by Donald O. Rudin

Abstract

Schizophrenia and certain forms of idiopathic mental retardation may result from covert immune complex disease of the basal lamina of the choroid plexus, a process already known to cause covert transport dysfunction in similar structures of, for example, skin, bowel, kidney, and endocrines. Plexial attack could lead to cerebrospinal fluid contamination and then, via an "open" ependyma, to neurotransmitter dysfunction in the periventricular limbic brain. The immune complex mechanism implies polygenic induction, direct or autoimmune, of immune sensitivity to exogenous agents and is thus compatible with the genetic picture in schizophrenia. Candidate agents include viral coat peptides and cereal grain glutens. The glutens are known to cause immune complex skin and bowel disease variants, and some empirical evidence links them to schizophrenia. Only newer immunofluorescence methods can detect the pathology, which is otherwise silent. Systemic lupus erythematosus provides a model for this mechanism.

Several studies indicate that psychoses, mostly of the schizophreniform type, occur with an average incidence of about 20 percent in SLE (Dubois 1974; Johnson and Richardson 1968). These psychoses appear to be inherent to the disease and not due to associated steroid therapy (Dubois 1974; Johnson and Richardson 1968). My examination of the published morbidity and mortality data for SLE (Cheatum et al. 1973; Grishman et al. 1973) suggests that if lethal renal and vascular disorders did not first interrupt its course, usually within 5 to 10 years of onset, nearly all SLE patients would in time succumb to a schizophreniform psychosis that tends to appear late in the course of the disease.

Damage to the choroid plexus in SLE patients with a history of psychoses has now been reported in three independent studies covering about half a dozen patients (Atkins et al. 1972; Lampert and Oldstone 1974; Sher and Pertschuk 1974). What is significant about these findings, as they may relate to schizophrenia, is that the damage was covert and revealed only by immunofluorescent examination: otherwise the brains, cerebrospinal fluid (CSF), and plexuses of these psychotic patients appeared perfectly normal to routine gross and microscopic examination, excluding nonspecific terminal effects.

The immune deposits lay in or near the basal lamina of the choroid...
plexus to produce lesions analogous to those occurring in the kidney, vessels, and other organs afflicted in SLE.

This covert damage can change the normal transport or barrier functions of the parenchymal cells associated with the basal lamina—for example, in kidney and joints—allowing the normally protected fluid spaces to become contaminated with various products generated locally or existing in the blood stream. Brightman (1968) injected high MW compounds (up to $5 \times 10^6$) into the ventricular CSF and found these diffused into periventricular synaptic clefts. Consequently, contamination of the CSF via a damaged choroid plexus could lead to the disturbed neurotransmitter function in the limbic system now implicated in schizophrenia (e.g., see Cools 1975).

Present theories of the cause of SLE point to a genetically determined abnormal immune response to some environmental antigen, possibly viral in nature (Mellors and Mellors 1976). SLE is distinguished from many similar, possibly immune complex, diseases by its extensive tissue susceptibility. In other cases the genetic factors typically lead to much more selective damage involving a single or small number of tissues.

The potentially universal nature of the schizophreniform psychoses in SLE, the associated covert plexial pathology, and the possible triggering of SLE by exogenous agents (apparently also true in schizophrenia) require that we go beyond the suggestion of Carr et al. (1978) and myself that SLE may be relevant to various mental disorders including schizophrenia. I, therefore, specifically propose a polygenic-based, exogenous-peptide, immune-complex choroid plexial hypothesis of schizophrenia and certain idiothetic mental retardations that may be forms of developmental schizophrenia.

In pursuit of the gene-peptide-immune plexopathy hypothesis we note two possible exogenous causal agents. First, Torrey and Peterson (1974, 1976) have concluded that the data on schizophrenia are consistent with a viral hypothesis which would fit very nicely into the above attack mechanism. Secondly, Dohan (1969) found evidence for a higher coincidence than chance between schizophrenia and celiac disease, which is a form of glutenism (glutens being the characteristic protein of all cereal grains). He also found a marked 40 percent decline in the admission rate of schizophrenia but not manic-depressive psychoses during World War II pari passu with a 40 percent decline in wheat and rye consumption. Further, Dohan and Grasberger (1973), as subsequently confirmed by Singh and Kay (1976), performed controlled studies indicating that total gluten-free diets for only 3 weeks ameliorate schizophrenia. Although Rice, Ham, and Gore (1978) report only 2 of 16 schizophrenics improved on a brief (weeks-long) low-gluten diet, these were mostly severe chronic patients, and it is known that similar patients having celiac disease may require a year or longer on a totally gluten-free diet before significant improvement is seen. Even then, some chronic patients never recover.

The possibility has been raised that gluten may block neuroleptic absorption from the gut as indicated by rat studies (Freed et al. 1978); if so, gluten removal would have caused an effective increase of neuroleptic dose, which might account for any improvement noted in patients on a gluten-free diet. This possibility is unlikely, for it implies that one need only raise the dose of these agents to achieve marked improvement. Moreover, it does not account for the epidemiological studies cited above, which involved patients during the period before the introduction of phenothiazines.

Stevens et al. (1977), using gastrointestinal biopsy, found no sign of celiac lesions in schizophrenic patients and drew the faulty conclusion that their findings “lead to the rejection of the hypothesis of a positive genetic relationship between schizophrenia and celiac disease” (p. 262). This statement overlooks the obvious possibility, for which there is much evidence, that schizophrenia and celiac disease are polygenic and may share only those genes permitting glutens to pass the gut barrier while not sharing those genes that select different organs for immunological attack. (See Dohan, 1978, for a detailed discussion.) Moreover, neuroleptics may ameliorate the local pathology of both the central nervous system and the bowel; the metabolism of serotonin and related amines is affected by neuroleptics, and these amines operate in the normal physiology of both organs.

I also observe that dermatitis herpetiformis is another genetically determined form of glutenism that shares many but not all the polygenic defects of celiac disease; dermatitis herpetiformis appears as a skin disorder, celiac disease as a bowel disorder—even though both are clearly gluten-dependent disorders (Fry et al. 1973; Kalser 1976; Seah et al. 1971). In fact, gut lesions may be absent in dermatitis herpetiformis, despite repeated biopsies, so gut lesions are not a sine qua non for glutenism.

In the nervous system, only the choroid plexus has the characteristic structure of skin and bowel with the existence of a basal lamina, a proteinaceous membrane secreted by
the parenchymal cells as a basis for organizing themselves into tissues (Rudin 1979). It is significant, therefore, that the immune pathology of the basal lamina revealed by immunofluorescent methods is similar not only in the bowel lesions of celiac disease and the skin lesions of dermatitis herpetiformis, but also in the lesions of the choroid plexus, skin, kidney, and other organs in SLE—all of which may occur in what appear to be clinically and histologically normal tissues.

Preliminary evidence from Klee, Zioudrou, and Streaty (1979) indicates that digests of wheat gluten contain potent endorphin-like peptides, as well as antigenic substances that might specifically interfere with dopamine and other limbic neurotransmitter mechanisms. It is unresolved whether these proposed peptides, or possible resulting immune complexes, might reach the brain directly through the classical blood-brain barrier or via a damaged alternative second blood-brain barrier, i.e., the choroid plexial route suggested here.

In any event, it would seem important to examine both immunologically and virologically the skin, bowel, blood, and other tissues of schizophrenics, including, above all, the choroid plexus obtained at autopsy. Arthus skin tests, circulating antiplexial antibodies, and immunofluorescent studies of tissue basal lamina immediately suggest themselves.

The cooperation of several disciplines and laboratories will be needed to conduct these tests adequately. For example, the immune complex mechanism might induce plexopathy in childhood or prenatally, which could account for certain idiopathic mental retardations and thus link these to adult psychoses as time-dependent functions of a common mechanism. For this reason, the above studies should also be conducted in these retardations. It should be noted that the extensive but inconclusive immunological studies in the mental health field have not yet been directed to the present question.

Regardless of mechanism, because of the evidence, and also because it is immediately approachable at reasonable cost with large possible therapeutic and economic benefits, there is a great need for controlled clinical trials under national auspices of the effect of a months-long totally cereal-grain-free, milk-free diet in acute and relapsed schizophrenics. Chronic patients continuously hospitalized for many years should be avoided at first; they may be irreversibly damaged or require treatment of up to 1 year for significant improvement if we extrapolate from experience gained in the treatment of celiac disease and dermatitis herpetiformis.

References


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