the world, the way he or she thinks, speaks, moves, and almost every other aspect of daily functioning. Unlike Alzheimer's disease, schizophrenia strikes its victims at the prime of their lives. For about a half to two-thirds of its victims, the illness is either catastrophically unrelenting in its course or comes in such frequent relapses that the rest of their lives are spent in the tormenting world of psychotic experience (Ciompi, 1988). Personally, I have always wondered about the origins of schizophrenia and what possible measures could be done to treat such a condition. My father has been schizophrenic for much longer than I can remember, and I would like to know how such a condition can take away so much from his life and the lives of all others that suffer with the disease. In addition to my dad, I have witnessed the tremendous emotional toll the disease has had on my mother, myself, and anyone else involved with schizophrenia. Hopefully with the floods of studies that have been coming out within the last few years, we can begin making sense of this most disabling of human travails.

Schizophrenia is a very complex disorder and describing its cause is a very difficult task. Many different areas of study, including biology, psychology, and sociology need to be addressed in order to understanding how one becomes schizophrenic. As Barlow and Durand (1995) describe, "The multiple layers of explanation that are needed to decipher what makes us behave the way we do are never in greater evidence than for the disorder schizophrenia" (Barlow and Durand, 1995). Although the risk of schizophrenia can be attributed to genetics, it does not conform to a simple Mendelian pattern like Huntington's disease (McGuffin, et al., 1995); thus environmental and sociological causes must also be included with biological ones. Most of us assume that once maturity is reached, the structure and function of our brains is "hardwired," or unable to be changed. Kandel proposes a new "plastic" model of nervous system development,

which suggests that the brain is subject to continual change as a function of interactions with the environment, even at the level of genetic structure. He suggests that the very genetic structure of cells may actually be changed as a result of learning (Barlow and Durand, 1995). This change could arise if genes that were normally dormant were induced somehow from the environment and later translated. This type of mechanism may lead to changes in the number of receptors on neuronal membranes that could affect brain function. This new found theory stresses the need to look at mental disorders as having environmental origins. Studying psychopathology using this multidimensional integrative approach may improve our understanding of psychological disorders.

Davidson and Strass (1995) have suggested that the "biopsychosocial model" that has been used for the last 40 years in describing mental disorder and dysfunction is not enough, since this model continues to view the biological, psychological, and social aspects as separate and independent spheres that may or may not interact in any one aspect of disorder. They suggest a "Life-Context" approach that looks at each *individual* involved and not their disease alone. These psychiatrists encourage researchers to look at the ongoing changes of the schizophrenic patient's life and the processes of improvement, while at the same time integrating things like biology and environment as part of the whole being. (Davidson and Strass, 1995). It is with this approach that I will discuss the etiology of schizophrenia, and I hope that researchers would also view this model when looking for methods of treatment.

As mentioned before, schizophrenia is a very complex disorder that has many possible causal theories, but none have any definite conclusions. The purpose of this thesis is to summarize these major areas of thought and try to suggest ways in which they are all related to

the etiology of schizophrenia. I will describe the disorder by summarizing psychological research and vulnerability factors, followed by outlining direct physical causes of schizophrenia. Finally, I will describe the relationship between the vulnerability factors and the underlining biological or chemical basis of the disorder. This relationship is the exciting mystery that will hopefully be solved someday, and I will do my best in summarizing what is already known. Schizophrenia truthfully defies our desire for simplicity, but hopefully by summarizing the most recent findings we can begin making some sense of this frustrating disease.

I. Introduction to Schizophrenia

Schizophrenia is a very serious cognitive and emotional disorder that includes delusions and hallucinations, disorganized speech and behavior, and inappropriate emotions. The disorder occurs consistently afflicting one to two percent of the adult population worldwide (Barlow and Durand, 1995). There is some recent disagreement about the distribution of schizophrenia between men and women, but most would believe that it is about equal between the sexes. The time of onset among the sexes differs, moreover, with men acquiring the disease most often at ages 16-35, while women show higher incidence rates from 35 onward. Overall, the average onset of schizophrenia is from ages 16 to 25, with a life expectancy slightly less than average, partly due to the higher rate of suicide among people with this disorder (Barlow and Durand, 1995).

In studying most other mental disorders, there usually exists a kind of behavior, a way of thinking, or an emotion that defines or is characteristic of that particular disorder. For example, depression always includes feelings of sadness, while panic disorder is always accompanied by intense feelings of anxiety. Although all schizophrenics are known to suffer from a thought disorder, they will often show different forms of the disorder at different times in their lives. Depending on the combination of symptoms displayed, two people could receive the same diagnosis but look very different. For these reasons, psychologists have often battled the issue of whether schizophrenia is in fact one distinct disorder or a combination of disorders (Barlow and Durand, 1995). Methods by which this heterogeneity of schizophrenia have been dealt with are wide and varied. One popular method has been to diagnose and organize schizophrenia by the investigation of its symptoms, which are summarized below.

Symptomology

The active phase symptoms of schizophrenia have often been divided into positive and negative categories. A diagnosis of schizophrenia requires that two or more of these positive and/or negative symptoms are present for at least one month (Barlow and Durand, 1995). *Positive symptoms* refer to more active manifestations of abnormal behavior, which include delusions, hallucinations, disorganized speech, and catatonia. *Delusions* are known as a misrepresentation of reality or a disorder of thought content. Two of the popular kinds of delusions are *delusions of grandeur*, where patients feel they are famous or have an important mission to carry out, and *delusions of persecution*, where patients feel others are out to get them. To the schizophrenic, this could mean anything from someone tinkering with their car, aliens sending dangerous waves, or evil demons haunting their soul! These types of delusions obviously create a great deal of anxiety for those afflicted. *Hallucinations* are the experiences of sensory events without any input from the surrounding environment. They can involve any of the senses; however, auditory hallucinations are the most common form experienced by schizophrenics. *Disorganized Speech* refers to problems with communication, where patients might not answer a question with a specific answer, but rather will go off on an unrelated tangent. The final type of positive symptoms is *catatonia*, where patients exhibit a wide range of motor dysfunctions from wild agitation to immobility.

Negative symptoms usually refer to the insufficiency of normal behavior, which include flat affect, avolition, alogia, and anhedonia. *Flat affect* refers to the behavior in which the patient's emotions do not match what is appropriate at that time. For example, patients might appear to be wearing masks all the time, as they will not show or talk with any emotion even

though they may feel the emotions inside. Another example of a negative symptom is *avolition*, which means the patient is unable to initiate and persist in many important activities. *Alogia* is a symptom where responses to questions are most often absent in the amount and content of speech. Experts believe alogia is a negative thought disorder rather than an inadequate behavior in communication skills (Barlow and Durand, 1995). Finally, *anhedonia* refers to individuals not being able to enjoy activities that would typically be considered pleasurable, including eating a nice meal or having a sexual relation.

Categorizing into Subtypes

Because the symptoms displayed can be so varied among those that are diagnosed schizophrenic, DSM-IV has differentiated individuals based on their differing presentations of symptoms. This separation is useful in understanding identifiable differences with each subtype and devising specific treatments for each. Also, by understanding the specific subtypes, we may be able to designate specific causes for specific subtypes. The revised DSM-IV now differentiates schizophrenia into the following types: Paranoid, Disorganized, Catatonic, Undifferentiated, and Residual.

Paranoid type of schizophrenia stands out because of its characteristic delusions and/or hallucinations, which usually have a theme like persecutions or grandeurs. Individuals do not normally have disorganized speech, flat affect, or cognitive difficulties, and they typically have a better prognosis than people with other forms of schizophrenia. *Disorganized type of schizophrenia* is characterized by marked disruptions in speech and behavior, and probably will include flat or inappropriate affect. Patients afflicted with this type generally show early signs of

difficulty, and the prognosis is more pessimistic than with other types of schizophrenia. Individuals that suffer from *catatonic type of schizophrenia* demonstrate poor motor responses by remaining in fixed positions, engaging in excessive activity, or being oppositional by remaining rigid. There has been some discussion about eliminating this type due to its relative infrequency and the treatment success from neuroleptic medications. *Undifferentiated type of schizophrenia* is the subtype that includes people who do have the major symptoms of schizophrenia, but do not fit neatly into a specific subtype. Finally, *residual type of schizophrenia* is reserved for people who have had at least one episode of schizophrenia, and may continue to have less severe problems, but who no longer manifest the major symptoms of the disorder (Barlow and Durand, 1995).

The recent attempt of DSM-IV to categorize schizophrenia has eliminated much past confusion of classifying schizophrenia through the use of narrower and more well-defined diagnostic criteria; however, the utility of these subtypes remains in question due to patients still often displaying symptoms from more than one subtype (Nicholson and Neufield, 1993). One recent attempt to overcome the previous limitations was made by Poreh et al. (1994), who compared results from the MMPI personality test with the Scale for the Assessment of Positive Symptoms (SAPS) and with the Scale for the Assessment of Negative Symptoms (SANS). They tested 125 coherent schizophrenics with varied histories using cluster analysis, a multivariate statistical method that can be used to identify consistent profiles of symptoms and signs from a large number of subjects. Poreh et al. (1994) found three correlations:

1) the SAPS Delusions scale and MMPI scale 6 (Paranoia); $r = .319$
2) the SAPS Positive Thought Disorder scale and MMPI scale F (Infrequency);

r = .313

3) the SAPS Positive Thought Disorder scale and MMPI scale 9 (Hypomania); r = .310

Correlations were also made between the SAPS and SANS subscale scores and the MMPI depression, hypomania, and psychotism scales, but none of these were found significant. As with past studies, no significant correlations were observed among negative symptom subscales and the MMPI clinical scales. According to the study, the overall relationship found was between recidivism (relapsing into crime) and a higher incidence of positive symptoms. The researchers also noted that their results imply that MMPI provides very little information regarding the particular symptom clusters that schizophrenic patients exhibit, as MMPI appears to be useful for screening but not for the detailed evaluation of Symptomology of schizophrenic patients. The group therefore suggests that clinicians who are interested in assessing the symptoms of schizophrenic patients should use such measures as interview-based rating scales, behavioral observations, and neruoimaging studies in addition to the MMPI (Poreh, et al., 1994).

Although the results of Poreh did not associate well with past models, the correlations made between the SAPS and SANS and the MMPI cluster solution did fit well with the two-dimensional classification model of Nicholson and Neufeld (1993). The first dimension of this model describes the severity of schizophrenia on a continuum from nonparanoid to highly paranoid. Nicholson and Neufeld (1993) classify the more severe disorder as having a longer duration, associated with poorer social competence, and as more pervasive. The researchers suggest that with increasing severity, paranoid symptoms decrease and nonparanoid symptoms increase. The second dimension describes the severity of schizophrenic symptoms from absent

to severe. Nicholson and Neufeld have mentioned that the severity of symptoms dimension may be measured by available positive and negative rating scales. Thus, amid the controversy regarding the classification of symptoms, there is evidence that positive and negative rating scales will continue to be used by researchers and practitioners for diagnostic purposes (Poreh, Chapin, Rosen, and Youssef).

Nicholson and Neufeld's two-factor model of schizophrenia is illustrated in Figure 1. Given the independence of the two factors on an x-y grid, it is not the severity of the symptom that reflects the severity of the disorder. The symptom could not be at a severe level, but may still be indicative of a more severe form of schizophrenia. Likewise, a symptom could be at a severe level but reflect the presence of a less severe form of the disease. The two-factor model readily accommodates the often observed mixture of paranoid and nonparanoid symptomatology, while allowing for the fact that symptoms may change over time. This theoretical model is a nice skeletal outline that can lead to additional avenues of clinical and research information in the classification of schizophrenia.

Developmental Course

Researchers have recently paid an increasing amount of attention to the developing course of schizophrenia, which some day may shed new light on the cause or causes of the disorder. In the past, schizophrenia was predominantly understood to be a purely organic disease that evolved almost inevitably and uniformly toward severe chronicity. Ciompi et al. (1988) have challenged this traditional thought on the course of schizophrenia. His study observed 289 cases of the disorder in Europe for an average duration of 36.9 years. Their findings suggest a complex

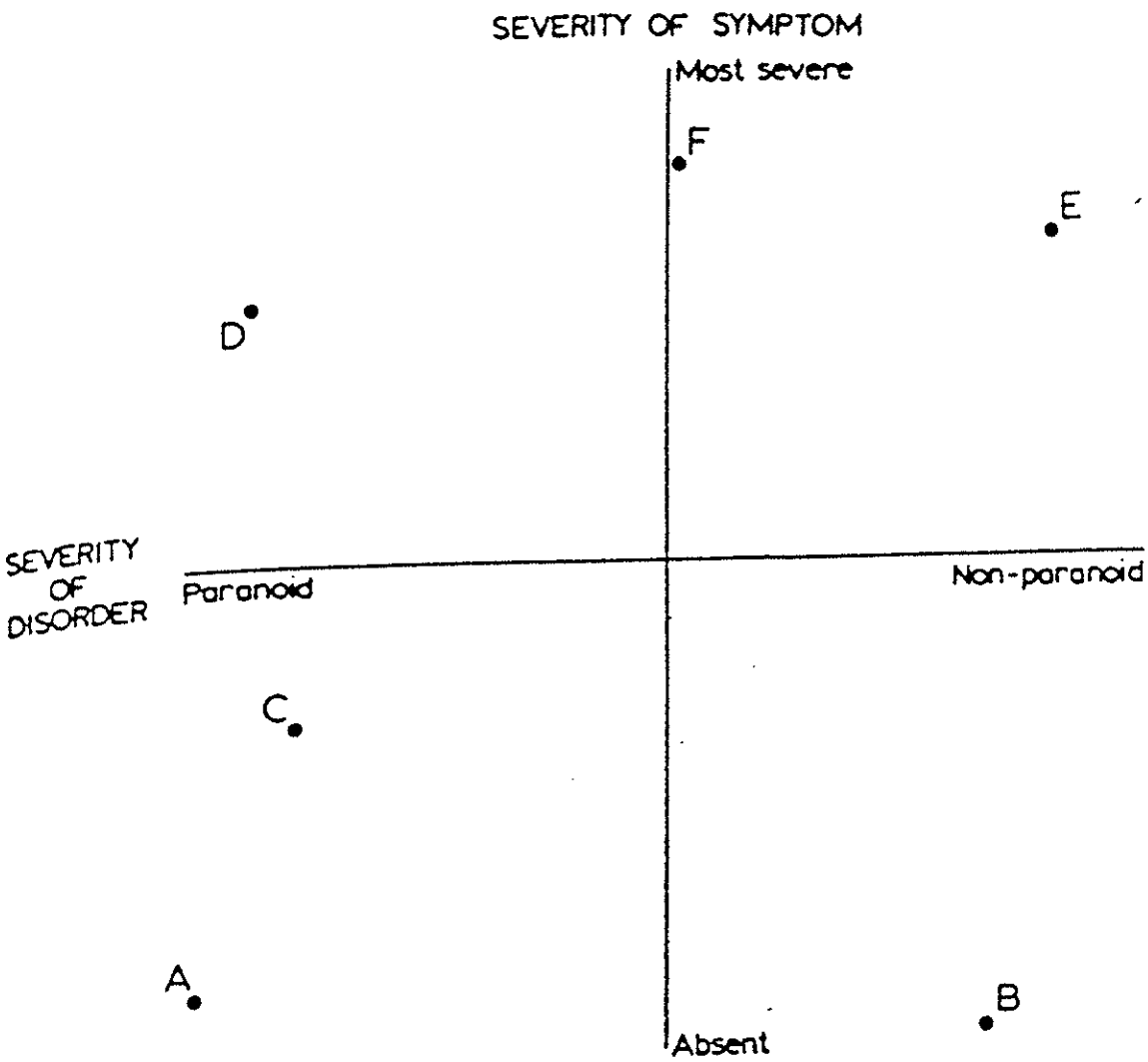

Figure 1. A two-factor model of schizophrenia: severity of symptom and severity of disorder. (Hypothetical patient locations in the two-dimensional plane are displayed as Points A through F.)

From: ***Journal of Abnormal Psychology*, 1993, Volume 102, page 263.**

pattern of outcome which was simplified into four sections (Ciompi, 1988):

1) 14%-24% of the patients deteriorated into severe chronicity with seriously incapacitating disorders of thinking, speaking, and behaving

2) 24%-29% of the patients had moderate symptoms making it impossible for them to function at anything near their natural endowment

3) 24-33% had only minor residual symptoms or infrequent relapses and may be able to achieve and even excel in a career

4) 20%-29% of the patients showed complete recoveries

A second conclusion Ciompi found was the enormous heterogeneity of the observed long-term evolutions, contrasting with the classical belief of an almost uniform course toward chronicity. Huber, another researcher that did a similar study, quoted 12 different evolutionary pathways in the course of schizophrenia! (Ciompi 1988). These results conflict with categorizing schizophrenia into distinct subtypes. Ciompi and others have demonstrated that not only does the course of schizophrenia change, but also there is little possibility of predicting what that change is for any individual case. For example, undifferentiated schizophrenics, who were thought to have the worst prognosis, were often seen by Ciompi to improve significantly or even fully recover. Ciompi extended this point into the field of family linkage as well, where he found no positive correlation between genetic loading (measured by several cases of schizophrenics among close relatives) and unfavorable long-term outcome (Ciompi, 1988). Therefore, Ciompi concluded that not only should the etiology of schizophrenia be looked at with a biopsychosocial model, but also that the course of schizophrenia depends on the psychosocial environment , no matter what subtype of schizophrenia is present. Ciompi's results are not without objection, but overall, studies worldwide support the claim that the old dogma of an inevitable poor long-term

outcome for schizophrenia must seriously be questioned (Barlow and Durand, 1995).

Deficits in Cognitive Function

Despite the notable heterogeneity in the behavioral presentation of schizophrenia, there is a general agreement regarding the presence of neuropsychological impairments that accompany the disorder. Impaired performance on standardized neuropsychological tests has frequently been reported with such cognitive abilities as abstraction, attention, language, and memory. One recent study found the rate of impairment in schizophrenics greater than patients with such disorders as major depression and bipolar disorder. 41.8% of the schizophrenic patients showed definite impairment on the Luria-Nebraska Battery (a screening test that assesses major areas of neuropsychological performance) compared to 31.3% of those with an affective disorder. In addition, 73.9% of the schizophrenics showed definite impairment on the Halstead-Reitan Battery (includes tests of rhythm, strength of grip, and tactile performance) compared to only 59.5% of those with an affective disorder (Bryson, Silverstein, Nathan, and Stephen, 1993). The following section will review specific neuropsychological research to see where this impairment might be coming from.

The first area of cognitive ability to be reviewed is abstract thinking. Watson et al. (1976) performed two tests comparing the abstract thinking ability between a schizophrenic group and a control group. The first test aimed to determine whether the past reports of schizophrenics suffering from abstraction difficulties was a product of cognitive impairment or generalized intellectual weakness. The test compared Shipley-Hartford abstraction scores of the two groups who had been matched for performance on three general intelligence tests. Watson et

al. found the two groups to produce very similar mean Shipley Abstraction scores and conceptual quotients (Schizophrenics 15.0/.55 and Controls 14.1/.53). These results suggest that the inability to abstract, at least measured by Shipley-Hartford Abstraction scores, may not be a specific schizophrenic deficit (Watson, Wold, and Kucala, 1976).

Watson also considered the possibility that some sort of specific abstraction might exist that was not shown by the general Shipley-Abstraction results. In the second study researchers tested both groups on abstraction tasks that included skill with verbal analogies, concept formation, letter/number sequence reasoning, and use of the rules of logic. Results from the Tests of Educational Ability and Schubert Abstraction Score Means were tabulated and showed no significant differences between groups in any areas *except* for logical answers, where the schizophrenic group was inferior to the controls. Watson suggests that several of the common conceptions in the abstraction deficit literature may be erroneous. However, although the inability to abstract may not be a major specific deficit for schizophrenics, the inability to use logic properly may be.

Memory deficit in schizophrenia has probably been discussed more often than any other cognitive function, as many past studies report schizophrenic memory to be disproportionate to the overall level of intellectual impairment and other deficits in executive functions (Heaton et al., 1994). However, few studies have assessed a specific pattern in which this memory impairment might follow. Recently, Clare et al. (1993) produced a study that eliminates this problem by first screening patients for showing moderate to severe degrees of memory impairment, followed by testing the group in the areas of semantic, procedural, and implicit memory. Clare tested a group of 12 schizophrenic patients who were chosen on the basis that

they showed poor memory in the absence of gross general intellectual impairment. Semantic memory was assessed using the sentence verification task, an unpaced category judgement task, and the Mill Hill Vocabulary Scale. The schizophrenic patients took longer to consider their responses and were more likely to give incorrect answers with each test. Procedural tasks included pursuit rotor performance, speed of assembling a jigsaw puzzle, and the rate of improvement of reading transformed script. The results showed that the schizophrenic patients performed overall poorer on pursuit rotor and jigsaw learning; however, the researchers determined the *rate* of learning on all three procedural tasks comparable to that of the controls. The implicit memory tasks involved biasing of spelling of homophones and word stem completion, in which the patients showed a normal degree of performance in both. These results were the first to show the sparing of implicit learning with schizophrenics in circumstances where explicit memory was substantially impaired (Clare et al., 1993).

Overall, the results of this study point to a pattern of impairment in long-term memory in schizophrenia that is both similar and different to that of the classical amnesic syndrome. Schizophrenic patients who show clear evidence of episodic memory impairment showed preservation of procedural and implicit memory; consistent with the classical amnesic syndrome. At the same time, schizophrenics show suggestions of a deficit in semantic memory, clearly differentiating schizophrenic memory from the amnesic syndrome. This pattern of episodic and implicit impairment while retaining procedural and implicit function is very similar to the early stages of Alzheimer's disease. However, schizophrenic patients show preservation of at least some aspects of short-term memory function, in contrast to the deficit typically found in Alzheimer's patients (Clare et al., 1993). Finally, more studies will need to be done to continue

looking for ways in which memory impairments in schizophrenia can be categorized, as this study was only conducted with 12 patients. While some form of episodic memory deficit is widespread, the more detailed analysis of other aspects of memory reveal complex and varying patterns of impairment in schizophrenia.

Heaton et al. (1994) performed a comprehensive examination of neuropsychological impairment in schizophrenic patients and its possible relation to current age, age at onset, duration of illness, and whether the impairment could be distinguished from that caused by Alzheimer's disease. The researchers used neuropsychological testing with a normal control group (n=38), a group of patients with Alzheimer's disease (n=42), and three ambulatory schizophrenic groups: early onset-young (n=85), early onset-old (n=35), and late onset (n=22). Tests were grouped and analyzed according to eight major ability areas, with the results summarized in Figure 2. All schizophrenic groups were worse than the normal control group on deficit scores for all the ability areas, *except* for memory; no schizophrenic group showed impairment on the Memory Deficit Score, contrasting with the conclusions of Clare (1994). In addition, the Alzheimer's group had a higher mean deficit score in nearly all other ability areas compared to the three schizophrenic groups, which were generally not different from one another. The results suggest that neuropsychological impairment in schizophrenia is unrelated to current age, age at onset, or duration of illness (Heaton et al., 1994). This study demonstrates that cognitive dysfunction in schizophrenia is essentially nonprogressive, and produces a pattern of deficits that is different from that seen in progressive dementias like Alzheimer's disease.

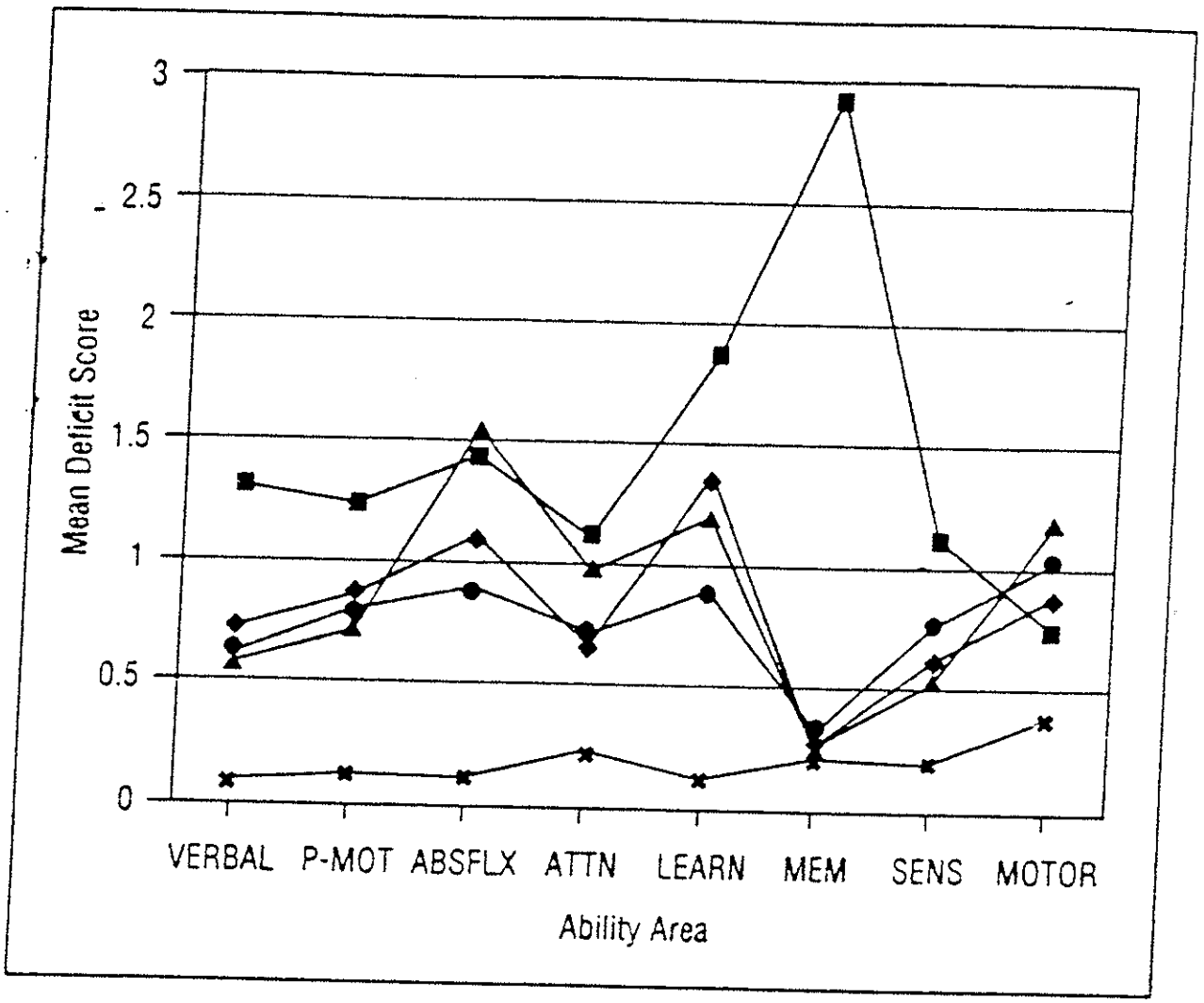

FIGURE 2: *Ability area deficit scores for the five subject groups. Mean deficit scores on the eight neuropsychological ability areas for the five subject groups. Please see the text for statistical comparisons. VERBAL indicates verbal abilities; P-MOT, complex perceptual-motor skills; ABSFLX, abstraction and flexibility; ATTN, attention; LEARN, verbal and visual learning; MEM, verbal and visual memory (forgetting); SENS, sensory perceptual abilities; MOTOR, motor skills; squares, patients with Alzheimer's disease; triangles, early-onset schizophrenics–old; diamonds, early-onset schizophrenics–young; circles, late-onset schizophrenics; and X's, normal controls.*

From: ***Archives of General Psychiatry*****, June 1994, Volume 51, page 473.**

II. Initial Causes:

Increasing Liability on the Multifactorial Threshold Model

The nature versus nurture controversy explaining the cause of psychosis has existed since the time of Darwin, and psychologists have tried to resolve this battle between biology and psychology with a broad model known as the *diathesis-stressor theory*. Diathesis refers to the biological predisposition needed in acquiring a disease, while the stressor element refers to the life events that trigger the biological vulnerability. Irving I. Gottesman, a pioneer in the understanding of schizophrenia, describes the significance of the diathesis-stressor theory: "...the vast array of facts gathered by both those scientist-clinicians typecast as hereditarians and those typecast as environmentalists can be reconciled without appeasement on either side" (Gottesman 1991). Recent research suggests that schizophrenia results from complex, multi-factorial causes with each possibly contributing something to a person acquiring the disorder.

For most of this century, psychologists have known that the development of all human characteristics requires contributions from both genes and environment. Theories of the etiology of psychosis that relate to the genetic or physical environment demonstrate that neither is sufficient for the emergence of psychosis. Nevertheless, it is generally assumed that, in some way, a biological predisposition is a necessary precondition (Gottesman 1991).

Gottesman (1991) has developed a new, more specific model for acquiring schizophrenia, known as the multifactorial threshold model, shown in Figure 3. The model recognizes genetics as a major part of the biological predisposition to schizophrenia, but also includes other biological factors including prenatal health. The model also demonstrates that the expression of

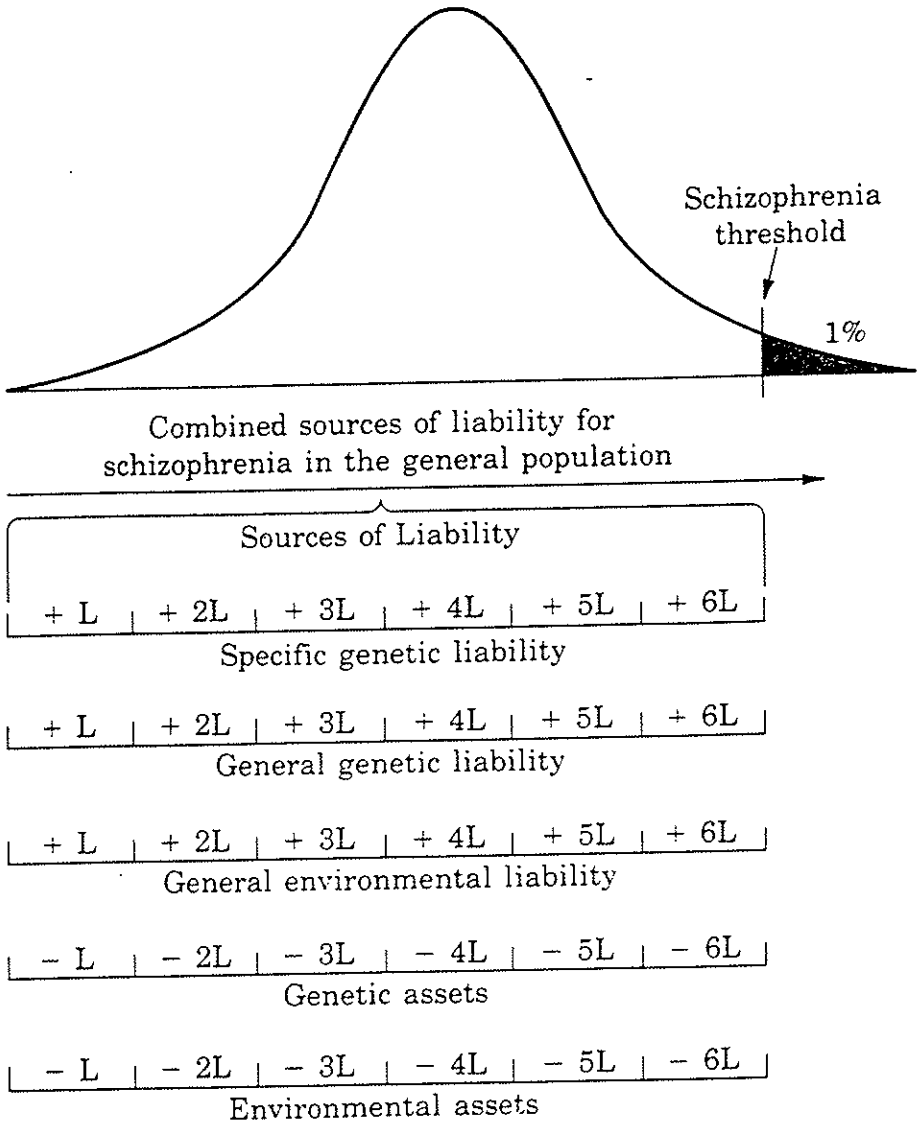

FIGURE 3 Schematic representation of the different genetic and environmental sources of the hypothetical liability for developing schizophrenia on the multifactorial threshold model; the sources take different "currency" values for assets and liabilities and sum, at a point in time, to a value above the threshold shown at the right of the graph (affected with schizophrenia) or below the threshold (well or recovered from schizophrenia).

schizophrenia-related genes at the phenotypic level depends on a person's liability to develop schizophrenia, a liability subject to dynamic fluctuations upward or downward depending on the major factors illustrated in Figure 3. In addition to liabilities, Gottesman proposes "antischizophrenia" genes and environments that actually help keep us from obtaining the disorder. The model is described as a balance sheet of genetic and environmental assets and liabilities, with each having their own weight depending on its importance to the individual. When these assets and liabilities are summed together, those clinically diagnosed as schizophrenic will have a bottom-line value that exceeds the threshold value for the onset of the disorder. Keeping the multifactorial threshold model in mind, the following section will first describe the genetic factors that influence vulnerability, followed by the prenatal developmental problems that make up the biological liability of acquiring schizophrenia.

Genetic Basis

--Family studies

For almost a century scientists have known that schizophrenia is more common among relatives of schizophrenics than with the population at large. However, the question has arisen as to whether the prevalence of schizophrenia in families results from genetic influences, or whether it can be explained partly or even entirely by shared environmental effects. Gottesman (1991) has summarized the lifetime risks of being affected with schizophrenia for the various kinds of relatives of a schizophrenic, shown in Figure 4. These grand average risks were compiled from 40 reliable family and twin studies conducted in European populations between 1920 and 1987. The chart has been broken down for first-degree, second-degree, and third degree relatives of

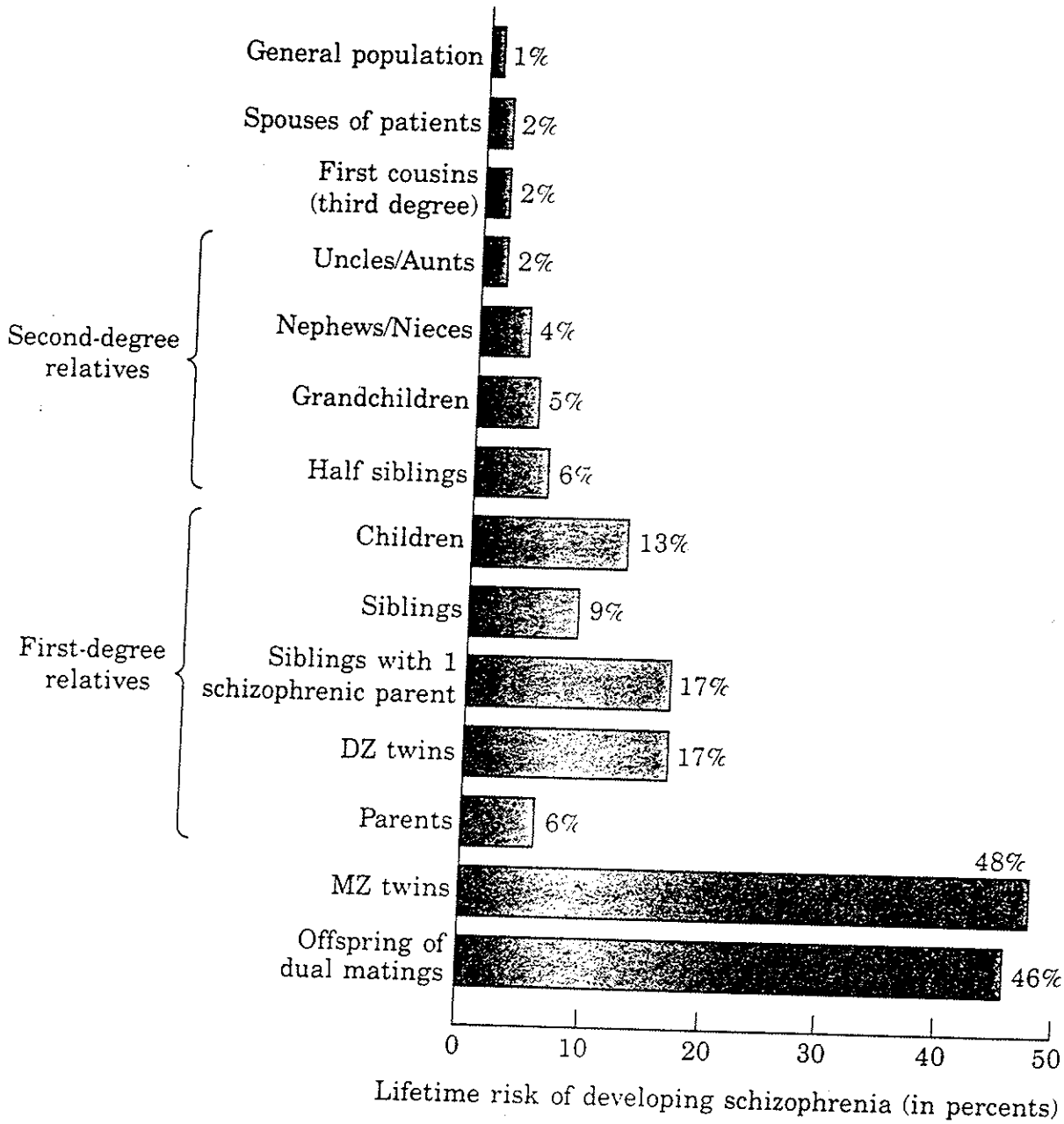

FIGURE 4 Grand average risks for developing schizophrenia compiled from the family and twin studies conducted in European populations between 1920 and 1987; the degree of risk correlates highly with the degree of genetic relatedness.

schizophrenics, where the degree of risk correlates highly with the degree of genetic relatedness. With the risk for a spouse (2%) double that of the general population (1%), the data support the idea of being able to induce schizophrenia in someone simply by sharing an intimate physical and psychological relationship. However, the overall pattern of risk in the relatives of schizophrenics strongly supports the conclusion that the magnitude of the increased risk varies with the amount of *gene* sharing, and not with the amount of *experience* sharing (Gottesman, 1991).

Recently, twin and adoption studies have helped evaluate the family data by separating genetic influence from the impact of the family's environment. If one assumes that both kinds of twins, monozygotic (MZ) and dizygotic (DZ), share environmental influences to approximately the same extent, then a significantly higher concordance for schizophrenia among monozygotes should indicate a genetic influence. Indeed, Figure 4 shows this to be true, as 48% of MZ twins possess a risk for schizophrenia, compared to only 17% in DZ twins. In a recent Norwegian study, the concordance rate for identical twins was 48.4% while the concordance rate for fraternal twins was only 3.6% (Barlow and Durand 1995), consistent with the pattern shown in Gottesman's family data.

Despite the consistency of twin data, many critics remained skeptical about a genetic contribution until the advent of results from adoption studies. One of the primary adoption studies performed was by Heston, who investigated 47 adoptees that had been separated from their mothers within three days of birth. Five of this experimental group developed schizophrenia compared with none of 50 control adoptees (Gottesman, 1991). The largest and most recent adoption study is currently being conducted in Finland, where 155 offspring of mothers with schizophrenia and 185 children of control mothers have been studied. As of 1991,

16/155 (10.3%) children born to schizophrenic mothers have acquired schizophrenia or some other psychotic disorder, compared to only 2/185 (1.1%) children from the control mothers (Gottesman, 1991). These adoption data show that increased rates of schizophrenia are found in the biological relatives of schizophrenics, but not in the control adoptives, suggesting further that shared genes rather than shared environments underlie the increased risk of disorder in the relatives of schizophrenics.

--Polygenic threshold model

Taken together, family, twin, and adoption data lead inevitably to the conclusion that there is a genetic contribution to schizophrenia. However, the *mechanism* in which this genetic contribution is transmitted has been the subject of considerable debate. What is known is that the risks of schizophrenia do not conform with those predicted by a simple Mendelian pattern of transmission as seen in Huntington's disease, cystic fibrosis, or Duchenne muscular dystrophy. The genetic liability of schizophrenia could be explained by the transmission of a single gene, the involvement of a small number of major genes (oligogenic model), or the additive effect of many minor genes taken together with environmental factors, known as the *polygenic threshold model* (McGuffin, Owen, and Farmer 1995).

The polygenic threshold model traditionally has been thought of as many small genes contributing to schizophrenia in an additive way, giving relatives of schizophrenics an increased liability compared with the general population. Relatives would thus lie closer to the threshold for manifesting the disorder. The results from the previously mentioned family experiments conform to a polygenic basis, where what is inherited is not the certainty to disease

accompanying a particular genotype, but rather a predisposition or liability to develop the disorder, consistent with Gottesman's Multifactorial Threshold Model.

In addition to being statistically more satisfactory than a single-gene model, the polygenic threshold model offers explanations of other observed phenomena. First, a polygenic model fits with the observation that the risk of schizophrenia increases with the number of other relatives affected, along with clarifying why there can be gradations of severity in people with the disorder. Second, the model accounts for the finding in some family studies of higher concentrations of schizophrenia among relatives of severe, early onset cases. Finally, a model involving several genes is easier than a single-gene model to reconcile with the fact that schizophrenia persists at high rates in the population, despite being associated with reduced reproductive fitness (McGuffin, Owen, and Farmer 1995).

Despite facing rigorous statistical criticism from twin and family studies, many researchers have recently put forward single-gene explanations for schizophrenia. They propose incomplete penetrance and mutation to explain the correspondence to Mendelian segregation ratios. Although a single-major-locus hypothesis is consistent with only a few studies, it is important to discuss what specific genes might be active in the transmission of schizophrenia. If specific gene-linkage results are confirmed, they would shed enormous light on the genetic aspects of mental illness, because they will turn the circumstantial evidence of genetic involvement gained from family studies into hard, physical evidence.

--Genetic markers

Until recently, the detailed study of psychotic disorders at a molecular level was

hampered by a lack of suitable *genetic markers*. Genetic markers are stable biological traits like blood types that can be reliably measured, have simple Mendelian modes of inheritance, and are polymorphic. Most notably, they mark a position or location in the genome. The development of recombinant DNA technology has led to the identification of new genetic markers that enable researchers to locate a disease gene without knowing anything of the gene itself or of the pathophysiological process. This approach, known as *reverse genetics*, examines DNA markers from the specified region in a series of multiply affected families. The reverse genetic process for finding linkage has been spectacularly successful in many other disorders, with Alzheimer's disease being a prime example (Bebbington, Walsh, and Murray 1994). If the pattern of inheritance of a particular marker allele appears to correspond with the pattern of inheritance of the illness, it may be that the disease gene and marker allele are linked, but could also be explained by chance. In order to establish which is most likely, the *LOD score method*, a statistical analysis, is applied to establish the probability of linkage. LOD scores of 3 (the possibility of chance findings being 1000:1) or more have traditionally been taken to indicate a high chance of linkage, while scores below -2 signify no linkage, and anything in between is equivocal.

One such linkage study for schizophrenia was performed by Basset et al. (1988), who suggested the possible involvement of the long arm of human chromosome 5 in schizophrenia. A family had been identified in which an uncle and a nephew, both suffering from schizophrenia, were noted as having similar facial dysmorphologies. Cytogenic testing revealed that both men possessed a trisomic segment of part of chromosome 5. Further studies from English and Icelandic pedigrees found further evidence of the same linkage and generated considerable

excitement. Just as startling as the discovery of a "schizophrenic gene" was found was how rapidly this finding was refuted by other studies (Bebbington, Walsh, and Murray, 1994). Within three years, more than ten linkage studies were conducted refuting evidence of a schizophrenic gene located in the fifth chromosome, as many stated this linkage was due to a rare genetic form of schizophrenic psychosis from a genetic isolate (Bebbington, Walsh, and Murray 1994). Another candidate gene marker for schizophrenia has been those involved in the monoamine pathways, such as the dopamine receptor gene or genes encoding enzymes like tyrosine hydroxylase, consistent with the dopamine theory of schizophrenia (see beyond). The gene encoding the dopamine D_2 receptor gene was mapped to chromosome 11q. However, just like the linkage studies done with chromosome 5, many reports came after to refute the 11q linkage (Bebbington, Walsh, and Murray, 1994).

Recently a study has provided new evidence for a genetic link to schizophrenia. Freedman et al. (1997) suggested that a schizophrenic's deficit in the regulation of response to sensory stimuli, which may underlie other symptoms like hallucinations and delusions, could be a positive genetic marker. Freedman et al. tested this regulation to auditory stimuli by using an electrically positive evoked potential occurring 50 ms after the stimulus, known as a P50 response. Inhibition of the P50 response, presented 500 ms after the first, was diminished in the schizophrenics' hippocampal system. Interestingly, nicotine in high doses transiently normalizes the abnormality in P50 inhibition in schizophrenics, and since over 80% of schizophrenics smoke, heavy nicotine use may reflect an attempt at self-medication of an endogenous neuronal deficit. Neurobiological investigations in both humans and animal models have indicated that decreased function of the α-7-nicotinic cholinergic receptor could underlie the P50 physiological

defect (Freedman et al., 1997).

Freedman performed a genome-wide linkage analysis of nine families with multiple cases of schizophrenia. With an LOD score of 5.3, their data strongly suggested that the P50 auditory sensory defect in schizophrenia is linked to a dinucleotide polymorphism at the α-7-nicotinic receptor gene on chromosome 15q14 (Freedman et al., 1997). In addition, the group found a similar phenotypic P50 deficit in family members that did not have schizophrenia, stressing the point that most people with a defective receptor do not get schizophrenia, but that it is another possible precondition to the disease. Linkage at the α-7-nicotinic receptor locus thus supports the neurobiological evidence that this gene has a role in the pathophysiological aspect of schizophrenia, which had not been previously considered, despite schizophrenic patient's well known heavy dependence on nicotine. Although this discovery and others greatly enhance our understanding of the genetic nature of schizophrenia, locating schizophrenic genes continues to be a daunting task for psychiatric geneticists.

--Anticipation genetics and unstable DNA

Although the bulk of the genetic section has explained and supported the traditional polygenic threshold model, it is not without its critics. The model is complicated and difficult to prove or exclude a link between the disease and specific genetic loci or environmental factors. Recent discoveries in human molecular biology have revealed other mechanisms that may explain the complex patterns of inheritance and phenotypic variability common to schizophrenia. A mechanism recently proposed has been *genetic anticipation*, or allelic expansion, in which the dynamics of unstable DNA may serve as another etiological theory of schizophrenia.

The term genetic anticipation is not new, as Mott first used the term in 1911 to describe his observations of progressively earlier age of onset and increased severity in successive generations of families with psychosis and mental retardation. This observation remained a statistical artifact until recently when unstable trinucleotide repeats were found to be the etiological factor in such disorders as the X-linked fragile-X syndrome, and the autosomal disorders myotonic dystrophy and Huntington's disease. Researchers found that each gene contained a unique trinucleotide DNA sequence repeated many times. While each repeated sequence is also present in the non-mutant allele of each gene, mutant alleles have significantly more trinucleotide repeats. For example, in Huntington's disease, the locus on chromosome 4 has a trinucleotide sequence CAG that is repeated greater than 36 times in affected individuals, whereas persons with less than 30 CAG repeats are apparently never affected. In several cases, the number of repeats increases with each subsequent generations, and a correlation has been found between a greater number of repeats and an earlier onset of mutant gene expression. This increase of trinucleotide repeats is the molecular equivalent of anticipation first observed by Mott three quarters of a century ago (Petronis and Kennedy, 1995).

Within the last few years researchers have observed the two components of anticipation, greater severity and earlier age of onset, in subsequent generations of families suffering with schizophrenia. Gorwood et al. (1996) have overcome the ascertainment biases that might mimic anticipation--namely, the fact that patients in different generations are not interviewed at the same age, resulting in a greater chance of finding a later age at onset in the older generation-- by using a method of calculation that finds the true age of onset from the age of the first interview. Gorwood found evidence for anticipation from a group of 24 affected families from the limited

geographical area of Reunion Island in the Indian Ocean (Gorwood et al., 1996). This study and others demonstrate earlier onset among younger generations with schizophrenia and provides support for the unstable DNA hypothesis over the multifactorial polygenic theory. In addition, the many deviations from Mendelian inheritance in schizophrenia could be explained by the Mendelian behavior of unstable DNA. The unstable DNA hypothesis may explain a simpler answer to several issues in schizophrenia genetics, such as the identical rate of psychosis in the offspring of discordant monozygotic twins, or the absence of environmental effects in monozygotic schizophrenia twins reared together and apart. These two phenomena are not well explained by the multifactorial polygenic theory (Gorwood et al., 1996).

However, our understanding about the basic mechanisms of genetic anticipation is still superficial. Little clinical evidence implicates anticipation for all cases of schizophrenia. In addition, most trinucleotide diseases have shown signs of *genetic imprinting*, in which an effect of the sex of the parent transmitting the disease is apparent. Currently no signs of genetic imprinting have been found in schizophrenia. In addition, if anticipation were to exist in all cases of schizophrenia, we should observe a negative correlation between age at onset and the ratio of affected to unaffected relatives. An analysis of several large families has shown that this correlation is not strong with schizophrenia (Petronis and Kennedy, 1995). Finally, most of the disorders that have been explained by trinucleotide repeats (myotonic dystrophy, fragile X syndrome, Kennedy's disease, Huntington's disease and spinocerebellar ataxia type 1) can be classified as Mendelian disorders in which a single locus is passed on with Mendelian proportions (Petronis and Kennedy, 1995). Schizophrenia does not show Mendelian inheritance. Therefore, I doubt whether genetic anticipation can fully describe it. My belief is that

trinucleotide repeats could be the method of expression of the genetic vulnerability to schizophrenia in some cases, but this expression comes from a fraction of the many genes that are expressed into schizophrenia and not by just a single locus.

Prenatal Developmental Problems

In addition to genetic factors increasing vulnerability, there has been an increasing amount of interest that schizophrenia might in some cases be a neurodevelopmental disorder. The most common prenatal mishap reported has been the maternal-virus theory, but other theories including nutritional deprivation have also gained attention. Research on a possible viral etiology of some cases of schizophrenia is now being performed using both direct and indirect measures.

--Indirect investigations of prenatal infections

Indirect measures, including prevalence studies, seasonality of schizophrenic births, and studies of identical twins, have indicated the possibility of a viral infection causing schizophrenia. If infectious agents are involved in the etiology of schizophrenia, variations in the prevalence of the disease, both geographically and temporally, should be apparent. Western Ireland is thought to have an unusually high prevalence of schizophrenia, along with the highlands of Papua New Guinea, where the disease is normally thought to be quite rare (Torrey, 1988). Takei et al. (1995) investigated any effect of prenatal exposure to influenza on subsequent risk of schizophrenia using a national sample from The Netherlands. Takei et al. (1995) have taken all dates of births of Dutch-born schizophrenic patients admitted to hospitals

between 1970 and 1992, and compared them to the number of deaths from influenza per month between 1947 and 1969. As part of their study, the research team also studied data by gender, subtype, and examined the period during gestation that the fetus was most vulnerable. They found modest evidence supporting the association between prenatal exposure to influenza and adult schizophrenia. For every 500 deaths attributed to influenza in The Netherlands, there was a 6% increase in schizophrenic births 3 months later. Although previous studies have suggested that prenatal exposure affects females more than males, this study found no significant data to support any claim by gender. Finally, the study found the maximum risk period related to exposure to influenza during the 7th month of gestation, which differs from other studies that found the increased risk confined to months 3-5. The authors suggested that the window of exposure might be wider than once thought and will vary according to the individual. They also described a possible inconsistency with their study since they realize those who are inflicted from influenza might not have died until several weeks later. However, the researchers are still confident in their findings that prenatal exposure to influenza does lead to typical schizophrenia without a gender difference (Takei et al., 1995).

Over the years, a common observation made by many researchers has been that a majority of schizophrenic births have occurred in late winter to early spring. A seasonal disease affecting fetal development may explain this finding. This seasonal effect on schizophrenia has been reported in populations drawn from the northern United States and Europe, but not for the southeastern United States, where seasonal changes are limited (Watson et. al., 1984). Watson et al. (1984) have studied over 3000 patients with different severities of illness (determined by marital status), and compared their birth date with the number of reported diseases during this

target year and the year before. In doing this, Watson not only was able to determine if seasonal diseases are associated with an increased risk for schizophrenia, but also whether this risk was prenatal or postnatal. If the effects were postnatal, one would expect winter birth seasonality in schizophrenics to be most apparent in years with high incidence of disease, while if the effects were prenatal, a high seasonal tendency would appear in the winters *following* a year with high incidence of disease. The research team also attempted to determine exactly what seasonal disorder was primarily responsible. Seasonal disorders considered were six winter diseases (diphtheria, pneumonia, scarlet fever, whooping cough, influenza, and measles), and two summer diseases (polio and typhoid fever). Influenza, measles, and polio are viral, while the remaining five are generally bacterial.

Overall, the results support the view that birth seasonality found in schizophrenia is associated with disease-related factors. However, the relationship is not a general one, since patterns were found that were specific to particular subsets of schizophrenics, seasonal diseases, and periods of risk. For instance, a positive relationship between schizophrenia and previous winter diseases was only found in single schizophrenics. Watson suggests that since most process chronic schizophrenics tend not to be married, this is the subgroup that seasonal diseases might affect. In addition, positive findings were found with schizophrenic birth seasonality and high previous-year incidences of the diseases studied, but not to same-year incidences, which suggest seasonal diseases affect fetal development. Finally, the birth seasonality was positively correlated with winter but not summer disorders. Watson's results suggest that previous winter viral diseases may lead to process schizophrenia in utero.

The high concordance for schizophrenia in monozygotic (MZ) twins has already been

cited as evidence for the etiological influence of genetics, but many researchers have forgotten that monozygotic twins can also provide a way to investigate the importance of the prenatal period, including the possible role of viral infections. Davis and Phelps (1995) used the fact that MZ twins produce a variety of placentation arrangements, or chorion types, that may experience very different intrauterine environments. Approximately 40% of MZ twins become dichorionic monozygotic (DC-MZ), in which the blastocyst separate early and arrive into the uterus independently, each with its own placenta, chorion, and amnion. The result in DC-MZ twins is that fetal circulation is almost never connected. On the other hand, 60% of MZ twins become monochorionic monozygotic twins (MC-MZ), where the inner cell mass splits later into two separate cell masses within the same blastocyst cavity, resulting in a *shared* placenta and chorion in which shared fetal circulation occurs. Thus, the probability of shared infections is likely to be greater in MC-MZ twin pairs than in DC-MZ twin pairs because of shared fetal circulation in the monochorionic pairs. Davis and Phelps have recently aimed to determine whether MC-MZ twins are more concordant for schizophrenia than DC-MZ twins, which would be consistent with our previous reported data that a mother's exposure to infectious disease, especially during the second trimester, increases the risk of schizophrenia later in her child's life.

Davis and Phelps used data from previous twin studies and used *handedness*, or the individual's hand preference, as a retrospective marker of placentation status. Common handedness in twins is just one example of *mirroring*, along with birthmarks, hair swells, and dermal ridge patterns, that has been shown to appear as a result of late twinning and a single placenta; thus it is a special marker for MC-MZ placentation (Davis and Phelps, 1995). One problem with using handedness as a marker is that only MC twins who split very late are mirror

imaged, so mirroring for handedness will fail to correctly identify the placentation status of nonmirrored MC twins. Thus, handedness is a very conservative marker in the sense that it reduces the sample size. However, the researchers can be reasonably sure that those who they identify as having complementing handedness will indeed be monochorionic twins.

After the group studied 71 carefully chosen monozygotic twins from three previous studies, they concluded that twin pairs who preferred opposite hands were more often concordant for schizophrenia. Of 15 pairs that included a left-handed and a right-handed twin, 9 (60%) were concordant for schizophrenia, while only 18 out of 56 (32.1%) twin pairs with same-hand preferences were concordant (Davis and Phelps, 1995). The researchers add that because only 21% of their cases were opposite-handed, and because the expected MC twinning is 60%, they assume that many of those that were same-handedness must also be MC. In this light, 32.1% for DC-MZ twins might be high and the rate shown for MC-MZ might be modest. Davis and Phelps conclude that twins with shared fetal circulation (MC-MZ) are more likely to acquire schizophrenia than those who have their own fetal circulation (DC-MZ), supporting an influence of viral infections on schizophrenia.

--Direct evidence of viral infection

If infectious agents are involved in the etiology of some cases of schizophrenia, evidence ultimately will need to come from more direct research approaches. One such direct study was done by Akbarian et al. (1993). This group studied deceased brains to prove that disturbances in brain development may play a contributory role in the etiology of schizophrenia. Disturbances of the medial temporal lobe during the second trimester may be responsible for the genesis of a

variety of positive symptoms, while dysfunctions of the prefrontal cortex have been blamed for the genesis of negative symptoms (Akbarian et al., 1993). The normal pattern of neuronal migration from the subplate to the cerebral cortex during the second trimester of fetal development may be affected in schizophrenics. Any disturbances of normal neuronal migration during this developmental stage would have serious consequences for the establishment of the normal pattern of connections, since axons of inappropriately positioned neurons are less likely to gain access to their correct targets (Akbarian et al., 1993). Influenza is one of the few viruses known to have the ability to disrupt normal developmental neuron migration (Barlow and Durand 1995).

Akbarian and his team have quantified potentially altered distributions of neurons by using a histochemical technique that stains a specific class of neurons containing the enzyme nicotinamide-adenine dinucleotide phosphate-diaphorase (NADPH-d). These neurons are present in substantial numbers in the adult gray and white matter, where they remain from the old fetal subplate. NADPH-d neurons were used for measurement in the cerebral cortex because their number and distribution is less likely influenced by acute or chronic neurodegenative effects. They compared postmortem brain tissue from five schizophrenic brains with tissue from five control brains and found that schizophrenic brain tissue contained a significantly lower number of neurons in the dorsal lateral prefrontal cortex (DLPFC) and subjacent white matter, but an abnormally high number of NADPH-d neurons in the deeper regions of the prefrontal white matter. These findings are consistent with a disturbance of the subplate during development in which the normal pattern of migration of neurons toward the cortical plate has been altered. This lack of migration, possibly caused by the presence of viral infection, is likely

to have serious consequences for the establishment of a normal pattern of cortical connections, leading to a potential breakdown of frontal lobe function in schizophrenics (Akbarian, 1993).

--Prenatal nutritional deprivation

In addition to viral infection, other factors may alter prenatal brain development, including nutritional deprivation. If prenatal malnutrition is a significant risk factor for schizophrenia, the disorder should be more common in regions of the world with a history of famine. Although this has not been shown to be the case, *specific* nutritional deprivation has been known to cause neurodevelopmental disorders even in countries with an adequate food supply (Brown et al., 1996). Maternal protein-calorie malnutrition is associated with disturbances in the fetal brain and decreased infant birth weight and body length. The Dutch famine study demonstrated that protein-calorie malnutrition during the third trimester impairs the growth of the fetal brain, as evidenced by significant reductions in infant head circumference and brain weight (Brown et al., 1996).

The most recent established relationship between a nutritional deficiency and a neurodevelopmental disorder is that between folate, a necessary coenzyme, and neural tube defects (NTDs). NTDs are a group of central nervous system anomalies resulting from a disturbance of closure of the neural tube and its submergence within the mesoderm. This neuropathological abnormality is analogous to those found in schizophrenia, including increased cerebral ventricle size. Folate supplementation to pregnant mothers following conception resulted in a significant decrease in the incidence of NTD's, compared with unsupplemented mothers. Other nutritional deficiencies have been shown to disrupt brain development, including

zinc, iodine, and vitamin B12 (Brown et al., 1996). Although not as popular as anti-psychotic drugs (see later), vitamin supplementation has been recently found to help some in their treatment of schizophrenia (Walsh, 1995). Certainly, the very recent theory of nutritional deprivation has been shown to be another risk factor of schizophrenia and warrants further study.

To conclude, infectious agents and nutritional deprivation continue to be very attractive candidates as etiological agents in some cases of schizophrenia. Viruses in particular have provided plausible explanations for schizophrenia with regard to observances in seasonality of birth, regional prevalence differences, and higher incidence among MC-MZ twins. Although clever indirect studies have suggested that mishaps in prenatal development is a risk factor, more direct evidence is needed to link these problems to schizophrenia to the same degree as genetics. As laboratory technology continues to improve and more direct experimentation is performed, neurodevelopmental disorders need to be increasingly recognized as important risk factors toward the onset of schizophrenia.

III. Direct Physical Causes:

The Neurological Basis of Psychosis

Returning to Gottesmann's multifactorial threshold model, once a person has reached the threshold level for schizophrenia, psychosis will result. The patient will eventually show symptoms of schizophrenia sometime during his/her life, usually between 16 and 25, leaving themselves and their loved ones wondering what changed their behavior so drastically. Most people can not believe that only social tension could begin such a state of confusion. As one family member stated:

> Many of us who have a son or daughter, or other relative with schizophrenia have observed so great a change in the person's behavior with the onset of the psychosis that we know intuitively that the cause had to be something basic, such as an alteration of the brain's functioning (Barlow and Durand, 1995).

Since the days of pioneer psychiatrists like Kraepelin and Alzheimer, schizophrenia has been thought to somehow involve a malfunctioning brain. Researchers began learning about the neuropathology of schizophrenia by studying postmortem tissue from deceased patients. However, no general anatomic patterns could be found, and by the mid-twentieth century, schizophrenia was known to anatomists as "the graveyard of neuropathology" (Andreasen, 1996). With the development of neuroimaging techniques such as MRI and PET, schizophrenic neuropathology has enjoyed a renaissance of new studies during this Decade of the Brain. Researchers can now avoid many of the disadvantages of postmortem tissue by studying brain function in vivo. These new techniques are showing possible links between cognitive symptoms and specific abnormal brain regions. In addition, the new studies complement earlier work in

neuropharmacology by directly studying the effects of drugs on brain function. This section will summarize the direct neurological causes of schizophrenia by first discussing abnormal neuropathology, followed by the role neurochemical imbalance has on the disorder.

Neurological Damage

Evidence of neurological damage in people with schizophrenia comes from a large number of observations; however, few have been consistent with all patients. One observation which has been consistent is that schizophrenia is not a neurodegerative process like Alzheimer's disease, since there has been no observation of depleted glial cells common to Alzheimer's (Andreasen, 1996). The neurological observation most common with schizophrenics has been abnormally large lateral ventricles. The fact that these liquid-filled cavities are large may not be a problem, but it does indicate that the adjacent parts of the brain have not fully developed (Barlow and Durand, 1995). When Kraepelin reasoned that the disease might be localized to specific regions, he speculated the prefrontal and temporal cortex were probable sites of abnormality, but was unable to find a specific pattern. Recent investigators have confirmed Kraeplin's speculations about the prefrontal and temporal cortex in some patients, and have found additional abnormalities with interacting areas such as the thalamus, hippocampal complex, and cingulate gyrus (Andreasen, 1996).

The current challenge facing neurologists is to identify a physiological process that could account for the diversity of the disorder's symptoms. One possibility is that a single focal lesion could be found common to all schizophrenics that affects each individual differently. Another possibility is multiple focal lesions may vary from patient to patient that could reflect the

different psychological traits unique to each individual. Andreasen (1996) quotes two methods for this current investigation. The "bottom up" strategy uses the traditional approach of focusing on a key symptom, while identifying the specific brain regions that produce this symptom. The more recent "top down" strategy seeks to identify a fundamental cognitive process and/or a crucial neural region that could account for the entire range of symptoms observed (Andreasen, 1996). Examples of each strategy will be given. Each study will show that one specific brain region can not be blamed for even a single symptom, and researchers are furously working to understand the complex circuit models that could explain the madness of schizophrenia.

--Direct observations of hallucinations

Neuroimaging has allowed investigators to observe the specific brain regions affected when a person performs a cognitive process or is suffering from a symptom. Silbersweig et al. (1995) have developed an ingenious experiment to examine brain scans that show where hallucinations occur in schizophrenic patients. The research group asked five paranoid schizophrenics to lay in a PET scanning machine and told them to push a button when they were hallucinating. Each patient's regional cerebral blood flow (rCBF) was recorded and compared to a time when the patient was not hallucinating. Silbersweig found maximal activity through a complex circuit of subcortical structures including the thalamus, putamen, and parahippocampal gyrus (Silbersweig et al., 1995). These findings suggest a complex mechanism for auditory hallucinations based on integration between these deep structures of the brain.

This observation refutes the earlier theory that hallucinations were caused by increased activity in the cerbral region Broca's area (speech center). This theory concluded that

hallucinating patients were not hearing the voices of others, but instead were listening to either their conscious thoughts or their own voices and could not recognize the difference (McGuire, Shah, and Murray, 1993). Silbersweig concludes that this inner speech theory might be involved, but that it is not the central pathological process for schizophrenia. He suggests that hallucinations are a much more complex problem, involving interactions between the thalamus, limbic system, and cerebral cortex. This interaction might start with conscious thought process or memory processing within the cortex, and would proceed to the deeper regions like the thalamus and limbic system. Silbersweig concludes that increased dopaminergic transmission in the thalmus, which filters sensory information, and the limbic system, which involves emotional states and behavioral drives, is responsible for the patient's internal sense of reality with the absense of sensory input (Silbersweig et al., 1995) (Martini, 1992). Increased rCBF in all of these deep regions supports Silbersweig's complex theory of hallucinations in schizophrenia.

--Hypofrontality

Researchers have recently proven Kraeplin's speculation that the prefrontal cortex is involved with some symptoms of schizophrenic patients. The findings have shown that this area of the brain may be less active in people with schizophrenia, a phenomenon known as *hypofrontality* (Barlow and Durand, 1995). Weinberg et al. (1992) have attempted to understand hypofrontality by using a "top down strategy." In their past experiments they have noticed that in monozygotic twins discordent for schizophrenia, the affected twin had a smaller hippocampal area than the unaffected twin. Weinberg used this fact in the current study to investegate a relationship between hippocampal size and hypofrontality in the same twin pairs. Nine pairs of

discordent monozygotic twins underwent MRI scanning to measure their hippocampal volume, followed by a rCBF measure of their dorsal lateral prefrontal cortex (DLPFC) during performance on the Wisconsin Card Sorting Test. This psychological test gives patients prefronal-type tasks, which include working memory, integration of sensory regions, and abstract intellectual functions (Martini, 1992).

The results showed that the smaller the hippocampal volume of the affected twin (relative to the unaffected twin), the less activation of the dorsal DLPFC was observed during the Wisconsin Card Sorting Test. Weinberger speculates that cognitive reasoning is based on connections between the hippocampus and the prefrontal cortex, which he calls "neocortical-limbic connectivity". Although other explanations are possible for this correlation seen in affected individuals, Weinberger states, "The fact that the anterior hippocampus and dorsal lateral prefrontal cortex may normally communicate with each other during the performance of such (cognitive) tasks implies that a defect in one part of this network might have functional implications throughout the network" (Weinberg et al., 1992). Reseachers still have a long journey ahead, but the works of Weinberg and Silbersweig have shown that schizophrenic symptoms do not occur from the damage to a specific brain region. Rather, they seem to be the malfunction of complex neural circuits that are interconnected from cortical sections to deeper lymbic regions.

Although we are still speculating on how these circuits directly cause schizophrenic symptoms, we are gaining a better understanding of which regions are responsible for negative and positive symtoms. Hypofrontality has been thought for some time to underlie negative symptoms of schizophrenia. Wolkin and his research team (1992) attempted to directly prove

this association by measuring glucose metabolism in the prefrontal cortex of schizophrenic patients. The study began by evaluating the severity of negative symptoms in 20 chronic schizophrenics. This was followed by using PET to measure the rate of metabolism of patients who did not receive any neuroleptic drugs. The results demonstrated a strong correlation between negative symptom scores and lower frontal metabolism, especially in the right dorsal lateral prefrontal cortex (DLPFC). Put more simply, a lower rate of metabolism in the DLPFC correlated with more severe negative symptoms. The group concluded that this relationship was not due to the patients age, cerebral atrophy, or severity of positive symptoms (Wolkin et al., 1992). This study can be compared to Silbersweig's (1995) observance of hallucinations. Although both positive and negative symptoms probably result from complex interactions between cortical and deep brain regions, the direct evidence for each symptom lies in distinct areas. Negative symptoms have been directly correlated with hypofrontality in the DLPFC, and positive symptoms (especially hallucinations) have been directly correlated with deeper subcortical regions.

Neurochemical Imbalance

For over a hundred years researchers have struggled to find a biological treatment suitable for schizophrenia. A breakthrough came in the 1950's with the introduction of several drugs, such as thorazine and haldol, that seemed to relieve hallucinations and delusions in many people (Barlow and Durand, 1995). Experts now began looking at schizophrenia as a chemical brain disorder. After several studies correlated the therapeutic effect of the new medications to their ability to block dopamine type 2 receptors, the dopamine hypothesis of schizophrenia was born.

Dopamine is a monoamine neurotransmitter that is concentrated primarily in limbic regions, basal ganglia, and the prefrontal cortex (Andreasen, 1996). The hypothesis suggested that schizophrenia was the result of a hyperactive dopamine system, especially in the limbic regions. Threrefore, the ideal neuroleptic was thought to serve as an antagonist at the D_2 receptors in this brain area. Although the dopamine hypothesis has endured for several decades, current researchers are now aware that many neurotransmitter systems are involved with hallucinations and dellusions. In addition, the dopamine hypothesis does not address negative symptoms. Davis (1996) argues, "None of the current drugs do anything for the most incapacitating symptom of schizophrenia, the cognitive deficits. Maybe it's time to get off the dopamine merry-go-round we've been on for 40 years" (Hooper, 1996). The succeeding section will begin by analyzing the traditional dopamine theory of schizophrenia, followed by summarizing recent theories that modify the dopamine hypothesis and explain how other neurotransmitter systems might be involved.

--The role of dopamine

Since the dopamine hypothesis has been one of the most enduring causal theories of schizophrenia, a careful analysis will be discussed. The first clue to researchers establishing a dopamine hypothesis was that antipsychotic drugs were shown to be effective blockers of dopamine. Once these drugs were used in excess, negative side effects similar to symptoms of Parkinson's disease were produced. Since Parkinson's disease is a disorder involving low levels of dopamine, this observance helped support the dopamine theory. Conversely, when excess amounts of the dopamine agonist L-Dopa was given to Parkinson patients, schizophrenic-like

symptoms were observed. Finally, amphetamines, which are known to activate dopamine, were found to elevate psychotic symptoms in some people with schizophrenia. All of these observations led researchers to theorize that schizophrenia was attibuted to excessive dopamine activity (Barlow and Durand, 1995).

Recently, evidence has surfaced that seems to contradict the theory that schizophrenia can only be explained by excess dopamine. The first argument is that there are many people with schizophrenia that have not been helped by dopamine antagonists. For instance, these drugs have only patially helped people suffering from negative symtoms. Another piece of confusion comes from genetic linkage studies, where a correlation between schizophrenia and the gene region for D_2 receptors was inconclusive (Barlow and Durand, 1995). In additon, although neuroleptics are known to block the reception of dopamine quickly, affected symptoms are reduced only after several days or weeks, which is much slower than one would expect. Finally, there remains some questions concerning the data received by early neuroscientists that reported excess dopamine in affected brains. These earlier neuroscientists studied neurotransmitter levels indirectly by measuring the dopamine metabolite *homovanillic acid (HVA)*in post-mortem tissue. Since there are many reasons why extra metabolite could be accumulated, meausurements of HVA can not give direct evidence of increased dopamine activity.

--New insights into the dopamine theory

Neuroscientists are now better understanding the complex relationship between neurotransmitter systems and schizophrenia. By using neuroimaging techniques, they are able to directly measure and compare levels of different neurotransmitters that have given new insights

into the classical dopamine theory. Davis (1991) is one such neuroscientist that has reviewed the historical development of ideas regarding dopamine's possible role in schizophrenia and has formed his own conclusions. Through his research, neuroleptics have been found to treat patients by decreasing the activity in *specific* dopaminergic neurons, and not *all* dopaminergic neurons as once thought. Also, five subtypes of dopamine receptors now exist, and it is not yet clear how each are involved in causing schizophrenia. Research has shown that traditional neuroleptics act by reducing dopamine activity in *mesolimbic* dopamine neurons (Davis, 1991). This may explain Silbersweig's (1995) observation of increased blood flow in the subcortical regions of hallucinating schizophrenics. Conversely, the low prefrontal activity common to negative symtoms has been correlated with insufficient activity of *mesocortical* dopamine neurons. This has been supported by Okubo et al. (1997) who studied PET scans that correlated the severity of negative symptoms to a reduced number of dopamine type 1 receptors in the prefrontal cortex (Okubo et al., 1997). Davis describes this relationship by suggesting that a low prefrontal dopamine activity may lead to greater dopamine turnover in subcortical regions that results in D_2 hyperactivity (Davis, 1991).

This new theory of dopamine is appealing since it provides a possible explanation as to why many schizophrenics are observed to change symptoms from positive to negative with increasing age. Also, this theory might explain why neuroleptics have been found not to relieve cognitive or negative symptoms. However, it is not clear whether patients will show *both* cortical hypodopaminergic activity and limbic hyperdopaminergic activity, since we do not necessarily observe all symptoms common to schizophrenia even in a lifetime. Despite this, Davis does reform our previous notions about dopamine and schizophrenia, and gives us a

potential neural distinction between positive and negative symptoms.

--Integrating neurotransmitter systems

Very recent advances in pharmacology have increased our knowledge of how neurotransmitters interact to form the psychosis of schizophrenia. A new class of drugs, called "atypical" neuroleptics, demonstrate that schizophrenia can no longer be treated by simply blocking dopamine receptors. This was first shown by comparing clozapine, an early atypical neuroleptic, to thorazine, a traditional dopamine-blocking neuroleptic. Clozapine's affinity to D_2 receptors was reported as being one-tenth that of thorazine, yet was a much more effective neuroleptic than thorazine and demonstrated fewer side-effects (Davis et al., 1991). With this finding, pharmaceutical companies moved swiftly to produce new "atypical" neuroleptics that were safer and more effective than clozapine.

Kapur et al. (1995) performed a study to determine what made risperidone, the new popular atypical neuroleptic, resistant to side-effects that were common to the traditional drugs. The researchers gave nine schizophrenic patients between 2-6 mg per day and used PET scans to measure the D_2 receptor occupancy each day. The mean level of receptor binding to risperidone was 66% at 2 mg, 73% at 4 mg, and 79% at 6mg. The researchers point out that at 4-6 mg, risperidone is shown to occupy receptors at the same level as typical neuroleptics, without the typical side effects. They hypothesize that risperidone is able to avoid side effects by being able to bind to 5-HT_2 (serotonin type 2) receptors. However, the researchers warn that a balance in dose is needed, since patients given 6 mg a day began showing more side effects that those at 4 mg per day. This excess dosage was shown to block D_2 receptors at a higher level, which seems

to counteract the 5-HT_2 blockade needed to control unwanted side effects (Kapur et al., 1995).

Kapur's study only introduces the fact that different neurotransmitters interact with each other in a complex manner to form the resulting symptoms. We have seen that the amount neuroleptics bind to a particular receptor (dopamnine, for example) might determine how a differing neurotransmitting system such as serotonin might respond. Currently, pharmaceutical companies continue to make new atypical neuroleptics that attempt to improve on the relationship between dopamine and seretonin to give the pateint the best outcome. Although we have come a long way in understanding schizophrenia as a neurochemical disease, there is a long journey ahead. According to Sedvall (1995), today more than 100 transmitters, gaseous messengers, growth factors, and 300 receptor molecules have been identified and shown to exist in the human brain (Sedvall, 1995). So far, we know the anatomical distribution and physiological role of only a few of them, and we are still not sure how even these interact with one another. As Nancy Andreasen describes (Andreasen, 1996):

> Contemporary thinking has progressed, therefore, from a "too much or too little of this or that neurotransmitter" model to models that postulate complex feedback loops involving excitatory and inhibitory interactions between multiple neurotransmitters, including both GABA and glutamate in addition to the classical biogenic amines.

Neurologists will continue to increase their understanding of these complex interactions between neurotransmitter systems. Hopefully this continued understanding will lead to new neuroleptics that will not only cover the full spectrum of schizophrenic symptoms, but also relieve unwanted side effects.

IV. Psychological Influences

The current discussion of how biological liabilities lead to neurological malfunction might lose sight of the role psychological stress has on the patient acquiring schizophrenia. Researchers have recently avoided the social theories of the middle of the century in fear of blaming the family as the cause of psychosis. Fromm-Reichmann's (1948) use of the term *schizophrenic mother*, meaning a parent whose cold, dominant, and rejecting nature was thought to cause schizophrenia in her children, is exactly the kind of psychological stress researchers have since discredited as being a direct cause (Barlow and Durand, 1995). However, although it is absurd to think a family member could cause psychosis, general psychological stress might form a bridge between a person being vulnerable to schizophrenia to actually manifesting the disorder. It has already been demonstrated that malfunctions of the brain may influence behavior, but Kandel's theories of brain plasticity proposes that environmental experiences may effect the brain (Andreasen, 1997). In addition, the risk for spouses of schizophrenics is 2% compared to 1% for the rest of the population (Figure 4), demonstrating that sharing an intimate relationship puts someone at a greater risk of psychosis. Unfortunately, psychosocial models are much tougher to research than genetic strategies and PET scans in determining the role stress might have on an individual acquiring schizophrenia. In addition, Gottesman (1991) suggests that environmental stressors are not single events, but rather long, cumulative experiences that makes them increasingly difficult to study (Gottesman, 1991). Although psychological influences are tough to prove, there are studies that suggest stress has a causation role in schizophrenia. Researchers have always been curious of the effect life-threatening events like wartime combat may have on someone becoming schizophrenic. Steinberg and Durell (1968)

examined recruits entering military service to determine whether basic military training by young men separated from their families and treated with impersonal harshness might precipitate schizophrenia. Hospitalization rates for schizophrenia were reported six times higher for the first year compared to the second, with many of these occurring in the first month. In addition, more cases were reported for draftees compared to volunteers. These soldiers might have developed schizophrenia in any case, but this study shows that a stressing event may influence the timing of the onset of schizophrenia (Bebbington, Walsh, & Murray, 1994).

Tienari et al. (1987) further demonstrated the relationship between psychosocial factors and schizophrenia with a modified adoptive study in Finland. His investigation compared the rate of schizophrenia in 112 children given up for adoption to the rate of 135 control adoptees. As expected from the genetic model, 8 out of the 10 psychotic cases reported were the offspring of schizophrenic mothers. In addition, Tienari psychologically assessed all the adoptive families blindly and determined which ones could be described as "disturbed." None of the schizophrenic patients were found to come from "healthy" adoptive families, while almost all of the psychotic cases occurred in adoptive families rated as "severely disturbed." Tienari concludes that the mental health of these adoptees depends on the integration of genetic vulnerability and rearing environment (Tienari et al., 1987). These studies demonstrate the current psychosocial stress model of schizophrenia. This model suggests that stressful environmental factors alone are not going to make an individual schizophrenic, but enough stresses could push someone vulnerable for schizophrenia over the threshold into psychosis (Gottesman, 1991).

V. Conclusions

Schizophrenia is a consistent disease with a rate of occurrence of one to two percent of the world's population. It is characterized by a broad spectrum of cognitive and emotional dysfunctions that disrupts a person's perception of the world into one of tormenting psychotic experience. Because this complex disorder does not have traits common to each individual, psychologists battle the issue of whether schizophrenia is one distinct disorder or a combination of disorders. Schizophrenia results from a variety of complex causes with each possibly contributing something to the disorder. Gottesman's multifactorial threshold model summarizes causation by describing biological liabilities that may cross the threshold to psychosis. The most popular biological liability known is genetics, but prenatal viral infection and malnutrition are also possible. Many recent neurological studies using neuroimaging technology have given a new understanding of how schizophrenia is an organic neural disease. However, we are becoming increasingly aware that social stresses might effect neuropathology, making someone vulnerable for schizophrenia into someone who actually suffers from the disease. Although we have come a long way in our understanding of schizophrenia, there remains many secrets unanswered. As Barlow and Durand (1995) state, "Given the great deal of attention schizophrenia has received, you would think that the question, 'What is schizophrenia?' would now be easily answered. It is not."

Although it is exciting that so much is being learned about schizophrenia, the real challenge is to use this knowledge for the benefit of the patients and their families. For example, we can hope for rapid advances in molecular genetics to fix responsible genes, but we also must understand the complexity of the genetic contribution and accept that genetic counseling for

schizophrenia is not coming anytime soon. Prenatal factors such as fetal infection and maternal malnutrition are much easier to prevent and should be further discussed. If a mother has been very sick during her pregnancy, physicians must discuss with her that the child may be more vulnerable to mental illnesses like schizophrenia. In addition, if a family is known to have a history of schizophrenia, parents should not be advised against having children, but rather understand that their child may be more *vulnerable* to psychosis and may need extra social support.

Our increasing understanding of schizophrenia can also help psychiatrists with their treatment of patients. Mental health providers must understand that schizophrenia is a very dynamic disorder that is specific to the individual (Gureje, 1993). With the new knowledge about neuropharmacology, psychiatrists need to match the right kind of neuroleptic with the observed symptoms. If a patient is suffering from negative symptoms, a dopamine antagonist will not help since the drug is not focusing on the right receptors. Even while treating hallucinations and delusions, new neuroleptics might cause unwanted side effects by altering the balance of other neurotransmitter systems. Society also needs to be careful not to put too much faith in these new "atypical" medications. We need to learn from past deinstitutionalization policies that have put many schizophrenics on the street. Mental health needs to evolve into a spectrum of treatment that addresses each of the multidimensional aspects of schizophrenia. In this way we can listen to Davidson & Strass (1995) and take care of the individual and not the disease.

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