Abstract

The conference on Fetal Neural Development and Schizophrenia which was held in Washington, DC, May 31–June 1, 1988, focused on factors of possible etiological significance in fetal development. Schizophrenia researchers joined experts in brain imaging, neuropathological, and neurochemical changes in brain development and investigators of potential genetic and neurobehavioral causes of psychosis. The combined evidence suggested dysfunction in frontal and parieto-occipital neocortex, basal ganglia, hippocampus, and amygdala. Dopamine transmission was implicated both in basal ganglia deficits and in widespread neocortical disturbances. Viral infection, or excessive stress, during the second trimester of pregnancy, as well as obstetrical complications, minor physical anomalies, and brain defects, correlated positively with incidence of adult schizophrenia. Autonomic nonresponding, birth complications, and ventricular enlargement were found to be closely related to negative symptom schizophrenia in high-risk populations. A dual factor model of schizophrenia was suggested, where genetic and environmental influences combine to produce psychosis.

A number of sophisticated imaging techniques have demonstrated that the brains of many schizophrenic patients are marked by deviance in structure and function (Weinberger 1984). These brain anomalies have been related to significant aspects of the clinical characteristics of schizophrenia. The anomalies seem to be present before the onset of the illness, and may play some role in its etiology or pathophysiology. Learning the sources of this brain deviance may aid in our understanding of the causes of schizophrenia and suggest treatment and primary prevention methods worthy of investigation.

Several findings implicate disturbances of fetal neural development as one of the possible sources of the brain anomalies seen in schizophrenia: (1) Recent neuropathological studies have found structural deviance that has been interpreted as evidence of disruption of fetal neural development, most likely in the second trimester (Kovelman and Scheibel 1984; Bogers et al. 1985; Jakob and Beckmann 1986). (2) Helsinki residents whose second trimester of gestation overlapped a particularly severe viral epidemic evidenced an increased rate of hospital diagnoses of schizophrenia. First or third trimester exposure was not associated with an elevation of rates of schizophrenia (Mednick et al. 1988). A recent study by Torrey et al. (1988) has found support for these results in the United States. (3) Two clinical studies have found that disturbances of gestation during the second trimester are linked to childhood and adult psychosis (Torrey et al. 1975; Huttunen and Niskanen 1978). (4) McNeil (1987) has reviewed the now extensive literature on the prenatal and perinatal experiences of schizophrenic patients; he presents convincing evidence that schizophrenic patients tend to have suffered considerably more prenatal and perinatal complications than controls. Indeed, some perinatal complications may
actively involved in schizophrenia research. These external signs have been used as indices of otherwise cryptic fetal neural maldevelopment. Several investigators have reported that schizophrenic patients have a significantly elevated incidence of these anomalies (see Green et al. 1989). (6) Several investigators have found that the brains of schizophrenic patients are significantly reduced in volume. Such findings could reflect a failure in fetal neural development.

These findings suggest that perinatal and perinatal disturbances may be responsible for some of the brain anomalies observed in schizophrenia. This possibility suggests that a new class of variables must be considered in investigations of the etiology of schizophrenia. In view of these considerations, we found it useful to bring together, for mutual education, experts from the fields of (1) fetal neural development and (2) schizophrenia research involving obstetrical complications, brain imaging, neuropathology, genetics, and clinical behavior.

To this end, Sarnoff A. Mednick (University of Southern California) and David Shore (Schizophrenia Research Branch, Division of Clinical Research, National Institute of Mental Health [NIMH]) organized a workshop involving prominent active researchers in these fields. The meeting was held in Washington, DC, on May 31 and June 1, 1988. Since this NIMH-sponsored event included many presentations of considerable interest for those involved in schizophrenia research, brief summaries of articles and discussions from the workshop are presented below.

### Brain-Imaging Findings and Subtypes of Schizophrenia

**Daniel R. Weinberger.** Dr. Weinberger reviewed evidence for a relationship between schizophrenia and increases in ventricular size and signs of frontal lobe dysfunction, as revealed by clinical tests, cerebral blood flow, and neurotransmitter activity in specific cortical regions. He found significant ventriculomegaly in schizophrenic patients, despite some overlap with the range of ventricular size in normal individuals. Although not indicating a clear anatomical localization for the relevant pathological process, Dr. Weinberger suggested that some degree of morphological pathology, as reflected in ventriculomegaly, is common to most schizophrenic patients, and not just to a subgroup.

Gray and white matter were investigated separately, using three-dimensional volumetric reconstructions of magnetic resonance imaging (MRI) brain scan sections, with highlighting enhancement by color. Dr. Weinberger and his NIMH colleagues found that schizophrenic subjects were differentiated from normals most clearly by a 60 percent increase in the volume of the ventricular system. There was also a 15 percent reduction in gray matter in the temporal lobe, but no change in white matter volume. Less gray matter was also associated with increased ventricular volume. No volumetric differences were found for the frontal cortex as a whole, but frontal cortical sulci were frequently wider and deeper, while this was not true for the parieto-occipital region. The temporal lobe sulci were not measured. (Compare with evidence in Dr. Goldman-Rakic’s presentation.)

Dr. Weinberger concluded that a generalized neuropathology may be present, dating back to a very early age. A reduced ventricular/brain ratio (VBR) may antedate behavioral symptoms, and brain scans repeated with a 9-year interval on the same individuals showed no change in VBR. Furthermore, there is no correlation between length of illness and ventricular size, suggesting that the loss, or developmental failure, occurs early and is not progressive in adults.

Poor social adjustment in children seems to be a prognostic indicator for increased risk of schizophrenia, and there is a correlation, in some studies, between negative symptoms, poor social adjustment, and ventriculomegaly.

Comparisons of the effects of the Wisconsin Card Sorting task versus a simple numerical identification task on regional cerebral blood flow measures show that frontal cortex activity is reduced in schizophrenia (Ingvar and Franzen 1974; Weinberger et al. 1986). In Dr. Weinberger’s studies, only the card-sorting task shows this difference, not the number-matching task, which suggests that the representation, in memory, of a previous stimulus, as opposed to simple recognition of visual stimuli, is more seriously affected. (See, also, Dr. Goldman-Rakic’s presentation.)

**Discussant: Seymour S. Kety.** Dr. Kety drew attention to the fact that VBRs were not increased in at least one subgroup of schizophrenia spectrum patients, the Mednick and Parnas Danish sample of “borderline” patients (now called schizotypal in DSM-III; American Psychiatric Association 1980). Dr. Kety also questioned the specificity of the VBR measures, noting that the relationship of VBRs to...
Neuropathological Abnormalities and Their Clinical Correlates in Schizophrenia

Bernhardt Bogerts. Dr. Bogerts reviewed the evidence derived from qualitative and quantitative post-mortem studies for structural abnormalities in various brain structures of schizophrenic individuals. He noted that, by means of qualitative brain tissue assessment, Nieto and Escobar (1972) and Stevens (1982) reported gliosis in several diencephalic periventricular, mesencephalic periaqueductal, and limbic temporal structures, whereas some recent quantitative studies could not find increased numbers of glial cells (Falkai and Bogerts 1986) or increased glial fibrillary acidic protein (Roberts et al. 1986) content in the limbic structures of the medial temporal lobe. Lack of gliosis in the latter structures was regarded as being consistent with the assumption of a very early acquired anomaly, but not with a progressive degenerative disorder, or viral infection, occurring later in life.

According to Dr. Bogerts, McLardy’s (1974) report of bilateral reduced thickness of the dentate gyrus granule cell layer in 12 out of 30 schizophrenic patients was the first description of limbic system structural abnormalities that were interpreted as due to prenatal or perinatal disturbances of brain development. Several authors came to a similar conclusion that brain damage acquired at a very early stage characterized a subgroup of schizophrenic individuals: (1) Kovelman and Scheibel (1984) found an alteration of pyramidal cell orientation in hippocampal CA-segments. (2) Jakob and Beckmann (1986) described signs of poor cellular migration in the rostral entorhinal region of the parahippocampal gyrus, an effect that strongly resembles similar cell-migrational disturbances seen in genetically controlled strains of mice. (See evidence in Dr. Nowakowski’s presentation.) (3) Benes (1987) found reduced neuron densities and smaller aggregates of neurons in the cingulate gyrus, and these changes were not accompanied by gliosis.

In his own morphometric studies of the Vogt collection, with brains from schizophrenic patients who had never received neuroleptic drugs, Dr. Bogerts found slightly, but significantly, reduced volumes of the parahippocampal gyrus, hippocampus, amygdala, internal pallidum, and diencephalic periventricular gray matter in about a third of the patients, whereas the volumes of all large thalamic nuclei, caudate, putamen, and nucleus accumbens were unchanged compared with normal brains (Bogerts 1984; Lesch and Bogerts 1984). Furthermore, increased numbers of glial cells could not be detected in either the hippocampus or the entorhinal cortex (Falkai et al. 1988). Some hippocampi of schizophrenic patients had a dysplastic configuration; however, only left hemispheres were available for this study. The findings were consistent with the assumption of an inherited dysplasia, or brain damage occurring before or during birth.

Dr. Bogerts also reported that in a number of recently collected brains of schizophrenic individuals there was a significant reduction in size of the anterior portion of the hippocampal formation on the right side only—for which he had no immediate explanation. This is one of the few reports of laterality differences in subcortical structures.

It was also pointed out that the hippocampus and pallidum are especially susceptible to perinatal hypoxia and that damage to these regions in organic brain diseases is frequently associated with schizophrenic-like psychoses.

During the later discussion, Dr. Bogerts mentioned that phencyclidine (PCP) has the highest concentrations of binding sites in the medial temporal cortex and to some extent in part of the frontal cortex; he suggested that PCP-psychosis, which was described by Dr. Kety as producing a potentially better analog of schizophrenia than amphetamine, is elicited by functional disturbances of the same brain regions that show hypoplasia, and hence a reduced functional capacity, in schizophrenic individuals.

Discussant: Henry Nasrallah. Dr. Nasrallah offered a critique of the neuropathological studies along several lines. The diagnosis of schizophrenia is unreliable across studies, and its subtypes are not always specified. Methodology is quite different across studies. He suggested that investigators share samples to confirm major findings, and attempt to correlate neuropathological abnormalities with certain clinical profiles (e.g., flat affect, formal thought disorder, and Schneiderian delusions). Dr. Nasrallah raised the issue of the primary (genetic) neuropathology in schizophrenia versus the secondary (developmental) neuropathology and the problem of distinguishing...
them. He pointed out our vast gap of knowledge as to the significance of the disruption of different neurodevelopmental processes such as neuron proliferation, neuron migration, and axon elimination of synapse pruning. He hypothesized that genetic and perinatal factors produce different cortical and subcortical changes in schizophrenia, and he urged that controlled animal studies be conducted to determine the neuropathological cascade resulting from adverse prenatal and perinatal factors (such as hypoxia) at a series of different developmental stages. Finally, Dr. Nasrallah pointed to the need for conducting neurochemical/neuropathological correlations in the same sample to shed light on the effects of neurodevelopmental lesions on neurotransmitter function in schizophrenia.

### Obstetrical Complications in the Etiology of Schizophrenic Disorders

Sarnoff A. Mednick, Tyrone D. Cannon, Chris E. Barr, and Melvin Lyon. Dr. Mednick and his colleagues cited several lines of evidence which suggest that pregnancy and birth complications (PBCs) play a role in the etiology of at least some forms of schizophrenia. This evidence includes the recent observation of an increased risk for schizophrenia following second trimester influenza exposure, as well as evidence that a sizable proportion of schizophrenic individuals show signs of disturbed neuronal migration in various brain regions (e.g., hippocampus), elevated levels of prenatal and perinatal complications, a heightened incidence of minor physical anomalies, and decreased brain size.

The authors indicated several possible mechanisms by which PBCs may increase the risk for schizophrenia. In view of the relatively higher incidence of schizophrenic genetic background and perinatal complications as compared to the incidence of actual schizophrenia, neither genetics nor perinatal complications are logically suited to be the sole cause of schizophrenia even in subgroups of schizophrenic persons. It seems more reasonable to hypothesize that genetic and perinatal factors interact in the determination of at least some phenotypic expressions of schizophrenia.

In support of this hypothesis, the authors reviewed findings relating to: (1) the neurological consequences of PBCs in unselected populations. (2) neurological findings and their relationships to PBCs in schizophrenic individuals, and (3) the incidence of PBCs in childhood psychotics, high-risk populations, and adult schizophrenic patients. The principal findings were as follows:

- Data from the Neurological Collaborative Perinatal Project (see also Gilles et al. 1983), as well as animal studies of hypoxia introduced at birth, provided the basic support for much of the following discussion of prenatal and perinatal brain development.

The second trimester encompasses the most critical period of brain development, including the formation of, and cellular migration to, several of the structures found to be deviant in schizophrenic patients (e.g., hippocampus, thalamus, and basal ganglia).

In particular, it was pointed out that the major reasons for fetal brain damage were hemorrhage, increased intraventricular pressure, and necrosis of the deep white matter of the hemispheres due to circulatory disturbances, infectious disease, or toxins. Because of ependymal weaknesses in the ventricular walls, there are certain points where hemorrhages and internal pressure changes may be especially critical. These points are in the ventricular walls of the third and lateral ventricles, under the rostral corpus callosum, beside the parieto-occipital white matter radiations, and over the CA2 region of the hippocampus. These are also the points clearly at greatest mechanical risk from bleeding or intraventricular pressure, and they are also exactly the points at which the cerebrospinal fluid-brain barrier can be weakened during development according to the work of Dr. Möllgård and others (see Dr. Möllgård's presentation). The dorsomedial thalamus, the entire region of the third ventricle, and subependymal white matter, including the fronto-occipital bundle, are also at risk.

At the end of the second trimester, dissolution of the germinal matrix within the ventricles is frequently the source of periventricular and intraventricular hemorrhages, which in turn may be related to necrosis of cells and enlargement of the ventricular system. In addition, both hemorrhage and ventricular enlargement are commonly found among low birth weight or premature infants and may be related to complications at delivery, although lasting ventriculomegaly usually does not result from perinatal insult alone.

- Neuropathological studies (see Dr. Bogerts' presentation) have found evidence of cytoarchitectural deviations consistent with (genetic or teratogenic) disturbance of neural migration in the second trimester. Brain-imaging studies (see
Weinberger's presentation) have likewise found evidence of structural damage in a sizable number of schizophrenic patients (i.e., those with predominantly negative symptoms and cognitive impairment); these anomalies are highly related to indices of pregnancy and delivery complications. In the Copenhagen high-risk project, a marked interaction effect was found: Individuals at elevated genetic risk who suffered severe delivery complications had a heightened incidence of enlarged third and lateral ventricles.

- Studies of childhood psychotic patients and adult schizophrenic patients generally were shown to agree in finding an elevated level of both pregnancy and delivery complications in these populations. High-risk studies demonstrated that the high-risk individuals who become schizophrenic or who show early signs of neurological impairment suffered more PBCs than those with favorable outcomes. Retrospective studies have obtained somewhat contradictory results.

There is also evidence from several studies, including adopted and nonadopted individuals (Jacobson and Kinney 1980) who became schizophrenic, and a large sample of process schizophrenic patients (McNeil and Kaij 1978), that obstetrical complications are significantly elevated among these individuals. Further support for the interaction hypothesis comes from studies of monozygotic twins discordant for schizophrenia. In this case, the schizophrenic twin is more likely to have a lower birth weight, suggesting an interaction of environmental and genetic factors.

Mednick et al. concluded with the presentation of new data from the Copenhagen high-risk project which support the hypothesis that genetic and perinatal factors interact in determining the risk for a certain subtype of schizophrenia. Individuals at elevated genetic risk who suffered severe delivery complications and who were autonomically nonresponsive in adolescence were significantly more likely than those without this pattern to develop schizophrenia with predominantly negative symptoms. Conversely, individuals at genetic risk who had escaped delivery complications, evidenced high degrees of autonomic responsiveness in adolescence, and had suffered extremely stressful early rearing experiences (e.g., separation from mother and institutionalization) were significantly more likely than those without this pattern to develop schizophrenia with predominantly positive symptoms.

Discussant: E. Fuller Torrey. Dr. Torrey commented that it was difficult to put together the many threads of evidence presented. He noted that Dr. Mednick had been among the first to present a theory of schizophrenia which involved the hippocampus and learning disturbances, and that this seemed now to be reviving as a theoretical concept.

Dr. Torrey also pointed out that animal studies have shown that in utero infections may be sustained without evidence of increased immunoglobulin M levels at birth. Was it possible that in utero infections and prebirth healing could dispose to long-term developmental damage? Exactly how the viral factor or other fetal influences could result in the much later appearance of schizophrenia was still unclear; nevertheless, the evidence for an excess of stillbirths and central nervous system malformations in the children of schizophrenic mothers pointed in the direction of abnormal fetal development.

New MRI Data

Henry Nasrallah. Dr. Nasrallah presented some preliminary data from MRI findings in schizophrenic patients with and without a history of perinatal complication or a first-degree family history of psychosis. He found an association between a high frequency of perinatal complications (based on standard interviews with the mothers) and a negative family history in schizophrenia. He concurred with the general criticism of the retrospective method, but pointed out the lack of an alternative for most adult schizophrenic patients.

On MRI scans, Dr. Nasrallah replicated previous findings of smaller midsagittal brain size in schizophrenia (Andreasen et al. 1986), but found that the diminution in total cranial, cerebral, and frontal area occurred mainly in male schizophrenic patients with a positive family history of schizophrenia. Perinatal complications were not correlated with smaller brain size in schizophrenia on MRI scans.

General Discussion. Dr. Kety commented in discussion that male brains are more susceptible than female brains to developmental complications, which may be the reason for increased dyslexia and other problems in males, as well as for the sex differences in the present findings.

Dr. Weinberger objected to the use of brain area measurements from single midsagittal MRI scan sections. Dr. Nasrallah explained that this method was used to replicate the 1986 study findings but said that multiple coronal sections
for area and volume measurements were being done on the same sample.

**Genetic and Epigenetic Regulation of Cortical Mapping**

Pasko Rakic. Dr. Rakic illustrated the nature of the neurochemical layering of transmitter substances in the cortex and how this layering developed in the process of cell proliferation and migration. The first wave of cell migration to the developing cortex was shown to set up radial glial fibers (Rakic 1972), along which the many later migrating cells climb to their cortical placement during the second wave of migration (Rakic 1974, 1978). The general plan of the cortical layers thus develops from inside out, as the neurons in the cortex stack up in the reverse order of their arrival. While cells migrate to the cortex, thalamocortical projections growing during the second trimester of gestation accumulate in the transient subplate zone, which is a "waiting" compartment for the cortical afferents (Rakic 1978). These terminals, in turn, could determine the end points for the second wave of cellular migration, which produces cortico-cortical connections.

Thus, changes in the input from the developing thalamus could alter the area of destination or reduce the thickness of superficial layers by preventing the second wave cells from reaching their proper position. Furthermore, the fascicles of radial glial fibers seem to act as the migration route for all the cells within a single cortical column (Rakic 1972). Partial migration would thus be marked by groups of cells lying along this projection path or even at its ventricular origin. Dr. Rakic discussed the significance of the radial unit hypothesis in the context of formation of proto-maps of the cytoarchitectonic areas in the proliferative zones which produce neurons destined for the cortex (Rakic 1988a, 1988b). This hypothesis provides a model for understanding the findings of Dr. Bogerts in the post-mortem schizophrenic brain (see Dr. Bogerts' presentation) and of Dr. Nowakowski in genetically aberrant strains of mice (see Dr. Nowakowski's presentation). The radial unit hypothesis was modeled by studying experimentally altered size of the lateral geniculate projection to the visual cortex in the rhesus monkey. By changing the size of the lateral geniculate nucleus early in fetal life, Dr. Rakic could produce animals with a smaller area of visual cortex (Rakic 1988a). When there was disturbance in the early migration, because of ionizing radiation, many ectopic cells (those without proper placement or connections) remained along the borders of the ventricles, in the region from which they originate (Rakic 1988b).

Clear evidence of a similar effect was seen in the brains of individuals who had been atomic radiation victims at Nagasaki and Hiroshima during the second trimester of their gestation (reviewed in Rakic 1988b). In these cases, brain scans revealed large numbers of ectopic cells accumulated near the ventricular surfaces and abnormal thinning of the thalamus and cortex. An increased number of these patients were also psychotic (Otake and Schull 1984).

Dr. Rakic's presentation thus emphasized the importance of interplay between genetic and environmental factors during pregnancy (e.g., radiation and viral infection) which could affect cell migration, and also, indirectly, cortical function.

Discussant: Richard S. Nowakowski. Dr. Nowakowski discussed briefly the implications of Dr. Rakic's findings and then presented additional evidence on how genetically controlled cell migration in the hippocampus and hippocampal gyrus, in eight strains of specially bred mice, resulted in specifically located groups of partially migrated cells. In certain autosomal dominant mutants, these genetically determined deficits in cellular migration produced not only misplaced groups of cells, but also seemed to result in divergent growth of the cell processes. Some of these cells seemed to receive input from axons in the layer to which they migrated, even though this was not the correct final position for the cells. Close similarities can be seen in this evidence of divergent cellular processes in partially migrated cells in the hippocampus and Kovelman and Scheibel's (1984) evidence for aberrant dendritic structure in human hippocampal cells in schizophrenic patients.

Dr. Nowakowski also noted that seven of the eight strains of mice tested also showed signs of being immunologically compromised. He then made an important suggestion about the way in which genetic and environmental factors (such as those related to the immunological deficit) might interact to produce abnormal behavior or psychosis. On the basis of his studies with mice, in which their behavior seemed largely adequate unless they were subjected to stress, he suggested the diagram shown in figure 1 for a "two-hit" hypothesis of interaction.

**General Discussion.** In the general discussion after the presentations of Drs. Rakic and Nowakowski, Dr. Bogerts provided some recent post-
Figure 1. A schematic diagram of a “two-hit hypothesis” suggesting a possible biological basis for the inheritance of susceptibility to an adult-onset neurological disease

Genetic mutant or variant (e.g., ectopia)

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<th>Genetic mutant or variant (e.g., ectopia)</th>
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An otherwise nondeleterious genotype (i.e., one producing no overt behavioral phenotype) and an environmental insult (or, perhaps, an independent genotype) that is also relatively benign may, if both occur in the same organism, produce an abnormal behavioral phenotype. Arrows and question marks indicate that a number of steps (e.g., neuronal migration and differentiation) are involved for each of the two “hits” and their hypothesized synergistic interactions.

Sources of Neurochemical Deviance in Fetal Neural Development of Schizophrenia

Edward Jones. Dr. Jones argued that the organic basis of schizophrenia is far from established, and he reasoned that the cognitive deficits, which are cardinal symptoms, suggested cortical involvement. He

similar results to those of Bogerts were reported by Dr. Roberts from a sample of brains collected from schizophrenic patients in England, and together with Dr. Nowakowski’s data, these observations focus increasing attention on the hippocampal formation in schizophrenia. It was also apparent that such divergent cellular migration could occur, in some cases, without extremely large losses of cellular material, and thus without extreme changes in ventricular volume because of lost tissue.

Addressing the point that such early developmental changes would probably not lead to abnormal postnatal progressive enlargement of the ventricles, Dr. Weinberger found support for his own findings of relatively stable ventricular enlargement. To this, Dr. Wyatt argued that the lack of progressive ventricular enlargement was not yet proved to hold in all cases, or even, perhaps, in the majority. However, Dr. Roberts stated that measurements from the brains of English schizophrenic patients apparently supported Dr. Weinberger’s view.

Dr. Jones raised the important question of what might be responsible for the first obvious symptoms of schizophrenia, since there appears to be a considerable delay between the time of brain defect origin and the appearance of the illness. Although stress, including that due to emotional upset or viral insult, was a potential cause, there was general agreement that no specific causal effect has yet been established. The facts that females tend to develop schizophrenia later than males, have less intense symptoms, and show an increased tendency toward schizophrenia after menopause were attributed to the generally antidopaminergic effect of the female sex hormones.

mortem evidence from the brains of schizophrenic patients showing similar groups of cells lying beneath the surface of the entorhinal cortex to which they normally migrate. These cells were grouped together in much the same way, and were in a roughly analogous region, as those found in the genetically determined patterning in Dr. Nowakowski’s mice.
then concentrated on the rapidly developing knowledge of neurotransmitter locations and interactions in cortical layers, and the potential significance of these findings. In particular, he pointed to evidence for differences in the layering of neurotransmitter-relevant endings in visual as opposed to other forms of cortex. Apparently, also, the visual cortex is organized differently from all other cortical regions in the average number of cells per cortical "column." When an arbitrary column size is used, there is remarkable uniformity in cell counts per unit vertical volume within all types of cortex except the visual cortex, and within all species from mouse to man. This suggests a strong parallel in structural planning and in cellular migration characteristics between species, which could be important in the development of animal models for brain growth disturbances.

Dr. Jones pointed out the functional importance of some known major neurotransmitters in the neocortex, but he also drew attention to the little-known complexities of the neuropeptide influences. Neurotransmitter effects in the cortex were shown to be roughly organized into two groupings: (1) GABA (γ-aminobutyric acid)/glutamate and (2) neuropeptides (with the latter exercising principally a modulatory influence). The pyramidal output cells of the cortex are principally glutamatergic, while the nonpyramidal intracortical cells are largely GABAergic. In contrast to the classical supposition of single transmitter specificity for each neuron, several different peptides may be found in the same neuron, where they seem to exert a modulatory influence. Of particular interest is cholecystokinin (CCK), which is always found in GABA neurons, and since anything affecting dopamine usually affects CCK, this is a potential avenue of influence for dopamine-relevant effects, which have long been considered a possible cause of schizophrenia.

In this connection, Jones pointed out that although dopamine, norepinephrine, and acetylcholine seem more often correlated with specific regions than with the whole cortex, this picture is now changing. Dopamine-reactive cells have now been found in small numbers in increasingly larger areas of the neocortex. Frontal, parietal, and temporal cortex are now included, not just the medial frontal and orbital regions previously recognized. It was suggested that the spread of dopamine-activated cortical neurons may be much greater in man than in the rat, a finding that was also supported by Goldman-Rakic from her studies of cortical neurotransmitters in monkeys (see Dr. Goldman-Rakic's presentation).

Discussant: Pasko Rakic. Dr. Rakic drew special attention to the growing importance of receptor changes in abnormal cortical function. He suggested that even very small changes in behavior might reflect major changes in receptor function at the cellular level. Great individual variation exists in neuropeptides, for example, and the distribution of such substances may prove to be more important than that of the major neurotransmitters such as dopamine, norepinephrine, and serotonin. Dr. Rakic mentioned that the exact placement of the receptors within the cell is of prime importance, since there is frequently a "mismatch" between the number of receptors available in toto, and their placement in the membrane (where they can have an effect on transmission) or in the cytoplasm (where they do not). Dr. Jones corroborated the necessity of uncovering such mismatches. The relevance of this to fetal development is manifold, since the neuropeptides' presence or absence at the appropriate location may be determined early in development, with subsequent functional disturbances to follow.

Sources of Structural Deviance in Fetal Neural Development of Schizophrenic Subjects

Patricia Goldman-Rakic. Dr. Goldman-Rakic reported studies of cognitive function in the monkey from a single-cell level—that is, in the layered dynamics of the cortex—with an eye to the possible relationships with thought disorder in schizophrenia (Funahashi et al., in press). She also discussed the circuitry of cortical networks: the dorsolateral frontal cortex, parietal associative cortex, medial temporal cortex, and the parahippocampal gyrus were all shown to be reciprocally interconnected with each other (Goldman-Rakic 1988a, 1988b; Selemon and Goldman-Rakic 1988).

The dorsolateral frontal cortex was especially chosen because of the evidence for delayed response deficits following lesions there. In Dr. Goldman-Rakic's view, the delayed response situation requires the animal to use a cognitive "representation" of the previously seen location of the reinforcement to guide its response (memory-guided), and this process is basically different from regulation of response by external stimuli (sensory-guided behavior) (Goldman-Rakic 1987). The latter would be a process most closely dependent on the parieto-occipital associative cortex, while the former would be...
the process that allows the planning of future behavior on the basis of knowledge and past experience, which is most closely related to frontal lobe function. Furthermore, as Dr. Goldman-Rakic pointed out, it is this frontally located ability that more frequently seems to be missing in schizophrenia. To support this conception of the frontal-parietal difference, she cited two human cases of cortical lesions from the literature—one with frontal and the other with parietal cortical damage. In the frontal case, the subject could not draw a picture from memory, while the parietally damaged subject could not copy a given drawing but could draw perfectly from memory.

Recording from single cells, Goldman-Rakic and her collaborators found that in monkeys which have been trained on an oculomotor delayed-response task, individual neurons in the dorsolateral frontal cortex increase their firing when a target disappears from view; the neuron continues to discharge throughout the delay and returns to baseline only after the animal initiates a response (Funahashi et al., in press). Different neurons have “memory fields” for different locations. This specificity of reaction indicates that neurons in prefrontal cortex gain access to visuospatial information by a labeled-line code, and are “hard-wired” into the sensory systems of the cortex.

Furthermore, studies of neurotransmitter receptors in nonhuman primates reveal local differences in the location of receptor subtypes and neurotransmitters within and between cortical regions (Lidow et al. 1988; Rakic et al. 1988). The dorsolateral prefrontal cortex has been shown to have a very high concentration of dopamine (Brown et al. 1979), and some tyrosine hydroxylase containing axons (indicators of catecholamine activity) terminate on pyramidal cells (i.e., on output cells). The fronto-cortical neurons are therefore being functionally characterized and then tested by iontophoretic stimulation for dopaminergic reactions. It is believed that such issues will clarify dopamine’s role in cortical function.

Discussant: Daniel R. Weinberger. Dr. Weinberger pointed out the similarity of the Wisconsin Card Sorting task to the delayed response test—a “mental representation” is needed, and schizophrenic patients have problems with this. In addition, he mentioned the interesting fact that the three-ring “Towers of Hanoi” problem is difficult for schizophrenic persons, while they solve the four-ring Tower problem equally as well as normal individuals. Dr. Weinberger suggested that this might be due to simplicity of the three-ring solution, which permits it to be internally represented, remembered, and planned, whereas the four-ring problem is so complex that it prevents any easy conception in advance. He also noted that blocking dopamine to the prefrontal cortex seems to raise dopamine activity subcortically, which would resemble the postulated dopamine overactivity that may occur in schizophrenia.

Brain Barrier Systems in the Developing Human Brain: Implications for the Neuro-pathology of Schizophrenia

Kjeld Møllgård. Dr. Møllgård spoke strongly for a complete reevaluation of the developmental process by which the blood-brain barrier (BBB) is said to operate in the fetus. It has been reported that in some species substances penetrate differently into the brain of the fetus as compared to the adult. It is also known that the concentration of protein in the brain of newborn infants—especially premature infants—is higher than in the adult brain. This has led to the false conception of a deficient or “leaky” BBB in the fetus.

Only tight junctions, which will not allow the passage of large protein molecules, are found in the fetal brain’s BBB, even in tests of fetuses only a few days old and in species ranging from sheep and wallabies to humans. In addition, a new type of barrier not reported in the original concept of BBB, the “cerebrospinal fluid-brain barrier” (CSF-BB), has been discovered to exist only in the fetal brain. The CSF-BB is also a very protein-tight barrier. In summary, the BBB and the CSF-BB are more complex and less penetrable in the fetus at an early stage than they are later in development. The barrier is neither immature nor penetrable to large proteins during fetal development.

However, though they do not come through a leaky BBB, there are many proteins in the brain in different locations, such as the layers of the cortex. Some proteins, such as the ion binding plasma protein transferin, are necessary for the development of cellular and brain structure and for the proper migration of cells. In fact, proteins are being transiently produced by the brain cells including the neurons. Substances also may enter the brain by specific transport mechanisms, but not through a leaky brain barrier.

Beginning with the end of the second trimester, when the germinal matrix breaks down at the ependymal wall of the ventricles,
some plasma proteins finally can enter through the ventricle walls, at spots where the ependymal membrane is temporarily missing. The medial wall of the ventricles or penetrating blood vessels can be damaged, especially in mid-gestation (second trimester), and this includes a thin-walled region near the hippocampus. For viruses such as the influenza virus to penetrate the brain known to be at greatest risk for perinatal damage or infection (i.e., at the surface of the basal ganglia under the rostral corpus callosum, over the CA2 region of the hippocampus, and in the posterior portion of the lateral ventricles) were not also those where the CSF-BB was most likely to be weakened or missing when the germinal matrix disappeared at the end of the second trimester. This was affirmed by Dr. Møllgård, who added that it was exactly in these locations that hemorrhage could most easily occur, intraventricular pressure have an adverse effect, and toxins or infections most easily find their way into the brain tissue.

General Discussion. In the open discussion following Dr. Møllgård’s presentation, Dr. Lyon asked whether the three regions of the brain known to be at greatest risk for perinatal damage or infection (i.e., at the surface of the basal ganglia, over the rostral corpus callosum, over the CA2 region of the hippocampus, and in the posterior portion of the lateral ventricles) were not also those where the CSF-BB was most likely to be weakened or missing when the germinal matrix disappeared at the end of the second trimester. This was affirmed by Dr. Møllgård, who added that it was exactly in these locations that hemorrhage could most easily occur, intraventricular pressure have an adverse effect, and toxins or infections most easily find their way into the brain tissue.

General Conclusions

The conference reaffirmed the well-documented findings of ventriculomegaly (lateral and third ventricles) and neuropathology in schizophrenic patients. The evidence suggests that these anomalies precede the onset of the disorder. Clinical and neuropathological evidence suggests the possibility that prenatal and perinatal developmental difficulties may be, in part, responsible for these brain anomalies.

Certain of the structural aberrations observed in the brains of schizophrenic individuals (e.g., hippocampus and parahippocampal areas, dorsolateral frontal cortex, globus pallidus, and amygdala) are most likely due to disorders occurring during fetal neural development. There is a strong possibility that an important component of the phenotypic expression of the genetic disorder in schizophrenia consists of a specific gene defect controlling the migration and interconnection of young neurons. Cortical malformations induced by these developmental disorders may be in part responsible for certain of the cognitive defects observed in schizophrenic patients.

The genetic liability also appears to provide a predisposition for elevated levels of periventricular damage associated with delivery complications in those at high genetic risk for schizophrenia. For instance, the periventricular damage may involve brain areas important to excitatory autonomic functioning, thus contributing to the anergia and defect symptoms seen in some schizophrenic patients.

There is a need for further study of these prenatal and perinatal factors, and for discovering the relationship between these predispositional factors and the delayed development of florid schizophrenic symptoms.

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