

Schizophrenia and the Hippocampus: The Embryological Hypothesis Extended

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Abstract

Recent studies suggest that consistent structural changes exist in the hippocampi of schizophrenic patients. These alterations are characterized by a significant degree of disorientation of the hippocampal pyramidal cells when compared with age-matched nonschizophrenic controls. The degree of neuronal disorientation seems to correlate positively with the severity of the clinical picture. A hypothesis on the pathogenesis of this process, suggested in an earlier article, is extended here. Putative maternal infection with one of several neuraminidase-bearing viruses, especially during the second trimester of pregnancy, may severely affect the migration of primitive neurons into the primordial hippocampus. The "neuraminidase effect," expressed through alteration of the normal sequential patterns of N-CAM (neuronal-cell adhesion molecule) maturation, may result in the cellular disarray we have noted. This alteration may prove useful as a cell marker for schizophrenia, even though its actual relation to clinical symptomatology has still to be evaluated. Genetic factors also are believed to be involved, perhaps in the form of certain patterns of reduced immunocompetence, which might render the mother more susceptible to viral infection.

The search for structural substrates of the schizophrenias has become one of the significant quests of 20th century psychiatry. On the basis of postulates firmly grounded in 19th century medicine, it has seemed intuitively improbable that so devastating a syndrome, gaining expression at almost every level of central nervous system function, could exist without visible traces.

Nonetheless, consistent failure to reproduce findings reported over the last 50 years added measurably to the concept of the schizophrenias as "functional psychoses," notions which peaked in the 1950's. The advent of psychopharmacology and the development of the dopamine hypothesis (for review, see Bowers 1980), along with scattered reports of structuro-functional differences in body systems including the neuromuscular endplate, lymphocytes, and platelets (for review, see Brill 1969), served at least to keep the question open. Simultaneously, scattered observations attesting to abnormal electrical phenomena in depth recordings from the temporal lobes of floridly psychotic patients could not be entirely ignored (Sem-Jacobsen et al. 1956; Heath 1958). Despite several intriguing reports of ventricular abnormalities in schizophrenic patients examined by pneumoencephalography (Haug 1962), it took the development of the newer, relatively noninvasive visualization techniques to establish ventricular enlargement as an interesting, though by no means regular, concomitant of the schizophrenias (for review, see Weinberger and Wyatt 1982). Renewed histological interest called attention to periventricular gliosis (Stevens 1982), although the nonspecificity of this histological sign, and the possibility that it represented a process unrelated to the psychotic illness, remained a difficult problem to surmount.

Origin and Development of Our Histological Studies

About 15 years ago, our laboratory

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began to participate in a clinical neurophysiological program dedicated to the neurosurgical treatment of intractable temporal lobe epilepsy. During the course of our study of Golgi-stained samples of block tissue resections which came to us from the operating room, we were impressed by structural changes in the dendrite systems of the hippocampal pyramidal cells (Scheibel et al. 1974). In reviewing the records of the patients, a number of their behavioral stigmata seemed reminiscent of the schizophrenic psychoses, leading us to examine a small number of brains from schizophrenic patients. The first group selected were patients who had been subject to very long, sometimes lifetime, commitment to a large State hospital. Although the records and diagnoses were sometimes ambiguous in this pre-*DSM-III* period, there was little doubt about the nature and duration of their illnesses. The brains from which our tissue specimens came had been fixed in formalin for varying lengths of time, some for several years. The specimens included brains from eight chronic schizophrenic patients (four paranoid, one hebephrenic, and three undifferentiated) and a control group that included patients suffering from manic-depressive psychosis, chronic alcoholism, and Huntington's disease. Despite problems with tissue preservation, we were able to obtain usable Golgi impregnations and thionine-stained sections from frontal and parietal cortex, and hippocampus from most of the specimens. It was immediately apparent that dendritic organization in the hippocampus of the schizophrenic patients was different from others. In particular the apical shafts of the hippocampal pyramidal cells were perceptibly, and sometimes dramatically, disoriented. The expected pal-

isade arrangement of apical shafts, regularly perpendicular to the curve of the cornu Ammonis (CA), had been replaced by disorganized intersecting groups of shafts which in some cases pointed 70 to 90 degrees away from their expected orientation. The laminae of hippocampal pyramidal cells somata seemed relatively intact, but the long axes of the individual cell bodies reflected the patterns of disorganization of the apical shafts which issued from them. This phenomenon was not seen in any of the control brains, although the quantitative studies which followed (see below) later revealed the existence of minor degrees of variation in cell orientation in virtually all human brains, including those without psychiatric or neurological diagnoses. No obvious structural changes were noted in the areas of neocortex we surveyed.

After our initial report calling attention to the qualitative features of this unexpected finding (Scheibel and Kovelman 1981), we decided to repeat the study in a more rigorous fashion, using quantitative techniques and working "blind" to prevent investigator bias. Since further brain specimens were no longer available from our previous source, we were able to obtain a series of schizophrenic brains and non-psychotic controls from a local Veterans Administration Hospital.¹

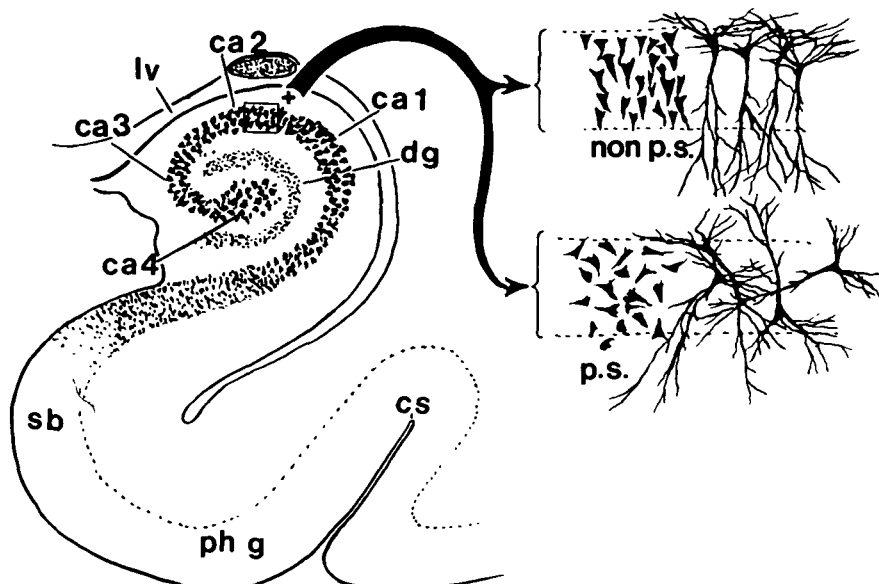
This second study was based on examination of 10 schizophrenic patients and 8 approximately age-matched nonschizophrenic controls. The schizophrenic patients all had a history of repeated hospitalization for chronic paranoid schizophrenia (*DSM-III*) and each had a final chart diagnosis of schizophrenia upon de-

mise. All had histories of inappropriate mood and affect, thought disorders, and hallucinations and delusions. Although we never saw these patients, in each case the diagnosis of schizophrenia had been concurred in by several physicians. Age of this schizophrenic group at death ranged from 28 to 66 years (mean 49.6 years, SD 12.44 years). The three youngest schizophrenic patients had committed suicide. All patients had been maintained on psychotropic medication for varying lengths of time. The course of each of these patients was marked by a number of hospitalizations, suggesting both remissions and exacerbations. Most were able to live for intermittent periods with families or friends, and several held jobs for varying periods of time when their symptoms appeared under satisfactory control. This life pattern contrasts with the severe and unremitting disease patterns of the original cohort of State hospital patients. We feel it may be significant to emphasize this point in view of the apparently more florid structural pathology shown by the State hospital group compared to the VA group. In view of the well-known uncertainties of Golgi impregnation, particularly in adult human formalin-fixed material (Scheibel and Scheibel 1978), it was fortunate that routinely stained Nissl material of the hippocampi from these patients and their controls proved adequate for determining cell orientation (figure 1).

Methods for establishing the position and orientation of hippocampal pyramidal cells have been described previously (Kovelman and Scheibel 1984) and will not be repeated here. It should also be noted that we have since appreciably modified the somewhat ponderous methods previously used for collecting the data.

¹We are grateful to Dr. Uwamie Tomiyasu for her cooperation in making this tissue available to us.

Figure 1. Slightly schematized coronal section through human ventromedial temporal lobe illustrating transition from cerebral neocortex to archicortex (hippocampal-dentate complex)



Histological appearance of organized nonschizophrenic, organized and disorganized schizophrenic, disorganized, hippocampus is shown at the right based on cresyl violet and modified Golgi stains. Abbreviations include cs, collateral sulcus; ph g, parahippocampal gyrus; sb, subiculum; ca 1, ca 2, ca 3, ca 4, divisions of the cornu Ammonis of the hippocampus; dg., dentate gyrus; lv, lateral ventricle. (From Kovelman and Scheibel 1984)

The newer techniques for measurement provide simpler and more sensitive indices of cell disorientation and should facilitate repetition of these experiments in other laboratories (Conrad and Scheibel, in preparation). Three basic findings emerged from the first quantitative study (Kovelman and Scheibel 1984): (1) Hippocampal cell disorientation patterns appear to exist along a continuum. There seems to be a rough correlation between the amount of cellular disarray and the chronicity and severity of the symptoms. Many of the nonschizophrenic patients also showed some degree of pyramidal cell disorientation, but always in significantly smaller degree than those with schizophrenic diagnoses. (2) Interface zones between the various subfields of the CA (i.e., CA

1-prosubiculum; CA 1-2; and CA 2-3) often showed more prominent pat-

terns of disorganization than other portions of the cortical fields of the hippocampus. The CA 4 (hilar) subfield was ignored because of the natural lack of orientation of its constituent cells. (3) Significant degrees of hippocampal cell disorganization were found only in the anterior and middle sectors of the hippocampus. The effect diminished or disappeared in posterior fields (table 1). We found this particularly intriguing in light of previous electrophysiological observations identifying anterior stations of the hippocampus and medial temporal lobe as the major source of abnormal discharge patterns in schizophrenic patients (Sem-Jacobson et al. 1956; Heath 1958).

Table 1 epitomizes the results of our study of almost 13,700 hippocampal pyramidal neurons. On the basis of cell rotation of 35 degrees or more as the criterion of disorientation in this analysis, the robust degree of significance of the effect in anterior and middle hippocampal stations is clear. The interface between prosubiculum and CA 1 appears to be the prime site for the

Table 1. Percentage of cells rotated 35° or more

Position	Controls	Chronics	χ^2	<i>p</i>
M CA 1/PS	1.63	13.14	24.274	0.0005
M CA 1/2	3.35	8.90	6.496	0.011
M CA 2/3	3.51	10.32	9.244	0.001
A-M CA 1/PS	1.51	10.62	17.745	0.0005
A-M CA 1/2	3.07	8.73	9.063	0.003
A-M CA 2/3	3.35	9.13	9.942	0.002
P CA 1/PS	3.60	4.26	0.089	NS
P CA 1/2	5.29	6.81	0.217	NS
P CA 2/3	6.56	7.96	0.380	NS

Note.—Results of BMDP3V analysis of the mean percentage of pyramidal cells, rotated 35° or more, in 10 schizophrenic patients and 8 controls. There is no significant difference at any posterior (P) hippocampal position. At all other hippocampal interfaces, cornu Ammonis (CA) 1, 2, 3, and prosubiculum (PS) in anterior (A) and middle (M) hippocampal positions, there are significantly greater numbers of pyramidal cells rotated 35° or more in the chronic schizophrenic group (from Kovelman and Scheibel 1984).

effect in this study. Note that all of these data were obtained from study of the left hemisphere alone. Early in the course of the work, it became clear that, because of the labor-intensive nature of the study, some limitation of the scope of investigation would be advisable. Persistent reports implicating left hemisphere dysfunction in the schizophrenic process (Gur 1977; Flor-Henry 1983) motivated this choice. Analysis of matched tissue specimens from the right hemisphere of the same cohort of schizophrenic patients and their controls is presently underway (Scheibel et al., in preparation).

Problem of Drug Effects as a Confounding Factor

During the early stages of the investigation, questions were raised as to the possible relationship of pharmacotherapy to the histological changes we were studying. Dendrites, especially the most peripheral portions of the dendrite ensembles, are known to be responsive to toxic agents such as alcohol (Hammer and Scheibel 1981), but we were unfamiliar with reports of neuronal disarray as a sequel to ingestion of drugs or substances of abuse, either at the experimental animal or human level. Fortunately, the Paul Yakovlev collection of human brain specimens at the Walter Reed Army Medical Center provided an opportunity to test this thesis, since the majority of the brains in this collection, both schizophrenic and non-schizophrenic, were collected in the period before the introduction of psychotropic agents in 1953. This hippocampal material was analyzed twice, once by qualitative (Kovelman and Scheibel, unpublished data) and once by quantitative (Altshuler et al., in press)

techniques.

Severe limitations in clinical documentation, tissue preparation techniques, and the number of cases ultimately available for analysis hampered the study. However, the spectrum of cell disorganization patterns was clearly greater in the small schizophrenic group than in the available control material. Another group of brain specimens, also obtained from schizophrenic patients during the predrug era, exists in Germany as part of the great collection of human brains amassed by Drs. Oscar and Cecile Vogt during the first half of the 20th century. More than a thousand photographs of this material have now been taken and evaluation of these data is underway.

Hippocampal Cell Disorganization: Conceptual Problems

The central conceptual problem associated with these data must rest in the ontogeny and the significance of this structural change. We are not aware of candidate mechanisms capable of "tilting" neurons once they are in their final position and immersed in a surrounding afferent and efferent neuropil. The one possible exception to this is what we have noted in areas where local gliosis develops, producing gradual cicatrizing lesions that may put tension on adjacent tissue sectors. We noted such effects during our analysis of brain tissue from the hippocampus of temporal lobe epilepsy patients we had examined previously (Scheibel et al. 1974; Scheibel 1980). Here, local gliotic areas, usually associated with neuronal cell loss, could be identified. Furthermore, all of the neurons in adjacent areas whose histological orientation was apparently disturbed by this

process were "tipped" or drawn in the same direction. In schizophrenic material, on the other hand, we have noted no areas of major neuronal loss and no gliotic fields. Equally important, neuronal disarray has appeared thoroughly random in nature. There is no specific pattern of disorientation and absolutely no evidence that ensembles of cells have all been "tipped" in a specific direction by an adjacent tissue-distorting process. To this, we should add that the pattern of disorganization seems to be "spotty" instead of continuous. Foci of rather profound cell disorientation are frequently separated from each other by small areas of relatively greater organization. In general, those areas marked by the most obvious cell disarray seem related to interface areas of the hippocampus, i.e., junction zones between prosubiculum and CA 1; CA 1, 2, and 3, although foci of more prominent cell disorganization may also be found within a single zone.

Hippocampal Cell Disorganization: Ontogenetic Hypothesis

Hippocampal development depends on the migration of postmitotic primitive neurons (neuroblasts) into the hippocampal primordium from the ependymal or neuroepithelial zone where proliferation has taken place. Migration is now believed to occur along radial glioblasts which provide both supportive stroma and directional cues for the migrating cells (Rakic 1972). The migratory process occurs within a sharply defined temporal window (during the second trimester), and there is evidence that migration into each of the ammonic subzones occurs at its own

precise time (for review, see Sidman 1974). Thus each zonal interface represents, to some extent, a temporal interface also: Furthermore, *in vitro* experiments on dissociated hippocampal neurons that are allowed to reassociate in tissue culture indicate that the lining up of such primitive neurons to form a hippocampal lamina is also critically time-dependent. Accurate alignment of murine hippocampal neurons occurs only when tissue from mouse embryos of 18.5 days is used. When the tissue specimen is taken approximately one-half day earlier, the alignment is only partial, and if the cell sample is taken one-half day later, at 19 full days, cells aggregate but show no tendency to align themselves (DeLong 1970; DeLong and Sidman, 1970; Sidman 1970). Converging bodies of data point to the presence of specific membrane molecules, cell adhesion molecules (CAMs), which favor restricted degrees of cell-cell adhesion during the migratory phase and increasingly vigorous adhesion during the subsequent alignment and lamination phase of hippocampal development (Rutishauser et al. 1979; Edelman and Chuong 1982). Correlative to this, precise patterns of disadhesion or uncoupling must occur so that migrating neuroblasts can leave the radial glia stalks when the proper depth in the hippocampal plate has been achieved. Similarly, lamination by clustering, with cells arranged side by side (never end to end) and with proper polar orientation, appears to depend on surface adhesion molecular mechanisms that operate during a similarly critical period. Adhesive properties of these molecules undoubtedly undergo further modification after the initial laminar pattern has been established to allow closely following waves of migrating neuroblasts to move through

as they seek their own final position in the inside-out developmental sequence (Chuong and Edelman 1984; Crossin et al. 1984). All of these elements must also be free to move away from each other as the hippocampal neuropil develops around them to produce the mature CA. Orchestration of this precise spatio-temporal sequence depends on many factors, one of which may consist in progressive modulation of the adhesive qualities of the N-CAM. Recent information suggests that alternative RNA (ribonucleic acid) splicing may result in formation of N-CAMs with different cytoplasmic domains which interact differentially with the cell membrane (Cunningham et al. 1987). Interference with any one of these steps may lead to abnormal hippocampal development.

Almost two decades ago, DeLong and Sidman (1970) showed that cultures of isocortical cells from reeler mice failed to align themselves in normal cortical laminar arrays. The disorientation and poorly polarized or unpolarized cell masses resembled the cortices of reeler litter mates allowed to come to term. Recently, Edelman and Chuong (1982) have called attention to the failure of the embryological form of the N-CAM moiety to convert to the adult form in the cerebellum of another mutant mouse, the staggerer. In addition, abnormally strong adhesiveness between radial glial guide cells and postmigratory cell elements in the reeler neocortex has been reported by Pinto-Lord et al. (1982). They suggest a relationship between this aberrant adhesiveness and disturbed patterns of cell migration and lamination.

We suggest that the disturbed processes of cell migration and laminar organization shown by the two species of mutant mice, reeler and

staggerer, might serve as a conceptual model, or perhaps a caricature, of a more subtle developmental anomaly in the schizophrenias. Although the hippocampal pyramidal cell disarray in the patients whose tissue we have examined is seldom as extreme as that shown by the mice, the amount of disorientation is significant and at times robust. Since we cannot presently identify a mechanism capable of producing such alterations in structure during the postnatal life of the individual, we have come to consider the process as developing during embryogenesis (Kovelman and Scheibel 1984). As in the case of reeler and staggerer, if dysfunction in the expression of certain populations of membrane molecules, cell adhesion molecules among them, were part of the intrinsic schizophrenic "diathesis," then a result of the type we have reported might be expected. So far, preliminary evaluation has not revealed similar structural problems in neocortex and, as already mentioned, the hippocampal pattern is less obvious than that shown by the mutant mouse. We conclude that the process itself is more subtle and perhaps more limited in scope.

The multiplicity of causative factors involved in the genesis of the schizophrenias now seems almost beyond question. A rapidly enlarging literature argues persuasively for the presence of familial or genetic components as well as environmental factors (Kety 1979; Meltzer 1979; Mirsky and Duncan-Johnson 1984). Since we conceive of the structural disorder just described as a necessary consequence of faulty neuronal migration during fetal embryogenesis, we have been particularly interested in the problem of maternal illness associated with pregnancy.

Possible Role of Climate and Infection in Human Neurogenesis

Beginning with the initial observations of Tramer (1929) and Lang (1931), it has become increasingly clear that seasonality of birth is a significant, if still puzzling, part of the picture. A significantly increased proportion of winter-early spring births of schizophrenic patients continues to be reported (Hare and Price 1968; Videbech et al. 1974; O'Hare et al. 1980; Shur and Hare 1983). It is interesting to note that in one study from Australia (Jones and Frei 1979) the peak period for schizophrenic births develops in the June-November period, obviously the coldest part of the year in the southern hemisphere. It is tempting to conclude that cold weather-related infectious processes, possibly viral, may be involved (Morozov 1983). Watson et al. (1984) postulate from their data that cold weather months with a high prevalence of infectious disease pose a greater risk of schizophrenia than those associated with a lower incidence of infection. Outbreaks of viral encephalitis have been associated with increased incidence of schizophrenic disease-like patterns (Torrey and Peterson 1974; Trimble 1984), and Torrey et al. (1978) report episodes of viral disease immediately preceding the onset of schizophrenia. Although the significance is unclear, antibodies to measles and/or cytomegalovirus (CMV) have been found in the cerebrospinal fluid of some schizophrenic patients (Torrey et al. 1978; Crow 1983; Stevens et al. 1984; Rimón et al. 1986), and Tyrell et al. (1979) reported the presence of a viroid type of agent in the cerebrospinal fluid of 13 out of 18 patients.

Reported cases of influenza or Ep-

stein-Barr virus (EBV) encephalitis being preliminarily misdiagnosed as schizophrenia are believed to occur fairly frequently (Maurizi 1984, 1985; Torrey 1986). From the case histories presented in these reports, it is reasonable to postulate that the viral encephalitis causes focal disruption of the brain. Reports such as these suggest that some schizophrenias may be caused by a viral encephalitis a short time before the onset of the disease. On the other hand, it is also noteworthy that some investigators have been unable to find evidence of significant differences in antibody levels to several of the more common viruses (e.g., herpes simplex virus [HSV] 1 and 2, CMV and EBV) between blood and/or cerebrospinal fluid samples of schizophrenic patients and nonschizophrenic controls (Delisi et al. 1986; Schindler et al. 1986). In addition, Taylor and Crow (1986) found no trace of viral DNA (deoxyribonucleic acid) fragments HSV 1 and human CMV in brain tissue from schizophrenic patients. Such negative findings are not surprising to us. On the basis of the morphological changes we see in hippocampus, we feel that they are unlikely to have followed an infection during the postuterine life of the individual. As indicated previously, structural disarray is far more likely to have developed in an embryonic milieu before the development of an extensive neuropil matrix.

We suggest that there must be a prenatal developmental event that perturbs the normal migration of hippocampal cells while the tissue is still in the process of developing. Mednick et al. (1987) report preliminary data on a longitudinal study of the children of mothers exposed to an influenza epidemic in Finland in 1957. On the basis of over 10,500 psychiatric admissions in 8 Finnish

hospitals, it was clear that the incidence of schizophrenia in the offspring was increased threefold in those cases where the mothers were in their second trimester of pregnancy during the epidemic (Helsinki report). This report is of particular interest in light of the fact that migration of the primitive neurons into the hippocampus reaches its height at this time (Stensaas 1968; Sidman 1970, 1974). Assuming the robust impact of maternal (especially second trimester) viral infection upon the fetus, we must consider the possible mechanisms of action of such infectious agents on the developing nervous system.

Possible Role of Disturbed N-CAM Maturation

It is increasingly clear that only some viruses are neurotropic, and of these an even more limited number may be significant factors during pregnancy. Among the latter, the influenza group, HSV, EBV and the CMV are the best known. A shared characteristic among these viral species is the presence of capsular neuraminidase, an enzyme known to affect sialic acid. The cell-binding properties of cell adhesion molecules like N-CAM are closely related to the amount of their sialic acid moieties (Crossin et al. 1984). The fact that neuraminidase may change the binding properties of N-CAM provides a putative connecting link between the presence of neuraminidase-bearing viruses and cell migration problems during neuroembryogenesis. We already have hypothesized that defective migratory patterns of primitive neurons as they enter the hippocampal primordium may adversely affect proper orientation and lamination of the developing hippocampal pyramidal cells. A broad range of binding

strengths seems to characterize sialic acids, states that may reflect varying concentrations of the A and E forms. It is increasingly clear that relatively minor changes in N-CAM expressed, its distribution on cell surfaces, and its expression relative to other adhesion molecules may significantly affect development (Cunningham et al. 1987). The A or adult form is normally more adhesive, whereas the embryonic form, E, is less powerfully adhesive (Edelman and Chuong 1982). It is conceivable that the carefully orchestrated temporal patterns of primitive neuronal influx into the presumptive hippocampus are altered by virus-induced variations in sialic acid concentrations. We can imagine periods of loss or decreased concentration of sialic acid moieties due to the presence of virus-introduced neuraminidase followed by reactive excess synthesis, followed in turn by increased removal, etc. Sequences of alternating decreased and increased cell adhesiveness might well result in the abnormal stacking and disorientation of hippocampal pyramids which we have described. Our laboratory is involved presently in testing this model as an explanation for the observed correlation just mentioned.

Following maternal exposure and infection, clinical or subclinical, the virus spreads to the developing infant via the placenta, easily passing from the fetal blood to the brain, which is as yet unprotected by a blood-brain barrier. While the virus is in the brain, its concentration must remain below some, as yet unspecified, critical level, or the child may be born with more robust clinically apparent evidences of an encephalitis. In the course of its life cycle, the virus produces neuraminidase as part of its coat proteins. This enzyme is also capable of

affecting the N-CAM molecule, removing sialic acid from its external structure, and converting it from the E to the A form. Normal binding and migratory behavior of the primitive neurons might be affected during the process. Hence, the focal patterns of disarray we have described in the hippocampus might be conceived of as the "scars" of this prenatal infection.

Relationships Between Neuroembryological Defect and Late Development of Clinical Syndrome

This intrusion upon the structural integrity of the hippocampus may not, in itself, provide sufficient cause for the characteristic clinical behavior patterns that follow, often many years later. However, the stage may be set in terms of a disturbed "hardware system," a system whose deficiencies may be more or less compensated for by the well-known plasticity of young brain and particularly that of the limbic system (Raisman 1969; Cotman et al. 1981; Lynch et al. 1982). However, later life stressors (e.g., puberty, leaving home for college or military service, marriage, and child rearing) may then be the critical factors in overwhelming the initially flawed system whose operational patterns have, perhaps, been maintained by means of unusual personality defenses. We call attention to the observation of Fish (1975, 1984), who has followed the often subliminal stigmata that characterize these patients before their first episode. If we assume that maternal infection, occurring within the period of maximal migration of hippocampal neuroblasts may disturb normal developmental patterns and increase vulnerability to schizophrenia, several questions arise.

1. How can this be reconciled with the weight of data suggesting schizophrenia has a strong genetic component? It is clear that not every pregnant woman who is exposed to a virus produces a schizophrenic child. It is also increasingly apparent that a genetic component somehow seems to be involved (cf. Rosenthal et al. 1971; Kety 1979; Walker and Emory 1983). We suggest that there may be no "gene for schizophrenia" as such but, rather, a gene or gene cluster that "lets schizophrenia in." The altered immunocompetence of the schizophrenic individual seems increasingly likely in view of recent studies by DeLisi et al. (1986) demonstrating significantly decreased function of natural killer cells in schizophrenic patients. Studies of Schindler et al. (1985) demonstrating decreased amounts of interferon production under conditions of mitogen-induced lymphocyte proliferation, in schizophrenic patients compared to controls, might also be considered indicative of disturbances in immunocompetence. Possible alterations in the human leukocyte-associated antigen (HLA) system have been supported by some authors but not by others (Smeraldi et al. 1976; McGuffin et al. 1978; Oger and Amason 1979; Gattaz et al. 1980; Goldin and Gershon 1983; Miyanaga et al. 1984). The ambiguous nature of these data suggest to us that the causative mechanisms may be considerably further "upstream" than these concrete markers. It is possible that mothers at risk for bearing a schizophrenic child are those who are, on a genetic basis, immunologically less competent. They might then be the ones most liable to viral infections of the sort we are considering.

2. Given the well-known plasticity of growing axonal and dendritic tissue, is this type of structural

disorientation sufficient to disturb hippocampal physiology in permanent and significant fashion and account for the thought disorders and emotional disturbances of the syndrome? Neither question is directly answerable. Our data do not yet indicate whether these hippocampal changes are relevant to behavior, or may function at best as a central nervous system marker for the disease complex. However, it should be pointed out that we have, as yet, no information on the connectivity of the schizophrenic hippocampus. As tissue supplies allow, we plan to begin a detailed analysis of Golgi impregnations and electron microscopic material in an attempt to compare dendritic and axonal patterns with nonpsychotic material. Clues may also be provided by the use of Timm's stain, a technique for visualizing zinc-containing structures. Since the mossy tufts in the hippocampus contain the largest concentration of zinc in the central nervous system, this method should give us some idea as to the concentrations and positions of these highly specialized presynaptic terminals compared with control material (based on a suggestion by John Haracz). Although the problems of mounting detailed immunohistochemical studies on human autopsy tissue are formidable, it is possible that some systems may prove sufficiently stable to enable their comparison between schizophrenic and control material.

3. If we assume that the structural changes are capable of exerting a significant effect on behavior, how does it happen that the clinical picture of psychosis almost invariably develops following puberty and often significantly later? The problem of apparently delayed appearance of overt psychotic symptomatology also is not readily

answerable. However, abundant documentation now supports the idea that stress can affect neurohormonal and neurotransmitter patterns, i.e., the software, of the central nervous system (Clowers et al. 1979; Yoneda et al. 1983; Weiss and Simpson 1985; Soblosky and Thurmond 1986). Profound changes in γ -aminobutyric acid, catecholamines, indolamines, peptides, corticosteroids, and their receptors may follow stressful manipulations in the experimental animal. As one example of this, the stress of rapid eye movement (REM) sleep deprivation for 48 and 96 hours significantly increases the number of adenosine A receptors in rat cortex and corpus striatum (Yanik and Radulovacki 1987). Human studies reveal similar effects (cf. Weiss and Simson 1985). Viewing the various combinations and levels of neurotransmitters as the binary digital (on-off) commands of the program, one can postulate that major stress impinging on a nervous system with an already compromised hardware ensemble could result in profound behavioral consequences. In other words, stress, whether emotional, physical, or toxic-infectious, can generate global alterations in chemical patterns. In the potential schizophrenic, induced alteration of these substances in the presence of already disturbed neuronal organization might then result in chronic patterns of schizophrenic disease. It should be remembered, however, that the schizophrenias are not unique insofar as the delayed onset of the clinical picture is concerned. For instance, it is well known that there are a number of diseases in which the defect, though presumably present at birth, is not expressed until much later in life, e.g., Huntington's disease. In addition, however, recent studies are in-

creasingly persuasive that the young preschizophrenic individual does not follow normal patterns of development, and that there may be a number of identifiable prodromata in the years before the first florid episode occurs. Retrospective and longitudinal studies of children at risk for the schizophrenias have revealed both neurological and psychological symptoms that may provide reliable predictive evidence for eventual psychosis (Fish 1975, 1984).

Conclusion

A significant body of literature argues for convergence of multiple causative factors in the development of the schizophrenias. Our studies have focused on an identifiable histological abnormality which, we believe, originates during embryogenesis. We suggest that difficulties in cellular migration and alignment during the development of the hippocampal primordium may stem from problems in expression and maturation of one or more species of cell adhesion molecules that are indispensable to this process. We further suggest putative relationships between maternal viral infection during a specified period of embryogenesis concurrent with a genetically linked decrease in immunocompetence. It seems clear to us that detailed analysis of the schizophrenic genome is required for solution of the problem.

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