Essays of an Information Scientist, Vol:6, p.188-196, 1983 Current Contents, #25, p.5-13, June 20, 1983

Current Comments®

What Do We Know about the Group of Mental Disorders Called Schizophrenia? Part 1: Etiology

Number 25 June 20, 1983

Many autobiographical and fictional accounts of "schizophrenia" have appeared in the popular literature in recent years. Several have become best-sellers and were read by thousands of people around the world. Among the better known are Hannah Green's *I Never Promised You a Rose Garden*[1] and *The Eden Express* by Mark Vonnegut.[2] Green's book was even turned into a movie. However, the people described in these books may actually have suffered from depression and not schizophrenia, as the authors claimed. Thus, they have unintentionally misinformed their readers about schizophrenia, one of the most debilitating and least curable of the mental disorders.

In 1981, Carol North and Remi Cadoret, University of Iowa School of Medicine, Iowa City, reviewed five popular books on "schizophrenia," including the two mentioned above.[3] They treated the books as case histories, analyzing each page for any symptoms described by the authors. The researchers diagnosed the mental disorders represented in each book using the third edition of the *Diagnostic and Statistical Manual of Mental Disorders*,[4] a standard reference work published by the American Psychiatric Association. They concluded that the popular accounts dealt mostly with depressive disorders, not schizophrenia. I've discussed depression previously in a three-part essay.[5-7]

But confusion about the true nature of schizophrenia is apparent in the scientific literature as well as the popular press. Schizophrenia is a general term, like cancer, that covers a variety of diseases with different causes, treatments, and outcomes. In the first part of this essay, I'll review current research on the causes of schizophrenia. The second part will focus on the diagnosis and treatment of schizophrenia.

Briefly, schizophrenia is one of the psychoses, that is, major mental diseases characterized by a loss of contact with reality. Schizophrenic symptoms have been classified as being "positive" or "negative." You should keep in mind that this distinction is made only for convenience.

Positive symptoms are those whose presence reflects pathology—delusions, hallucinations, and thought disorders.[8,9] For example, schizophrenic delusions include the belief that one's thoughts are being broadcast for everyone to hear, or that thoughts are being inserted into one's mind or controlled by some external agent. The most common schizophrenic hallucinations are auditory—a single voice provides a running commentary on the individual's actions or thoughts, or two or more voices carry on a conversation. The schizophrenic's disordered thinking is characterized by loose or illogical associations, abrupt and nonsensical changes of subject, and incoherence.

Negative symptoms of schizophrenia are defined by the absence of emotions, the lack of goal-directed behavior, poverty of speech, deteriorated functioning, and the lack of close personal ties.[8,9] The schizophrenic's expressed emotions may be inappropriate to the context—news of a death or other tragedy might be met with laughter or indifference, for example. Schizophrenics also behave oddly—they grimace, exaggerate normal movements, or assume one position for a long time without moving at all.

Eventually, people with schizophrenia can no longer perform the functions they did before the onset of the disease—they lose their jobs, drop out of school, or simply no longer care for themselves or their friends and relatives. Gradually, the schizophrenic withdraws from social contacts and is isolated in his or her own private, personal world.

The first clinical descriptions of schizophrenia were provided independently by two European doctors in 1809.[10] (p. 27) John Haslam, Bethlehem Hospital, London, published case histories of patients with symptoms of what we would today call schizophrenia.[11] He described its onset in adolescence and its deteriorating course over time. Phillipe Pinel, Hôpital Salpêtrière, Paris, discussed patients with a type of disordered thinking different from melancholia or mania.[12] He called it *demence* to reflect the profound deterioration he observed in these patients.[13] And in 1852, a Belgian physician, B.A. Morel, described a 14-year-old schizophrenic boy who began hating his father. Morel named the condition *demence précoce* to stress its onset in adolescence.[13]

In 1896, the German psychiatrist Emil Kraepelin studied hospitalized psychiatric patients and recognized a difference between manic-depressives and those suffering from *demence précoce*.[13] He also included paranoid patients in the group with *demence précoce*, and Latinized the name to *dementia praecox*.[10] (p. 31) In the early 1900s, Eugen Bleuler, a Swiss psychiatrist, believed that *dementia praecox* was actually a group of diseases with similar symptoms. He observed that some patients did not become profoundly demented, and noticed the disease did not always become manifest in adolescence.[13] Bleuler renamed the disease "schizophrenia," from the Greek "schiz" or split and "phren" or mind. He intended the name to reflect the splitting in thought processes and emotions from reality.[10] (p. 31) But people commonly confuse schizophrenia with split personality, a completely different mental disorder.

Today, an estimated ten million people worldwide suffer from schizophrenia. In the US alone, between 100,000 and 200,000 new cases of schizophrenia are diagnosed each year. Schizophrenics account for 20 percent of those treated for mental disorders, and 35 percent of psychiatric hospitalizations in the US. More than half of the beds in psychiatric hospitals are occupied by schizophrenics. And there is a one in a hundred chance that a person living in the US will be diagnosed as schizophrenic in his or her lifetime.[14,15]

Epidemiologic studies show that schizophrenia begins earlier in males than in females. The onset and first hospitalization for schizophrenic males peak while they are in their early 20s. Women are first diagnosed and hospitalized for schizophrenia in their late 20s and early 30s.[16,17] Also, the lowest socioeconomic groups typically have the highest rates of schizophrenia.[18,19]

The onset of schizophrenia seems to follow a seasonal cycle. Hospital admissions for schizophrenia peak in the early summer months—June and July.[20] This is true for so-called "affective psychoses" as well, particularly mania, but not for nonpsychotic disorders such as neuroses and neurotic depression.[21] A sea-

sonality in the birth dates of people diagnosed as schizophrenic has also been observed. Persons with schizophrenia are more likely to have been born in the winter months in the northern hemisphere—January through March.[21] A season-of-birth effect has also been documented for the winter months in southern hemisphere countries—June through August—but it is less pronounced.[10] (p. 159)

After more than 50 years of research on the etiology of schizophrenia, researchers are still unsure of what causes this disease.[13] But most psychiatrists now agree that a genetic influence is involved. Researchers have studied the families of schizophrenic individuals to learn if they had a higher rate of schizophrenia than the general population. As I stated earlier, the risk of schizophrenia in the general population is about one percent. But for "first-degree" relatives of schizophrenics—parents, siblings, and offspring—the risk increases to between eight and ten percent.[22] If *both* parents happen to be schizophrenic, there is a 39 percent chance that their children will be schizophrenic.[23] First-degree relatives share half their genes with the schizophrenic family member.[24] For second-degree relatives—aunts, uncles, nephews, and nieces, who share one-fourth of their genes with a schizophrenic relative—the incidence of the disease is about 2.5 percent.

The results of these studies also suggest that the family environment may contribute to the development of schizophrenia. Simply spending a lot of time with a schizophrenic relative might cause a family member to become schizophrenic. For example, fraternal twins and sibling pairs show a higher "concordance rate" for schizophrenia when the pairs are of the same sex. That is, brothers of male schizophrenics are more likely to be schizophrenic than their sisters, presumably because the brothers spend more time together in shared activities. For the same reason, sisters of female schizophrenics are at greater risk than their brothers for developing the disease. This cannot be explained genetically, because siblings share genes to the same extent no matter what their sex.[20]

A number of adoption studies have been carried out to determine if schizophrenia is caused by the family environment or by genetic factors. Persons adopted soon after birth who later became schizophrenic were identified, and the rates of schizophrenia in their biological and adoptive families were examined. These rates were compared to the incidence of schizophrenia in the biological and adoptive families of "normal" adoptees. The biological relatives of the schizophrenic adoptees were five times more likely to be schizophrenic than their adoptive relatives, or the adoptive and biological families of the normal adoptees.[22,23]

Also, adoptees with a schizophrenic biological parent had a higher rate of schizophrenia than adoptees whose biological parents were not psychotic. And children of nonpsychotic biological parents who were adopted by schizophrenic foster parents did *not* show a higher rate of schizophrenia than those adopted by nonpsychotic foster parents.[23] These results strongly indicate that genetic factors, not the family environment, have a role in the etiology of schizophrenia.[22,23]

Studies of twins offer even more convincing evidence of a genetic factor in schizophrenia. Monozygotic twins are genetically identical, but dizygotic, or fraternal, twins are no more genetically alike than ordinary brothers and sisters. Thus, if schizophrenia is genetically transmitted, identical twins should show a higher rate of schizophrenia in both members of the pair than fraternal twins.[22,23] And this is the case—the con-

cordance rate for schizophrenia in identical twins is between 35 and 58 percent, and for fraternal twins it is between nine and 26 percent.[20]

But these twin studies also indicate that schizophrenia is not purely a genetic disorder. If it were, the concordance rate for identical twins would be 100 percent.[20,23,24] Researchers suggest that genetic inheritance may only predispose people to other factors—biochemical defects or environmental stress, for example—that cause schizophrenia.[9]

Much recent research has focused on the role of neurotransmitters in the etiology of schizophrenia. Neurotransmitters are substances that affect how nervous impulses cross synapses in the brain. Perception, cognition, memory, mood, and behavior all depend on what happens at the synapse. Thus, a biochemical defect involving these neural "substrates" might result in mental illness.[24]

Several lines of evidence implicate dopamine (DA) as the specific neurotransmitter involved in schizophrenia. In 1952, a group of drugs called neuroleptics were used to treat schizophrenics. The neuroleptics succeeded in reducing some symptoms of schizophrenia—hallucinations, delusions, and thought disorders. In 1963, Arvid Carlsson and Margit Lindqvist, University of Göteborg, Sweden, showed that the main effect of neuroleptics in the body was to *prevent* DA from interacting with its receptors in the brain.[25] Thus, if blocking DA receptors in the brain reduces schizophrenic symptoms, then schizophrenia may be caused by an *excess* of DA in the brain's pathways.[26,27]

Researchers also examined those drugs which exacerbate schizophrenic symptoms to determine what effect they have on DA pathways. Amphetamines are known to worsen symptoms in schizophrenic patients. This effect is not noticed in other psychiatric illnesses. Even normal individuals develop acute paranoid schizophrenic symptoms as a result of amphetamine abuse. One of the main biochemical effects of amphetamines in animals is to *increase* DA levels in the brain.[9,26] Levodopa, a drug used to treat Parkinson's disease, also produces schizophrenic symptoms in subjects with no history of psychiatric disorder—it, too, increases brain DA. Thus, schizophrenia seems to be caused by hyperactivity of DA neurons in the human brain.[9,26,27]

Researchers have noticed a lag time of about two weeks between the administration of DA-blocking drugs and the reduction of schizophrenic symptoms. This suggests that the primary defect in schizophrenia involves a mechanism other than the DA neurons. For example, neurons that release gamma-aminobutyric acid (GABA) also suppress DA activity. If the GABA system is defective, an increase in DA levels results. Autopsies on schizophrenic patients show that GABA concentrations are lower than normal in two areas of the brain. These preliminary findings indicate that more research is needed on the role of GABA in schizophrenia.[27]

Another system that possibly affects DA activity in the brain involves the endorphins, endogenously produced opiates found in the brain and pituitary gland. Paranoid symptoms of schizophrenia have been exaggerated by alpha-type endorphins. Large amounts of beta-endorphin can produce catatonic symptoms, the rigid posturing observed in some schizophrenics.[28] And gamma-endorphins are like the antipsychotic neuroleptic drugs in that they prevent the retention of newly learned information.[29] Gamma-endorphins also interfere with DA activity in a particular part of the brain. Thus, a defect in the brain's gamma-endorphin system may result in an increase in DA levels, causing schizophrenic symptoms to appear.[28]

In addition to these defects in the brain's biochemical systems, researchers have focused on physiological abnormalities in the brain. Recently, M.S. Buchsbaum and colleagues, National Institute of Mental Health (NIMH), measured glucose metabolism in the brains of schizophrenics and normal controls.[30] Glucose is the main source of energy for the brain, and active areas of the brain use up more glucose than inactive areas.

They found that the frontal cortex of schizophrenics was less active than in normal persons. This area of the brain is believed to be the center for goal-directed behavior. Thus, low activity in the frontal cortex may explain the lack of goal-directed behavior and deteriorated motor ability that are characteristic negative symptoms of schizophrenia. The researchers also found reduced activity in the left central gray matter in schizophrenic brains, an area thought to be involved in various schizophrenic symptoms, such as perceptual-cognitive disorders and motor-behavioral deterioration.[30]

Various structural abnormalities in schizophrenic brains have also been identified. Several studies suggest that the cerebral ventricles in some chronic schizophrenics are larger than in normal persons.[31-33] The ventricles are chambers in the cortex of the brain that are filled with cerebrospinal fluid. The larger the ventricles, the less cortex there is—that is, the loss of cortex creates more "space" in the schizophrenic brain.

Also, those chronic schizophrenics with increased ventricular space appeared to do poorly on various tests of intellectual ability.[32,33] The results may indicate that chronic schizophrenia is associated with increased ventricular size and reduced intellectual capacity, at least for a subgroup of patients with negative symptoms. But these preliminary findings need to be studied further before we can draw any conclusions on the relationship between enlarged ventricles and schizophrenia.

Other structural abnormalities have been observed in the brain stems of schizophrenics. The brain stem has been implicated in many schizophrenic symptoms, including disorders of attention and perception, hallucinations, and delusions. M. Fisman, Kingston General Hospital, Ontario, Canada, examined the brain stems of 24 mental patients and ten normal controls after autopsy. Lesions on various areas of the brain stem were found in six of the seven patients diagnosed as schizophrenic, but not in the other mental patients or controls. Fisman observed, "The nature and distribution of the [lesions] is similar to that described in herpes B infection in simians and [herpes] zoster in man."[34]

Recently, researchers have suggested that viral infections play an important role in the etiology of schizophrenia. If viral infections cause schizophrenia, schizophrenics should have antibodies to these viruses in their cerebrospinal fluid. Two studies demonstrated that levels of antibodies to cytomegalovirus (CMV) in schizophrenics were significantly higher than in controls or other mental patients.[35,36] The data indicate that the viral infection probably occurred years before the onset of schizophrenia.[35]

What we know about CMV makes it a likely candidate as a cause of schizophrenia. CMV, like the other herpes viruses, is neurotropic—that is, it infects nervous tissue. More specifically, it infects the limbic system of the brain, an area thought to be affected in schizophrenia. CMV attacks newborns, even infecting fetuses while still in the uterus, and can result in mental retardation in later life. It also remains inactive for many years before clinical symptoms appear. Lastly, the lowest socioeconomic

groups have the highest rates of both CMV infection and schizophrenia.[35] I've reviewed the literature on herpes viruses in previous essays.[37,38]

There is some evidence that schizophrenics were infected by viruses very early in life. Adult schizophrenics have a higher than expected incidence of dermatoglyphics, or abnormal fingerprints. Viruses attacking fetuses in the first few months of pregnancy are known to interfere with the formation of fingerprints. Thus, the high rate of dermatoglyphics in schizophrenics may indicate intrauterine viral infections.[10] (p. 165)

The viral hypothesis also fits in well with the seasonal effects in schizophrenia mentioned earlier. Remember that schizophrenics are more likely to have been born from January to March. Several viruses have seasonal peaks in the winter months—in particular, rubella, measles, and varicella zoster.[10] (p. 164) And as with many viral infections, hospitalizations for schizophrenic illnesses peak in the early summer months.[39,40]

If viruses cause schizophrenia, it is logical to ask whether or not the disease can be transmitted between people. Evidence suggesting this possibility can be found in the family and twin studies reviewed here. As I pointed out earlier, concordance rates for schizophrenics are higher in pairs of relatives when both members are of the same sex. This cannot be accounted for in genetic terms, but it may be due to the fact that same-sex family members are in closer contact than opposite-sex pairs.[20] Also, fraternal twins have a higher concordance rate for schizophrenia than siblings of different ages, even though they share genes to the same extent. Again, fraternal twins are more likely to be in closer contact with each other than with their older or younger siblings.[20] And identical twins have a higher concordance rate for schizophrenia when they are living together at the time of onset. That is, when one identical twin becomes schizophrenic, the second twin is more likely to be affected if both live together than if they live apart.[41] However, more studies of twins are needed—at present, the transmission of schizophrenia between people is only a hypothetical possibility, *not* a definite fact.

The evidence supporting a viral hypothesis in schizophrenia is compelling but circumstantial. More research is needed to confirm the presence of a virus in the brain or cerebrospinal fluid of schizophrenics. However, it is very difficult to identify viruses in neural tissue.[40] Many viruses, such as polio, rabies, and herpes simplex and zoster, attack a specific part of the central nervous system, a single cell type, or a very small section of the brain.[10] (p. 180) But the isolation of a virus in schizophrenics would be a significant advance in our understanding of the etiology of this disease.

This brief survey of the literature on the causes of schizophrenia is by no means exhaustive. For reasons of space, I cannot review in detail several other factors that have been implicated as causes of schizophrenia. For example, stressful life events—marriage, divorce, birth, death, loss of a job—were thought to "trigger" schizophrenic episodes. But most researchers now agree that stress plays only a trivial role in the etiology of schizophrenia.[42-44] Specific foods have also been implicated in schizophrenic disease, for example, cereal grains and, in particular, wheat gluten.[45-47] But more recent studies have refuted the "food allergy" hypothesis.[48,49] Another nutritional hypothesis suggests that vitamin deficiencies cause schizophrenia. But these "orthomolecular hypotheses" are out of the mainstream of orthodox

Table 1: *ISI/BIOMED®* research fronts on the causes of schizophrenia. A=research front number. B=research front name. C=number of *core* papers in the research front. D=number of *citing* papers in the research front.

A	B	C	D
81-0617	Endorphin and opioids in schizophrenia	9	144
81-0939	Stressful life events and schizophrenia and neurotic depression	5	95
81-1372	Dopamine receptors and schizophrenia	4	180
81-1794	Hemispheric brain asymmetry in schizophrenia	8	108
81-1951	Use of CAT-scan in schizophrenia	5	114
81-2684	Inheritance of bipolar illness, manic depression and schizophrenia	2	61
81-2731	Platelet monoamine oxidase activity in schizophrenia and healthy subjects	6	104
81-2862	Platelet monoamine oxidase in schizophrenia	2	28
81-3019	Clinical studies of schizophrenia and catecholamines	2	31
82-1535	Neurochemical and genetic basis of schizophrenia and other psychopathological diseases	5	46
82-1758	Studies of platelet monoamine oxidase in normal subjects and patients with schizophrenia	7	58
82-2114	Computed tomography of brain of chronic schizophrenia patient	11	89
82-2418	Clinical significance of increased noradrenaline and dopamine in CSF and plasma from patients with schizophrenia	2	22
82-3133	Role of dopamine receptors in schizophrenia	3	48

psychiatry, and controlled studies have shown vitamin therapies to be ineffective in treating schizophrenia.[10] (p. 185)

A large number of papers on various aspects of schizophrenia are published each year. This can be seen in our *Index to Research Fronts in ISI/BIOMED®*.[50] We've identified almost 40 research fronts on schizophrenia in the *ISI/BIOMED* data base. Research fronts are created when a group of current papers cite one or more papers identified as core papers for that topic.

Table 1 lists the names of the 1981 and 1982 research fronts dealing with the etiology of schizophrenia, and the number of core and citing papers in each. For example, if you are interested in DA and schizophrenia, you could retrieve a total of 228 current papers on that topic. In 1981, 180 papers cited the core literature in research front #81-1372, "Dopamine receptors and schizophrenia," and 48 papers in 1982 cited the core documents in research front #82-3133, "Role of dopamine receptors in schizophrenia." In order to retrieve these citing papers online, you simply enter the code numbers

Table 2: Institutions receiving $250,000 or more in schizophrenia-related grants and contracts from the National Institute of Mental Health (NIMH) in fiscal year 1980.

Institution		Amount of NIMH Funding
Univ. California		$2,299,661
Berkeley	19,098	
Los Angeles	1,333,884	
San Diego	454,354	
San Francisco	427,842	
Santa Barbara	64,483	
McLean Hosp., Belmont, MA		1,156,038
Yale Univ., New Haven, CT		1,142,353
New York State Psychiat. Inst., NY		1,069,771
New York Univ., NY		923,538
Stanford Univ., CA		850,758
Univ. Rochester, NY		797,705
Columbia Univ., New York, NY		693,782
Univ. Chicago, IL		686,204
Harvard Univ., Cambridge, MA		609,157
Univ. Pittsburgh, PA		593,133
Boston Univ., MA		399,087
Univ. Wisconsin, Madison, WI		390,393
Univ. Iowa, Iowa City, IA		377,003
Univ. Washington, Seattle, WA		347,070
Washington Univ., St. Louis, MO		342,062
Charles R. Drew Postgrad. Med. Sch., Los Angeles, CA		285,419
Univ. Maryland, Baltimore, MD		272,218
World Health Org., Geneva, Switzerland		250,000

Source: *Schizophrenia Bull.* 8:142-97, 1982.

in your terminal and command it to print out complete bibliographic information on all of them. In fact, most of the papers cited in this essay were retrieved by a research front specialty search of the *ISI/BIOMED* data base.

It is surprising that only one journal is devoted entirely to research on schizophrenia. *Schizophrenia Bulletin* is a quarterly publication of NIMH. In addition to presenting original research articles and critical reviews, this journal includes a bibliography and abstracts of recent publications on schizophrenia. The abstracts are taken from the files of the National Clearinghouse for Mental Health Information, Rockville, Maryland.

NIMH administers the US federal government's funding of research in mental health. Universities, hospitals, mental health centers, and community clinics receive grants and contracts from NIMH to study various aspects of mental disorders. Table 2 shows those institutions that received at least $250,000 from NIMH in fiscal year 1980 for schizophrenia-related research. Table 2 is adapted from data reported in *Schizophrenia Bulletin*. The list is intended to give you an idea where important research on schizophrenia is being conducted—it is not meant to be exhaustive.

The second part of this essay will discuss the diagnosis and treatment of schizophrenia. It will include a list of private organizations that help schizophrenics and their families cope with the disease.

* * * * *

My thanks to Linda Cooper and Alfred Welljams-Dorof for their help in the preparation of this essay.

REFERENCES

1. **Green H.** *I never promised you a rose garden*. New York: Holt, Rinehart and Winston, 1964. 300 p.
2. **Vonnegut M.** *The Eden express*. New York: Praeger, 1975. 214 p.
3. **North C & Cadoret R.** Diagnostic discrepancy in personal accounts of patients with "schizophrenia." *Arch. Gen. Psychiat.* 38:133-7, 1981.
4. **American Psychiatric Association.** *DSM-III: diagnostic and statistical manual of mental disorders*. Washington, DC: APA, 1980. 494 p.
5. **Garfield E.** What do we know about depression? Part 1: etiology. *Current Contents* (19):5-12, 11 May 1981.
6. ----------. What do we know about depression? Part 2: diagnosis and treatment. *Current Contents* (20):5-12, 18 May 1981.
7. ----------. What do we know about depression? Part 3: children and adolescents. *Current Contents* (27):5-11, 6 July 1981.
8. **Sargent M.** Keith: success of drug treatment may mask psychosocial needs of schizophrenics. *ADAMHA News* 8(25):4-5, 1982.
9. **Crow T J.** Molecular pathology of schizophrenia: more than one disease process? *Brit. Med. J.* 280:66-8, 1980.
10. **Torrey E F.** *Schizophrenia and civilization*. New York: Jason Aronson, 1980. 230 p.
11. **Haslam J.** *Observations on madness and melancholy*. London: J. Callow, 1809. 345 p.
12. **Pinel P.** *Traitē mĕdico-philosophique sur l'alienation mentale ou la manie*. (Medical-philosophical treatise on mental alienation or insanity.) Paris: Richard, Caille et Ravier, 1809. 318 p.
13. **Guirguis W R.** Schizophrenia: the problem of definition. *Brit. J. Hosp. Med.* 25:236-47, 1981.
14. **Cassem N H.** Managing the person with major psychiatric illness. (Rubenstein E & Federman D D, eds.) *Scientific American medicine*. New York: Scientific American, 1982. Vol. 2. Sect. 13(II). p. 1-18.
15. **Adler D A, Astrachan B M & Levinson D J.** A framework for the analysis of theoretical and therapeutic approaches to schizophrenia. *Psychiatry* 44:1-12, 1981.
16. **Lewine R R J.** Sex differences in schizophrenia: timing or subtypes? *Psychol. Bull.* 90:432-44, 1981.
17. **Seeman M V.** Gender differences in schizophrenia. *Can. J. Psychiat.* 27:107-12, 1982.
18. **Dohrenwend B S, Dohrenwend B P, Gottesman I I, Link B & Neugebauer R.** Epidemiology and genetics of schizophrenia. *Soc. Biol.* 26:142-53, 1979.

19. **Kohn M L.** Social class and schizophrenia: a critical review and a reformulation. *Schizophrenia Bull.* (7):60-79, 1973.
20. **Crow T J.** Is schizophrenia an infectious disease? *Lancet* 1(8317):173-5, 1983.
21. **Hare E H.** Seasonal variations in psychiatric illness. *Trends Neurosci.* 3:295-8, 1980.
22. **Kessler S.** The genetics of schizophrenia: a review. *Schizophrenia Bull.* 6:404-16, 1980.
23. **Kinney D K & Matthysse S.** Genetic transmission of schizophrenia. *Annu. Rev. Med.* 29:459-73, 1978.
24. **Kety S S.** The syndrome of schizophrenia: unresolved questions and opportunities for research. *Brit. J. Psychiat.* 136:421-36, 1980.
25. **Carlsson A & Lindqvist M.** Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacol. Toxicol.* 20:140-4, 1963.
26. **Fredrickson P & Richelson E.** Mayo seminars in psychiatry: dopamine and schizophrenia—a review. *J. Clin. Psychiat.* 40:399-405, 1979.
27. **Berger P A.** Biochemistry and the schizophrenias. *J. Nerv. Ment. Dis.* 169:90-9, 1981.
28. **Van Ree J M & De Wied D.** Endorphins in schizophrenia. *Neuropharmacol.* 20:1271-7, 1981.
29. **Van Praag H M & Verhoeven W M A.** Endorphin research in schizophrenic psychoses. *Compr. Psychiat.* 22:135-46, 1981.
30. **Buchsbaum M S, Ingvar D H, Kessler R, Waters R N, Cappelletti J, van Kammen D P, King A C, Johnson J L, Manning R G, Flynn R W, Mann L S, Bunney W E & Sokoloff L.** Cerebral glucography with positron tomography. *Arch. Gen. Psychiat.* 39:251-9, 1982.
31. **Weinberger D R, Torrey E F, Neophytides A N & Wyatt R J.** Lateral cerebral ventricular enlargement in chronic schizophrenia. *Arch. Gen. Psychiat.* 36:735-9, 1979.
32. **Johnstone E C, Crow T J, Frith C D, Husband J & Kreel L.** Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet* 2:924-6, 1976.
33. **Johnstone E C, Crow T J, Frith C D, Stevens M, Kreel L & Husband J.** The dementia of dementia praecox. *Acta Psychiat. Scand.* 57:305-24, 1978.
34. **Fisman M.** The brain stem in psychosis. *Brit. J. Psychiat.* 126:414-22, 1975.
35. **Albrecht P, Torrey E F, Boone E, Hicks J T & Daniel N.** Raised cytomegalovirus-antibody level in cerebrospinal fluid of schizophrenic patients. *Lancet* 2:769-72, 1980.
36. **Torrey E F, Yolken R H & Winfrey C J.** Cytomegalovirus antibody in cerebrospinal fluid of schizophrenic patients detected by enzyme immunoassay. *Science* 216:892-4, 1982.
37. **Garfield E.** Herpes simplex virus infections. Part 1. How widespread they are, and who is most threatened. *Current Contents* (25):5-11, 22 June 1981.
38. ----------. Herpes simplex virus infections. Part 2. Sexually transmitted diseases without a cure. *Current Contents* (26):5-11, 29 June 1981.
39. **Crow T J.** The biology of schizophrenia. *Experientia* 38:1275-82, 1982.
40. Schizophrenia: the case for viruses. *New Sci.* 97(1344):365, 1983.
41. **Abe K.** The morbidity rate and environmental influence in monozygotic co-twins of schizophrenics. *Brit. J. Psychiat.* 115:519-31, 1969.
42. **Day R.** Life events and schizophrenia: the "triggering" hypothesis. *Acta Psychiat. Scand.* 64:97-122, 1981.
43. **Dohrenwend B P & Egri G.** Recent stressful life events and episodes of schizophrenia. *Schizophrenia Bull.* 7:12-23, 1981.
44. **Rabkin J G.** Stressful life events and schizophrenia: a review of the research literature. *Psychol. Bull.* 87:408-25, 1980.
45. **Dohan F C.** Cereals and schizophrenia: data and hypothesis. *Acta Psychiat. Scand.* 42:125-52, 1966.
46. **Dohan F C & Grasberger J C.** Relapsed schizophrenics: earlier discharge from the hospital after cereal-free, milk-free diet. *Amer. J. Psychiat.* 130:685-8, 1973.
47. **Singh M M & Kay S R.** Wheat gluten as a pathogenic factor in schizophrenia. *Science* 191:401-2, 1976.
48. **Kinnel H G, Kirkwood E & Lewis C.** Food antibodies in schizophrenia. *Psychol. Med.* 12:85-9, 1982.
49. Gluten in schizophrenia. *Lancet* 1(8327):744-5, 1983.
50. **Institute for Scientific Information.** *Index to research fronts in ISI/BIOMED 1983.* Philadelphia: ISI, 1983. 544 p.