

Can "Schizophrenia" Reflect Changes in the Blood-Brain Barrier System?

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Introduction

Possible pathophysiologic alterations which might lead to the clinical behaviors and way of life which are termed schizophrenic have been postulated by some investigators for many years and have most recently been championed as causative agents by such investigators as Heath¹, Osmond, Hoffer, Callbeck, Kahan²³ and Pauling.⁴

In the early decades of this century, specific neuropathologic lesions were sought at autopsy in many schizophrenics but lesions were never found in consistent patterns and it became apparent that if a specific organic cause of schizophrenia exists, it must be subtle. Over the past several years, much research on the nature of schizophrenia has been undertaken and some exciting new theories presented. Unfortunately, a great many of these theories have suffered from assuming isolated, parochial views of the schizophrenic process.

Thus, there are psychological and organic theories to explain the etiology of these complex collections and systems of behavior and within these two groups there are genetic theories, neurochemical theories, abnormal metabolite theories, analytic theories, behavioral theories, cognitive theories and many more.

Lloyd Allan Wells wrote this paper as a student at the University of Rochester in the M.D.-Ph.D. program. He received his B.A. degree at Harvard. Since writing this, he has received his Ph.D. degree. His Ph.D. work concerned the blood-brain barrier - at an anatomical level.

The need for a holistic approach to such a complex illness and way of life seems apparent and indeed, Dr. Oliver Wendell Holmes⁵ seems to have recognized this need a century ago, when he wrote about a mad woman:

Contemplate them charitably, remembering that nine-tenths of their perversity comes from outside influences, drunken ancestors, abuse in childhood, bad company ... I think also that there are special influences which work in the blood like ferments.

Thus Holmes perceptively suggested that "dementia" had a complex etiology, which included societal, familial, genetic and even biochemical inputs.

Several biochemical hypotheses about the etiology of schizophrenia are currently under investigation. These include the possibilities of abnormalities in plasma proteins, alterations in glycoproteins in the extracellular and cerebrospinal fluids, unorthodox transmethylation of catecholamines, abnormal serotonin metabolism, (Hawkins⁰); and these possibilities are far from exhaustive.

Most of these current approaches assume a generalized metabolic defect, either directly in brain chemistry or in body chemistry leading to the introduction of abnormal metabolites into the brain—essentially Dr. Holmes' "ferments in the blood." I wish

to suggest that a primary etiologic agent might be a defective blood-brain barrier system, which, when coupled with genetic and societal factors, could lead to aberrant behavior.

The Blood-Brain Barrier System

There is an unfortunate general attitude that the blood-brain barrier is a sort of membrane which surrounds the brain—or, at least, most of the brain. In fact, there is increasing evidence that the functional barrier is really a complex system of interacting components. Proteins, for example, are presumably restricted from entry into the brain by the tight junctions between adjacent cerebral endothelial cells, on the basis of work performed with horseradish peroxidase, Reese and Karnovsky⁷, Bright-man et al.⁸

These endothelial cells lack fenestrations and may have a lower rate of micropino-cytosis than is found in many other areas of the body. It is unlikely, however, that ions, many of which are excluded from entering the brain (Mandel et al.⁹), are kept out by such mechanisms. Rather, coupled active transport across the capillary wall, perhaps through small pores, may play an important role in determining which ions are allowed to enter the brain in significant quantity, as is probably the case with sugars (Eidelberg et al.¹⁰), and perhaps amino acids as well. Further structural specializations include the dense network of pericapillary astroglial end feet adjacent to the endothelium throughout most of the brain, and the small extracellular space of the brain. The system is complex and has many components.

Schizophrenia and the Blood-Brain Barrier System

I suggest that a lesion in some part of this complex system could play an important role in the establishment of schizophrenia. Several investigators have made somewhat similar suggestions, Melander and Martens¹¹, Pauling⁴, Borenstein et al.¹² In general, however, such suggestions have not been accompanied by heuristic hypotheses amenable to testing—largely because of the uncertainty which persists about the exact nature of the blood-brain barrier system. In fact, such hypotheses often seemed to be black boxes and last resorts for the inexplicable. This situation need not persist for much longer.

What evidence is there to link the barrier system with schizophrenia? It is, admittedly, very slim. First, some animals with barrier lesions acquire behavioral defects, Angel et al.¹³ Second, profound

hypothermia results in an increased permeability of the brain to certain tracers (Lourie et al.¹⁴, Baldwin et al.¹⁵, Wells¹⁶), and profound hypothermia in man has resulted in behavioral changes for transient periods after recovery, Niazi and Lewis.¹⁷

Adrenal steroids have been shown to have a moderating effect on the barrier system in rats (Angel and Burkett^{18,19}) and man (Eisenberg et al.²⁰), and full-blown psychoses have been reported in patients treated with large doses of steroids, Clark et al.²¹ Some diseases which are sometimes associated with transient psychoses, including uremia, hepatic failure, and tumors of the central nervous system, have been shown to be associated with altered permeability of the barrier system in man (Bakay^{22,23}) and other mammals, Freeman et al.²⁴, Angel and Hartman²⁵, Bakay.²⁶

While it would not be predicted from the adrenolutin hypothesis (Hoagland²⁷), there appears to be a low incidence of concomitant psychosis in pheochromocytoma. On the other hand, this finding would be consistent with the hypothesis that a malfunctioning blood-brain barrier system, rather than excessive blood levels of an abnormal metabolite, is an etiologic agent for schizophrenia—the excess medullary metabolites may be kept out of the brain by a relatively intact barrier system.

Bogoch et al.²⁸ gathered data to indicate that the concentration of neuraminic acid in the cerebrospinal fluid of

schizophrenic patients is significantly different from that found in control groups and they suggested that schizophrenic patients might have a "chemically immature" barrier system.

Coppen's²⁹ work demonstrated that after 48 hours, bromine concentrations in the cerebrospinal fluid of schizophrenics and controls is the same, but that the controls reached equilibrium before the schizophrenics, thus again suggesting a moderately disrupted barrier system in schizophrenics.

Finally, electroconvulsive therapy is associated with a transient increase in permeability of the brain to some tracers, Aird³⁰.

HYPOTHESES

There are several specific hypotheses about the barrier system and its relationship to schizophrenia which might be suggested and partially tested. For example, abnormal endothelial tight junctions might allow plasma proteins to enter certain areas of the brain which normally exclude these proteins. Similarly, the normally stringent barrier against hematogenous serotonin might be relaxed in schizophrenia. Electrolyte penetration, or that of carbohydrates, might be altered. Areas such as the pineal, which normally have a high blood flow (Goldman and Wurtman³¹) and a relatively ineffective barrier system, might let in more metabolites than normally.

It is admittedly difficult to test such hypotheses on mentally deranged human patients. It might be possible, however, to at least perform some ultrastructural work on schizophrenic patients coming to autopsy and, in willing patients, to carefully study rates of entry of various tracers into the cerebrospinal fluid.

DISCUSSION

Should results prove positive, they could be placed in the context of the following broad framework. Schizophrenia, in this model, is viewed as being of three types, which all begin in a similar manner.

The first stage, Fig. 1, to be discussed is that of the potentially schizophrenic person. Such a person might be from a high or low socioeconomic status and have a bad or good family relationship. Inheriting a "schizophrenogen" gene, which has been suggested to be an autosomal dominant with incomplete penetrance (Huxley et al.³²), he would have an immature blood-brain barrier system which would lead to an excess permeability of the barrier system to some substances. As long as such a person led a reasonably sheltered life, with little stress, he would behave within the confines of "normality".

The second stage, Fig. 2, illustrates the model of reactive schizophrenia: fairly acute onset, fair previous life adjustment and hopeful prognosis. Such a person might come from a high or low family and economic background and his family might be supporting or double-binding. At first, he would be one of the potentially schizophrenic persons discussed in the previous paragraph. However, he would at some time be placed under a fair amount of stress, either of a short- or long-term nature. Stress has been shown to alter the permeability of the barrier system to some tracers, Angel.³³

Thus, in a person with initially altered permeability, stress would lead to a further alteration, which might be of sufficient magnitude to lead to altered thought, altered coordination and altered behavior. These alterations would be perceived by the person experiencing them and would cause him further stress, resulting in still further permeability changes and consequently further changes in thought and behavior, leading to his perception by others as "odd". Recognizing this perception, he would be under further stress, and, with further changes in thought and behavior, he would perceive himself as different from others. The cycle is obviously one of positive feedback and would be difficult to

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FIRST STAGE: Potentially Schizophrenic Person

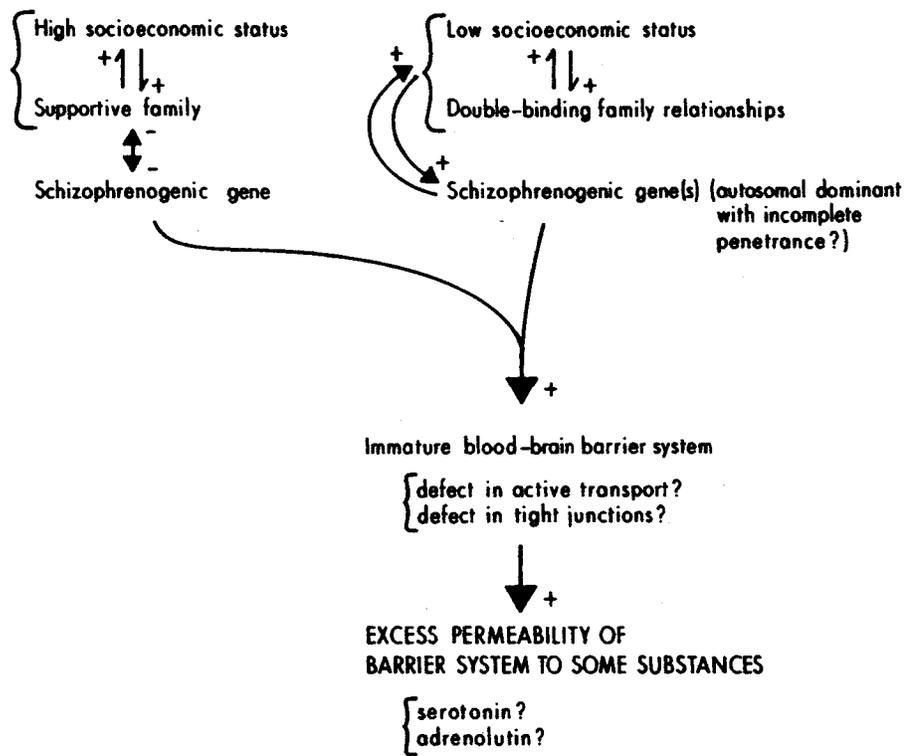


FIGURE 1.

SECOND STAGE: Reactive Schizophrenia

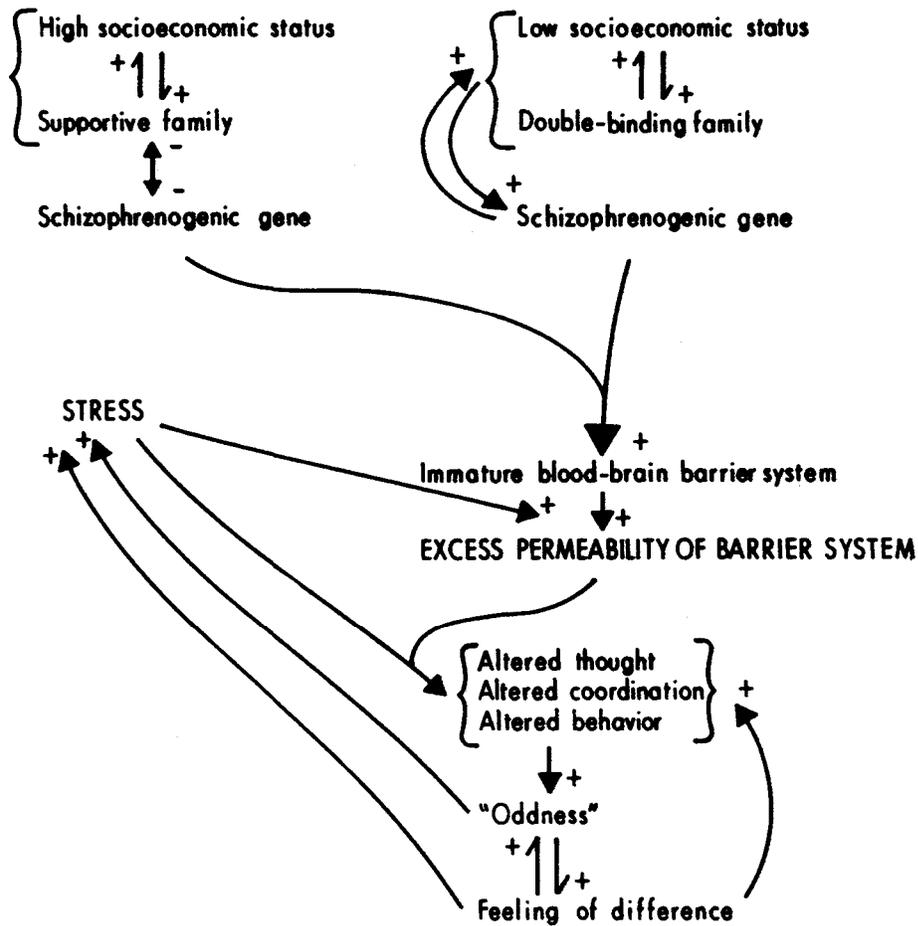


FIGURE 2.

THIRD STAGE: Process Schizophrenia

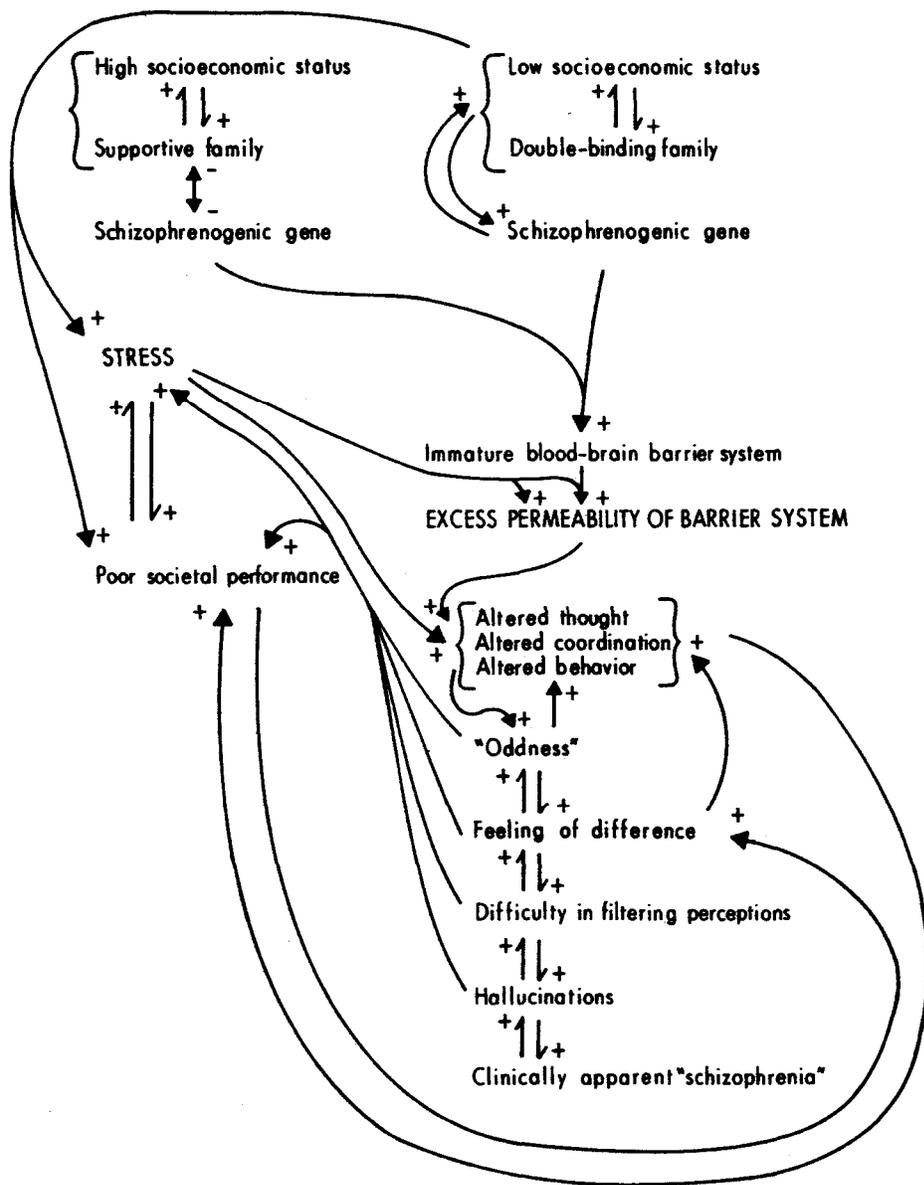


FIGURE 3.

break.

It would be far easier to break, however, than the cycle in which the process schizophrenic would find himself, see Fig. 3. A process schizophrenic generally is considered to be from a very poor environment, often with double-binding parents, is of moderately subnormal intelligence, has seemed strange from an early age, has never made a good adjustment to life, especially sexually, and has a very bad prognosis and an excellent chance of becoming a classic "backward schizophrenic".

In the hypothesis, this person, too, would begin life as a potentially schizophrenic person, usually in a lower-class family. (The odds against rising in the class structure are obviously limited by being in the schizophrenic gene pool, although the chances of falling lower are very good indeed—these reflections might help explain the fact that schizophrenia has a genetic but also a class pattern, and might help elucidate some of the totally profitless nature-nurture controversy which has plagued the subject.) The family might have one or more schizophrenic members.

Coupled with the genetically initiated excess permeability of the blood-brain barrier system, the child would be subjected to considerable stress from an early age by such a family, thus initiating the increase in barrier permeability by positive feedback from very early childhood.

Altered thought, coordination, and behavior would lead to "oddness" and more stress, as with the reactive schizophrenic. All these factors would lead to a poor societal performance, which would engender more stress. The person would experience a feeling of difference and incompetence—not suddenly, as with the reactive schizophrenic—but throughout his life and his mode of learning would depend on such a perception of himself.

Given such a massive failure, he would become less and less adept at filtering perceptions and often would add illusory hallucinations to make up for these defects. More stress would result, as would

the full-blown picture of schizophrenia—madness as a way of life—in this frightening cycle of positive feedback which would be extremely difficult to break.

It is, thus, interesting to speculate that the classical picture of the schizophrenic as a person who cannot keep strange percepts out of his mind might be secondary to that of a person who cannot keep strange substances out of his brain.

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