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SCHIZOPHRENIA: CAUSED BY A FAULT IN PROGRAMMED SYNAPTIC ELIMINATION DURING ADOLESCENCE?

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Summary—Converging evidence indicates that a profound reorganization of human brain function takes place during adolescence: the amount of deep sleep and the rate of brain metabolism fall sharply; the latency of certain event-related potentials declines; the capacity to recover function after brain injury diminishes; and adult problem-solving "power" appears. A reduction in cortical synaptic density has recently been observed and might account for all of these changes. Such synaptic "pruning" may be analogous to the programmed elimination of neural elements in very early development. A defect in this maturational process may underlie those cases of schizophrenia that emerge during adolescence.

INTRODUCTION

BIOLOGICAL theories of schizophrenia* have made use of two main models. One model postulates abnormal prenatal or neonatal development of the central nervous system (CNS) as a result of genetic or intrauterine defect. The second model proposes a specific functional abnormality (e.g. excess dopamine secretion) that may have a genetic component and that is either always present or else triggered later in life by a discrete biologic or psychosocial event. Both models find it difficult to explain the frequent onset of schizophrenia in adolescence—sometimes in patients whose psychological development was entirely normal prior to falling ill. Under these circumstances, diathesis-stress models are usually introduced. These models hold that severe environmental or psychological stress acts on an underlying biologic vulnerability to produce the clinical disease. However, these interpretations are often embarrassed by one's inability to demonstrate the occurrence of grossly stressful events at the onset of illness. In such cases, rather convoluted hypotheses have been advanced to explain how ordinary life experiences act as stresses sufficiently severe to produce lifelong madness.

In this essay, I propose a third kind of biological model for the etiology of schizophrenia, a model that more comfortably fits the clinical facts. This model is also consistent with a newly emerging theme in contemporary neurobiology—that the structural development of the CNS continues much longer after birth than was previously believed and that rather profound morphologic rearrangements take place in the brain at a time when maturation was thought to have been complete.

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*Schizophrenia is mentioned in the singular for convenience. This does not mean that I consider it an homogeneous entity with a single etiology. The converse is probable. In this paper, the term is intended to designate one subgroup of patients manifesting this syndrome.

In what follows, I will first review evidence that suggests that a major rearrangement of brain structure and function takes place during early adolescence and then discuss the implications of these changes for the onset of schizophrenia. Since my interest in these issues was stimulated by observations made in research on sleep, I will begin with these data.

SLEEP EEG CHANGES IN INFANCY AND ADOLESCENCE

In general, the sleep electroencephalogram (EEG) manifests the most marked age-related changes demonstrated in human brain physiology after the first year of life (FEINBERG, 1976). These changes are measurable over the entire lifespan, but there are two periods of exceptionally high rates of change—early infancy and adolescence.

Neonatal sleep patterns and their development have been described by several investigators including DREYFUS-BRISAC (1958) and PARMALEE *et al.* (1967). Briefly, the sleep EEG at birth consists of poorly-formed, relatively low-voltage slow waves. The differentiated patterns characteristic of the sleep EEG over most of the lifespan, including high voltage delta waves, sigma spindles and K-complexes, develop rapidly during the first year of life. The sleep cycle pattern of the newborn infant also differs from that of the adult since rapid eyemovement (REM) often precedes non-REM (NREM) sleep; later in infancy, and over the rest of the lifespan, NREM sleep almost always occurs first. The proportion of REM sleep is high at birth (50% of total sleep time) but approaches the adult ratio (about 25%) by the middle of the first year.

By age 2 yr, all of the EEG characteristics of adult sleep are present, although EEG frequencies are slower and amplitudes higher than those in later life. NREM sleep regularly precedes REM at sleep onset, and the occurrence of high amplitude delta (0.5–3 Hz) waves, K-complexes and spindles permits the classification of NREM sleep into stages 2, 3 and 4 according to increasing proportions of delta waves in the epochs being scored.

A neuroanatomic basis for the sleep EEG changes of infancy is grossly apparent. The brain grows explosively in the first years of life, with increases in neuronal arborization, synaptic density, myelination and cell size (CONEL, 1939–1963; DOBBING and SANDS, 1973). These morphologic changes, along with neuronal maturation, could account for the increased amplitude of EEG waves (see below) and the appearance of those other EEG characteristics which are absent or in rudimentary form at birth.

During adolescence* the changes in sleep EEG are quantitative rather than qualitative, but are nonetheless striking. The time spent in deep (stage 4) sleep declines by about 50%. The amplitude of the delta waves that characterize this stage also declines markedly, so that the total reduction in the underlying biological process is probably greater. Hand measurements of visually scored EEG sleep records (Fig. 1) suggest that peak delta wave amplitude falls by about 75% between age 10 and 16 yr (FEINBERG *et al.*, 1977). In addition to the reduction in stage 4 EEG, total sleep duration declines by about two hours (WILLIAMS *et al.*, 1974). Thus, in the first few years of adolescence, the sleep EEG shows maturational changes greater in magnitude than those produced by aging over the next four decades.

*The greatest part of the changes described above occurs between ages 10 and 14 yr, but the rate of change remains substantial until the end of the second decade, when it becomes much slower.

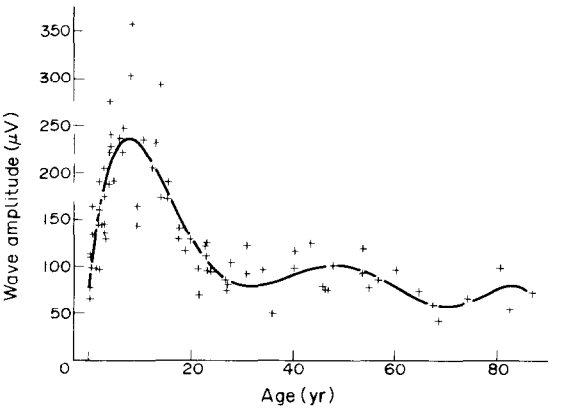

FIG. 1. Average amplitude of EEG slow waves during sleep in normal subjects between the ages of 0.25 and 86 yr. Each point represents the mean of 50 waves for one subject selected as described in FEINBERG *et al.* (1967). The curve is a sixth degree polynomial which significantly improves goodness of fit over lower-order functions. The main points of interest in this curve are the marked increase in amplitude during infancy and the marked decline during adolescence. The later fluctuations are of doubtful significance. [A recent computer analysis revealed a 30% decline in amplitude of 0.5–3 Hz waves between ages 23 and 72 years (Feinberg and co-workers, unpublished data).] [Reprinted with permission from FEINBERG *et al.* (1967).]

Elsewhere, we proposed (FEINBERG and CARLSON, 1968; FEINBERG *et al.*, 1967) that the sleep changes of adolescence are related to decreases of brain metabolic rate and brain plasticity which occur at this time. This hypothesis—(FEINBERG and CARLSON, 1968; FEINBERG *et al.*, 1967; FEINBERG and EVARTS, 1969) that sleep processes reflect brain plasticity—requires brief comment. Fundamentally, it stems from the notion that one function of sleep is to reverse the effects of waking on plastic brain neurons. MORUZZI (1966) put forward a similar view at about the same time. In 1974, we extended our interpretation by indicating that the reversal process must be carried out during NREM sleep, and must occur at its highest rate during deep (stage 4) sleep. (Stage 4 EEG is characterized by dense, high voltage, slow [delta] waves.) Evidence supporting this view includes the close relation of stage 4 sleep to duration of the waking period that precedes sleep, the sharp decline in occurrence of stage 4 EEG across the sleep period (as though a substrate was being consumed), the effects of aging on sleep, and certain effects of napping on subsequent sleep. For further discussions of this hypothesis and its supporting evidence see FEINBERG (1974), FEINBERG and FLOYD (1982) and also papers by BORBELEY *et al.* (1981) and BORBELEY (1982) who have adopted this view.

CHANGES IN EVENT-RELATED POTENTIALS IN EARLY LIFE

Electrophysiological evidence of marked maturational brain changes between childhood and the end of adolescence is not limited to the sleep state. Event-related potentials (ERPs) recorded during waking also change substantially over this age range. Of special interest is the decline in latency of the P300 wave. This positive wave occurs about 300 ms after certain experimental "events" and is closely linked to cognitive processes. The

P300 wave can be elicited by the intermittent *absence* of an expected stimulus as well as by infrequent, randomly-occurring stimuli, to which the subject must respond. COURCHESNE (1977) found the latency of the P300 wave in children aged 6–8 yr was 702 ms as compared with 417 ms in adults aged 23–35 yr, a difference of 41%. This result was confirmed by GOODIN *et al.* (1978) who showed, in addition, that the decline in P300 latency occurs between ages 5 and 15 yr.

This age trend is of special interest for two reasons. First, a change in latency is likely to result from mechanisms different from those responsible for the change in amplitude of sleep EEG delta waves already described, thereby providing relatively independent evidence that the human brain is undergoing important maturational change between ages 5 and 15 yr. Secondly, the P300 is closely related to cognitive processing of an attended event, suggesting that this maturational change involves the biological substrate for information-processing.

DECLINE IN BRAIN METABOLIC RATE BETWEEN CHILDHOOD AND ADOLESCENCE

Another striking change in brain physiology between childhood and the end of adolescence is a marked decline in cerebral metabolic rate as measured by brain oxygen consumption ($CMRO_2$). Overall $CMRO_2$ has been measured with the nitrous oxide method (KETY and SCHMIDT, 1948) in normal children and adults; for a summary, see KETY (1956). Oxygen uptake remains constant between ages 5 and 10 yr (5.1 and 5.3 cm^3/100 g of brain/min). It declines by 20% to 4.0 at age 13, to 3.7 at age 19, and then remains at about 3.5 cm^3/100 g of brain/min, about 30% below the childhood value, through normal old age. Some perspective on the magnitude of this maturational change is provided by the fact that the average difference in metabolic rate between ages 10 and 13 yr is as great as that found between normal and senile elderly (FREYHAN *et al.*, 1951; LASSEN *et al.*, 1960).

While the maturational changes in $CMRO_2$ reach a high level of statistical significance, they are necessarily—in view of the demands of the nitrous oxide method—based on relatively few subjects. It would be of great interest to have more extensive measures of the rate of change in this variable, especially between ages 10 and 20 yr. Such data may soon become available as a result of the growing application of positron emission tomography; this method estimates brain metabolic rate less invasively than the nitrous oxide technique and it yields measures of regional as well as overall rates of brain metabolism.

Elsewhere we suggested (FEINBERG and CARLSON, 1968; FEINBERG *et al.*, 1967) that the decline in $CMRO_2$ between late childhood and adolescence is a correlate of the decline in brain plasticity over the same period, reasoning that the most plastic neurons would have the highest metabolic demand. If sleep reverses the effects of waking on plastic neurons, and if more plastic neurons have higher metabolic rates, it follows that the curves for total sleep time and $CMRO_2$ across age should be parallel, as in fact they are (FEINBERG *et al.*, 1967).

NEUROANATOMIC BRAIN PLASTICITY AND FUNCTIONAL "POWER"

The alterations in brain electrophysiology and metabolism in late childhood and adolescence suggest that a major reorganization of brain function is taking place. Further

evidence that the brain is changing in some fundamental way during this period is decreased ability to recover function after injury. (I shall designate this capacity as neuroanatomical plasticity since it probably depends upon anatomic connections as well as functional changes.) Clinical neurologists have long been aware that destruction of speech areas in the left cerebral hemisphere in children is usually followed by complete recovery of speech within one to two years if the right hemisphere remains intact. In contrast, the same lesions occurring in later adolescence and adulthood usually result in a permanent aphasia. The literature on this question has been carefully reviewed by SATZ and BULLARD-BATES (1981). Their analysis indicates that rapid recovery from aphasia in pre-pubertal children has been clearly established but that the data in this area are unsystematic and too scanty to permit one to construct an age curve for the neuroanatomical plasticity* reflected by such recovery.

At the same time that neuroanatomical plasticity diminishes, the ability to solve complex problems and to carry out prolonged logical analyses emerges in full flower. One might designate these skills as functional "power". While the 10 yr old has remarkable intellectual ability, the difference between the 10 and the 16 yr old in problem-solving skills is enormous; indeed, it is probable that sheer analytic power is, at the end of adolescence, at its highest point in the lifespan. This emergence of adult problem-solving skills ("operational thinking" in Piaget's terminology) in adolescence is usually viewed as an incremental effect of continued learning. However, it is possible that this development also requires substantial changes in the neuronal substrate of thought. It may seem paradoxical that functional power should increase while neuroanatomical plasticity is decreasing. An attempt to reconcile this paradox will be found below when the evidence for morphologic brain changes in adolescence is described.

ONSET OF SCHIZOPHRENIA IN ADOLESCENCE

The emergence of schizophrenia during and shortly after adolescence is so well-known a phenomenon that it needs little description here. In some patients, to be sure, frank schizophrenic behavior develops after a long history of behavioral deviance and thus does not appear to be a *de novo* phenomenon. However, the disease can also appear suddenly in youngsters who have shown normal or even outstanding pre-morbid accomplishment; these are often our most tragic and poignant patients.

The high incidence of schizophrenia in adolescence has not yet been adequately explained. Familiarity with this statistic does not mean one understands its cause. It has been generally assumed that schizophrenia has its onset in adolescence because of the intense psychosocial stresses of this period, which act upon an existing vulnerability. But this vulnerability itself may be an emergent phenomenon, the result of a defect in an extensive reorganization of brain function that normally takes place during the early years of adolescence.

*It is in any event unlikely that a single age curve represents all of the plastic functions of the brain. The loss of ability to recover from brain injury probably bears a different relation to age than less drastic challenges to plasticity, such as learning a new language or acquiring complex psychomotor skills [see FEINBERG and CARLSON (1968) for a discussion of the relations between age and several behavioral manifestations of plasticity].

SYNAPTIC DENSITY AND AGE

I noted above that there is evidence that the brain is, morphologically, in a dynamic state much later in life than was previously thought. Recent observations by Peter Huttenlocher of the University of Chicago are particularly striking in this regard. HUTTENLOCHER (1979) measured synaptic density in relation to age in the middle frontal gyrus in post-mortem specimens of 21 normal human brains. Figure 2 shows the main results. After birth, synaptic density increases to an apparent maximum at ages 2–3 yr and then declines steeply in late childhood and early adolescence to levels that are maintained until extreme old age. The shape of this curve is remarkably similar to that shown in Fig. 1 for delta wave amplitude (when the different age-scales are taken into account).

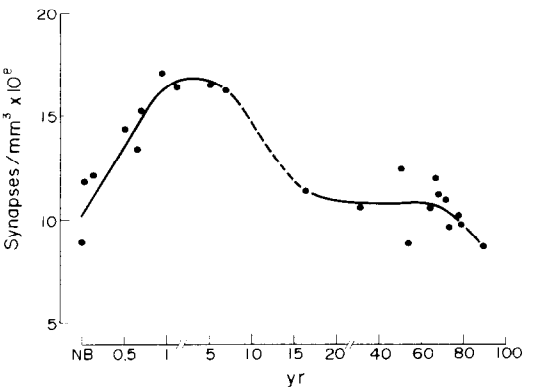

FIG. 2. Synaptic density in layer 3 of the human mid-frontal gyrus as a function of age. Note that age is scaled differently from Fig. 1; with this difference taken into account, the curves are quite similar. [Reprinted with permission from HUTTENLOCHER (1979).]

Huttenlocher suggested that the changes he observed "may well form the anatomical substrate for changes in electrical properties of cerebral cortex that occur in late childhood, including maturation of electroencephalographic patterns and increase in seizure threshold" (HUTTENLOCHER, 1979; p. 202). He went on to suggest that, "Late neuronal and synaptic loss in human cerebral cortex may account for loss of ability to recover from certain types of brain injury, such as from aphasia after dominant hemisphere lesions. Ability to recover speech decreases markedly late in childhood, at about the time when synaptic and neuronal density decline to adult values" (p. 203).

As Huttenlocher himself pointed out (personal communication), his observations are not yet conclusive. The number of data points is small and observations are lacking for the crucial years of early adolescence. Certain technical problems in estimating synaptic density independently of brain volume have not been fully resolved. In spite of these uncertainties, it may prove worthwhile to assume that the changes in brain morphology suggested by Huttenlocher's data are both real and substantial and to consider how they may account for the changes in brain function and physiology characteristic of adolescence.

In the discussion that follows, we use the term "reduced synaptic density" to imply qualitative change (reorganization) as well as quantitative reduction. This qualitative change involves, presumably, a gain in "specialization" at the cost of neuroanatomic plasticity. It need not imply a reduction of synapses "across the board". For example, the reorganization may involve fewer inputs/neuron but an increased number of synapses/input, such as occurs in certain simple systems during early development (see below). It is also quite possible that some of the brain changes of adolescence are unique to this period and have not as yet been described.

RELATION OF CHANGE IN SYNAPTIC DENSITY TO BEHAVIORAL CHANGES

I have noted that the ability to solve highly abstract and complex problems (functional "power") emerges during adolescence. This change may seem inconsistent with the hypothesis that it is produced by diminished synaptic density in the neuronal substrate for thought. One might plausibly assume that the largest possible neuronal networks are required for the most complex cognitive activity. However, it is possible that this intuitive assumption is wrong and that, with neuronal connections, there are situations in which "less is more". Some qualitative observations of problem solving in children are relevant in this regard. For example, while studying spatial problem-solving in the laboratory of Piaget (FEINBERG and LAYCOCK, 1964), I was struck by the fact that even quite young children could propose sophisticated and conceptually correct strategies that, however, they were unable to implement. Many of their failures of execution could be attributed to lack of experience and simply not knowing which methods were practical. But another apparent source of difficulty was an inability to pursue an idea to its conclusion because of multiple competing ideas.

If this interpretation is correct, the paradox mentioned above—a decrease in neuroanatomical plasticity concomitant with an increase in functional power—is eliminated: too many neuronal connections could make it difficult to distinguish and organize functionally the particular neuronal chains required for sustained logical thought and the solution of complex problems. The long latency of the P300 in children also may be a manifestation of this change in connectivity. The P300 paradigm requires processing of a single, quite simple event (e.g. counting an infrequent stimulus). It seems more likely that its longer latency in children results from some anatomical difference—such as more dense and highly branched pathways—than from a fundamental difference in the way this simple cognitive act is carried out.

It might become possible to test some of these ideas by studying those forms of mental retardation that are associated with abnormally *high* rather than low synaptic densities (HUTTENLOCHER, 1979; CRAGG, 1975). If it becomes possible to diagnose these patients *ante mortem,* one could compare their behavioral, cognitive and electrophysiologic characteristics with those found in patients with retardation syndromes characterized by pathologically diminished synapses.

SYNAPTIC DENSITY AND DELTA WAVE AMPLITUDE

A decline in synaptic density between childhood and late adolescence could directly account for the decline in delta wave amplitude that occurs at about the same time.

EEG waves recorded from the scalp are produced by slow voltage changes (inhibitory and excitatory post-synaptic potentials) occurring synchronously in large groups of neurons (cf. ELUL, 1972). The magnitude of these voltages (i.e. the amplitude of the waves) is a function both of the size of the potentials generated by each neuron and of the number of neurons varying synchronously. A decrease in the size of neuronal networks could therefore account for the reduction in delta wave amplitude during adolescence in a fairly straightforward way. (The alternative possibility is that the average voltage change/neuron diminishes, because of changes in either neuronal responsitivity or in the intensity of the synchronizing stimuli. This possibility cannot be ruled out, although there is no evidence that now suggests it.)

While a decline in the size of neuronal pools (interconnected groups of neurons) could directly account for the fall in amplitude of delta waves, it need not cause a reduction in the number of waves (FEINBERG *et al.*, 1967). Nevertheless, the stage 4 decline in adolescence involves a reduction in number as well as amplitude of delta waves. If both phenomena are related to diminished synaptic density, it would imply that greater neuronal connectedness is associated with (or requires) more as well as higher delta waves.

LATE BRAIN MATURATION AND SCHIZOPHRENIA

The evidence cited above leaves little doubt that the neuronal substrate for thought and behavior changes importantly in adolescence. Let us assume that, to an important extent, these changes result from a programmed decrease in synaptic density and that an error or defect in this process gives rise to schizophrenia. We do not know enough about the neural substrate of mental activity to designate the brain systems involved. Nevertheless, one can distinguish the cognitive operations which are usually spared in schizophrenia from those that are impaired. BLEULER (1950), perhaps the most acute observer of the phenomenolgy of schizophrenia, was among the first to note that "simple" functions are preserved in this illness. These include memory, orientation, and those other cognitive operations whose impairment is now recognized as the hallmark of gross or "organic" brain disease.* Bleuler believed that the crucial defect in schizophrenia was of the *"integration"* of mental functioning—i.e. the hierarchical organization of thought, the integration of thought and feeling and of ideas and perceptions. Thus, under "Definition of the disease" he wrote, "In every case we are confronted with a more or less clear-cut splitting of the psychic functions. If the disease is marked, the personality loses its unity; at different times different psychic complexes seem to represent the personality. Integration of different complexes and strivings appears insufficient or even lacking. The psychic complexes do not combine in a conglomeration of strivings with a unified resultant as they do in a healthy person; rather, one set of complexes dominates the personality for a time, while other groups of ideas or drives are 'split off' and seem either partly or completely impotent . . ." (BLUELER, 1950, p. 9).

Strikingly similar interpretations were expressed by other observers at about the same time. Thus, Wernicke hypothesized a defect of neuronal integration he called "sejunction"

*We would not, of course, consider these "simple" in any literal sense. We also recognize that a variety of subtle alterations in these cognitive processes have been shown experimentally in schizophrenia. However, it is not yet clear whether any of these changes is intrinsic to the pathology of schizophrenia. They may all be secondary phenomena resulting from varying degrees of cooperation, of arousal levels, of medication effects, etc.

and Stransky used the rather colorful term "intrapsychic ataxia" [for a scholarly review of these early conceptualizations, see MAY (1931)]. These interpretations imply a defect in the integration of relatively large neuronal systems which are themselves normal.

Faulty integration usually implies disconnection, but inappropriate or supernumerary connections would also impair integration. Thus, it is not possible to predict whether, if the brain defect in schizophrenia indeed results from deranged synaptic pruning during adolescence, the abnormality is due to the elimination of too many or too few synapses or from the wrong ones. Elsewhere (FEINBERG, 1978), I suggested that impairment of "feed-forward" or "corollary discharge"* mechanisms in thinking could give rise to some of the characteristic symptoms of schizophrenia, including auditory hallucinations, thought-insertion, thought-control and loss of self-boundaries. The very function of feed-forward mechanisms is, of course, to serve neural integration. Feed-forward systems could be impaired by uncoordinated redundant connections as well as by their reduction below required levels.

SLEEP STUDIES IN SCHIZOPHRENIA

Some empirical evidence relevant to these speculations arises from studies of sleep in schizophrenia. About 40% of schizophrenic patients show extremely low levels of visually-scored stage 4 sleep. Indeed, low amounts of stage 4 sleep are the most consistent abnormality of brain function yet detected in schizophrenia [see FEINBERG and HIATT (1978) for a review of these data]. Computer analysis indicates that reduction in the amplitude of delta waves is mainly responsible for the low stage 4 levels (Hiatt, Floyd and Feinberg, unpublished observations).

We have already noted that the decline in EEG amplitude in childhood and adolescence could result from a decrease in the size of neural networks capable of synchronous change in potential. This reasoning suggests that some kinds of schizophrenia might be produced by excessive synaptic loss in adolescence. However, since stage 4 EEG can be reduced by anxiety, it remains possible that the low levels in schizophrenia are a secondary response to the illness rather than a direct manifestation of neuronal change. It would seem important to clarify this issue by determining the clinical correlates of low stage 4 in schizophrenia with special emphasis on a possible relation to anxiety, as measured physiologically and by clinical ratings. This important research problem has been neglected for the past decade. This neglect is surprising and, in view of the paucity of clues to abnormal brain function in schizophrenia, regrettable.

MODELS FOR LATE SYNAPTIC PRUNING: PROGRAMMED CELL DEATH IN EMBRYOGENESIS AND AXONAL ELIMINATION IN NEONATES

We have argued that a decline in synaptic density in adolescence might account for several striking brain developments of this period: the loss of (neuroanatomical) brain plasticity, the emergence of adult problem-solving skills; large and rapid changes in

*These mechanisms have been studied in relation to the control of movement [see EVARTS (1971)]. If, as Hughlings Jackson (1978) suggested, thought is the most complex of all "movements", the same control mechanisms might be employed.

brain electrophysiology, including a decline in delta wave amplitude and in P300 latency; the fall in brain metabolism; and, when the process is faulty, the onset of schizophrenia. We now pursue our speculations to consider what mechanisms might produce a programmed elimination of synapses.

There is clear evidence that, much earlier in development, the nervous system initially overproduces neural elements and then systematically eliminates some of them. During embryogenesis, this process involves overproduction and elimination of neurons ("programmed cell death"). In the neonatal period, there is a reduction of axonal processes. Thus, programmed elimination of synapses during early adolescence might represent a third general example of elimination of redundant neuronal elements. The biological value of a mechanism that involves initial overproduction of neural elements with subsequent elimination of those that fail to meet some standard of functional effectiveness is obvious: the information requirement for nervous system development is vastly reduced.

Programmed cell death, the most extensively described of these phenomena, has been observed in many systems—motor, sensory, and inter-neuronal [for an early review, see COWAN (1973)]; for a recent collection of reviews, see *Neuroscience Commentaries,* **1** (2) (1982), especially the paper by HAMBURGER and OPPENHEIM. It is believed to play an important role in regulating the number of neurons in the nervous system. What happens is that, at certain points in embryologic development, large numbers of neurons die over a short period. The phenomenon is entirely predictable in the systems in which it has been observed and thus, in a broad sense, is genetically determined. Most of the neurons that die are not aberrant in the sense of having connected with grossly inappropriate targets. Instead, cells that die are randomly interspersed with those that survive. Since the number that survive can be increased or decreased by varying the size of their target, it is believed that survival depends upon successful competition by the neurons for a trophic (nourishing) factor. This factor is probably made available by functional neural activity which "selectively stabilizes" (CHANGEUX and DANCHIN, 1976) certain connections.

A second period of rapid elimination of neural elements has recently been described in mammalian neonates. INNOCENTI (1981) reported the loss of callosal axons in the visual cortex of the kitten during the first two post-natal months. IVY and KILLACKEY (1982) recently reported a similar elimination of callosal axons originating in the parietal cortex of the rat, occurring between post-natal days eighteen and twenty. In agreement with INNOCENTI (1981) and O'LEARY *et al.* (1981), IVY and KALLACKEY (1982) showed further that this loss of axons was not the result of cell death and that, moreover, the ipsilateral processes of these neurons were retained. Thus, in this case, the elimination of the callosal axons was selective.

PURVES and LICHTMAN (1980) have summarized observations on neonatal elimination of axonal elements in several simpler neuronal systems, including striated muscle, the superior cervical and the submandibular ganglia of the rat. In each of these systems, there is a reduction in the number of axons serving each target cell resulting in a diminished convergence of inputs. However, the number of synapses for each retained terminal increases at the same time so that the effectiveness of the residual connections is heightened.

Evolution is conservative in the sense that mechanisms effective at simpler levels are

often retained and used in complex systems. Thus, a "programmed synaptic elimination" during adolescence could represent a third and final systematic reduction of neural redundancy, a reduction that adjusts the neural systems involved in the most complex and characteristically human brain functions. One possible model is that the human brain develops virtually all potentially useful neuronal interconnections in the first years of life since it cannot be specified in advance which connections will actually be needed. However, the excess connections impose a substantial cost on information-processing capability; evidence of this cost is a relative inability to sustain the prolonged logical thought required for complex problem-solving. At the end of childhood, when the kinds of neuronal connections required for adaptation have been determined by the individual's interactions with his environment, little-used connections are eliminated.

How might such an elimination take place? We have already stated that, in earlier development, neuronal (and axonal) survival depends upon successful competition for some trophic factor in the target cell whose availability is enhanced by function (cf. HAMBURGER and OPPENHEIM, 1982). Perhaps in human adolescence there occurs a programmed decrease in availability of some similar trophic factor required for synaptic maintenance. Alternatively, synaptic elimination could be caused by an enhanced synaptic requirement for the trophic substance due to change in neurochemical milieu. Because early adolescence is a period of profound endocrine change, and because endocrine factors play an important role in controlling cell death in simpler organisms (cf. TRUMAN and SCHWARTZ, 1982), one is tempted to speculate that this process is triggered or perhaps entirely controlled by neuroendocrine mechanisms.

A late reduction in synaptic processes must not, of course, be blind with respect to their utility: it would hardly do to eliminate heavily used connections and leave unneeded ones intact. Whatever process is involved must be sensitive to the "life experience" of the neurons, i.e. their history of activity. This consideration permits some role for environmental and experiential (including "emotional") factors in the model proposed here for the neuropathology of schizophrenia, as my colleague Professor Simon Auster (personal communication) pointed out.

Is the possibility that, during adolescence, the brain makes use of control mechanisms similar to those found in embryogenesis too remote and far-fetched? Informed opinion suggests otherwise. Professor Dale Purves of Washington University (St. Louis) has written:

> "The idea of a competitive balance of synaptic connections is by no means the exclusive province of developmental neurobiologists. It is well known that mature axons sprout and make additonal synapses if their target is partly deprived of innervation, and conversely, that adult axons can reduce the number of synapses they make on target cells under a variety of conditions. These phenomena suggest that the number of synapses present in maturity *continues to be regulated by interactions at the level of the target,* much as competition between neurons for survival is regulated at an earlier stage of life" (PURVES, 1980, p. 585, emphasis added).

HAMBURGER and OPPENHEIM (1982) express quite similar views:

> "In a more general vein, neuronal death may only be the most extreme case of what is actually a continuum of regressive, neurogenetic events that have both ontogenetic

and phylogenetic significance. Cellular overproduction, exuberant growth of axonal and dendritic processes and excessive synapse formation may reflect only the most obvious cases in which regression acts to mold the final product . . ." (p.49).

They go on to suggest that abnormalities in these maturational processes could cause disease and might even underlie individual differences in normal behavior:

". . . the possibility that altered natural neuronal death is a factor in various neuropathological disorders cannot be ignored. Genetic defects in the cell death process could alter cell numbers either directly or transneuronally. . . . Environmental factors such as drugs given to pregnant females could also affect neuronal numbers by altering the normal cell death process. Conceivably, even benign neurobehavioral differences between 'normal' individuals could, in some instances, be associated with differences in neuron numbers resulting from subtle genetic or environmentally induced alterations in neuronal death" (p. 49).

Purves, Hamburger and Oppenheim and others arrived at their views from observations of the early development of the nervous system. I independently (FEINBERG, 1982) arrived at a quite similar notion from what struck me as compelling, albeit circumstantial, evidence that a substantial reorganization of the brain invariably takes place in human adolescence and that so drastic and complex a change might sometimes be defective and thereby cause mental illness.

IMPLICATIONS FOR RESEARCH

Several implications for research stem from these ideas. The main one is that the morphology, neurotransmitter characteristics and functional relations of neurons be carefully investigated in early adolescence to seek anatomic correlates of the maturational changes in EEG sleep patterns, event-related potentials, cerebral metabolic rate, brain plasticity and sustained logical thought.* More extensive and systematic measurement of synaptic density as a function of age will be of considerable basic importance. Neurotransmitter levels, some of which are already known to show marked ontogenetic changes must of necessity be measured in parallel with morphologic studies. In this context, it is of interest that PETTIGREW and KASAMATSU (1978) and KASAMATSU and PETTIGREW (1976) have reported data suggesting that norepinephrine can facilitate plastic rearrangements in the brains of kittens and older cats.

The "dopamine hypothesis" is our strongest clue to the etiology of schizophrenia.† For this reason, it is of special interest to determine whether the density of synapses in dopaminergic systems changes importantly in adolescence. The possibility of spontaneous remission in schizophrenia, taken in association with the ability of neuroleptics to reverse schizophrenic symptoms, suggests that this disorder results from a partial rather than

*Studies of such questions in man must be indirect and will be extremely difficult. I don't know whether closely-related animals such as the chimpanzee experience adolescent brain development of a sort that could provide a model for the brain changes of man.

†This hypothesis stems from the observation that all drugs effective in the treatment of schizophrenia block dopamine receptors and produce extra-pyramidal symptoms. Of course, it remains possible that neuroleptics act to reverse a dysfunction which has its origin in non-dopaminergic systems. Under this circumstance, they would ameliorate schizophrenia by altering the balance between (normal) dopaminergic and the (unknown) abnormal brain systems.

complete dis-connection or dis-integration; the abnormality is therefore likely to be quantitative rather than qualitative, perhaps explaining its elusiveness. [Investigators (including this writer), who have worked in facilities that care for patients with chronic schizophrenia, have sometimes observed startling remissions in patients who had been unequivocally schizophrenic for many years. The fact that schizophrenic symptoms of long duration can occasionally remit raises the possibility that none of the behavioral changes observed in this illness is of necessity irreversible and should further encourage research.]

The idea of searching for quantitative abnormalities of synaptic arrangements in a brain with ten billion neurons, each capable of several hundred thousand synaptic connections, is unlikely to inspire even the most obsessive neuroanatomist. Some narrowing of the search is suggested by the available evidence regarding axonal elimination in late development and in the neonatal period; these data were recently summarized by PURVES and LICHTMAN (1980). They point out that, as with programmed cell death, axonal elimination appears controlled by feedback from the target cell, and that the innervating neurons appear to compete for some trophic factor required to maintain the connection. Availability of this trophic factor depends upon neural activity and, during the early development of some systems, it has been shown that asynchronous input to the target favors axonal elimination.

If schizophrenia results from a defect in synaptic elimination programmed to occur during adolescence, the following sequence of events might be hypothesized:

In early adolescence the neuronal environment changes in some way to accelerate sharply a process of synaptic elimination that has been taking place during childhood at a slower rate. It is a reasonable guess that this change in milieu is under endocrine control. The control may be exercised by determining the availability of, or the requirements for, the trophic factor that maintains synaptic connections. In at least one instance of programmed cell death, this factor is a protein, nerve growth factor (PURVES, 1980). As a result of some abnormality in this process, too many, too few or the wrong synapses are eliminated. (Regrettably, we have no basis to choose among these possibilities.) As a consequence of this "bug" in the genetic program, defects of neuronal integration develop, producing the symptomatology of schizophrenia. If dopamine systems are directly involved in the etiology of this illness, they may act by affecting in some deleterious way the production of or response to the trophic factor. Dopamine is already known to play the major role in controlling the level of one neuropeptide (prolactin) and it is of special interest that a subgroup of mesolimbic neurons contains both dopamine and cholecystokinin (HÖKFELT *et al.*, 1980).

Taken along with our earlier comments, these considerations suggest that research directed towards discovering proteins or peptides that act as trophic factors controlling synaptic maintenance/elimination involving integrative or feed-forward neurons—and that are themselves controlled by or interact with dopamine—might shed light on the etiology of schizophrenia. The production of, or requirements for, this substance should change markedly in early adolescence and might show a curve parallelling those shown in Figs 1 and 2. Since our understanding of these processes is so rudimentary, these suggestions point more for a direction of basic than of clinical research.

A more practical implication of our speculations applies to investigations of children who are at high risk for schizophrenia because one or both parents suffer from the illness. These studies tend to focus mainly on the years of infancy and early childhood. The hypothesis advanced here suggests that at least equal emphasis should be placed on the adolescent years, since the biological abnormality being sought may not be expressed before puberty.

One need hardly emphasize the speculative nature of this discussion. The probability of guessing correctly the brain mechanisms causing schizophrenia is, with our limited knowledge, vanishingly small. I hope, nevertheless, that this essay will prove useful to psychiatrists in at least three respects: first, by reminding our profession that we don't know why schizophrenia usually has its onset in adolescence and that this phenomenon remains an important part of the puzzle. Secondly, by pointing to the widespread evidence that a major reorganization of brain function underlies the behavioral changes of adolescence and that this possibility must be taken into account in psychological theorizing. Thirdly, by directing attention to the phenomena of neuronal competition in programmed cell death and synaptic elimination, phenomena that are extraordinarily interesting as mechanisms that evolved to regulate brain development and, to an as yet unknown degree, its continued function. The broad importance of these processes was suggested by PURVES (1980) who recently commented:

> "Neuronal competition is thus emerging as the denominator of important processes (neuron death, neonatal synapse elimination both in the periphery and centrally, synapse proliferation and regression in maturity) that previously seemed unrelated. As such, it is likely to be one of the dominant themes in neurobiology for some time to come" (p. 586).

ADDENDA

1. HUTTENLOCHER *et al.* (1982) have recently reported findings in the visual cortex that are consistent with his initial observations in frontal cortex. In visual cortex, the decline to the adult level of synaptic density is completed earlier (at about age 11 yr) than in frontal cortex, as might be expected for a simpler and less plastic system. Huttenlocher *et al.* also showed that the change in synaptic density was not an artifact of a change in cortical volume. The volume of the visual cortex, whose boundary is anatomically delimited (in contrast to that of frontal cortex) and thus susceptible to measurement, reaches its adult level at about 2 yr of age. One hopes that these observations will stimulate further investigations so that reliable age curves for synaptic development can be compared to those for other aspects of brain development.

2. A molecular basis for the late brain maturational changes proposed here is suggested in a recent report by N. CHAUDHARI and W. E. HAHN (1983). They found a progressive increase in complex, non-polyadenylated [poly(A)$^-$] messenger RNAs with age in mice. These rare poly(A)$^-$ sequences may act as regulatory genes. They are absent at birth and the full complement is not reached until young adulthood. Chaudhari and Hahn note that "Surprisingly, about 20 percent of the adult poly(A)$^-$ mRNA complexity ($\sim$18,000kb) is absent from the polysomes even after 35 days of postnatal development, suggesting the appearance of $\sim$10,000 new proteins in the brain during the period of development from

'adolescent' to young adult . . ." (p. 926). These studies were carried out in the mouse but, as Chaudhari and Hahn point out, "The extensive genetic program that emerges during a few days of postnatal development of the mouse brain, if also the case for the human brain, may take years to complete. It is likely that various environmental inputs, including a wide array of social interactions, influence the outcome of postnatal development of the brain more in some species than in others" (p. 927). These suggestions are entirely consistent with our own speculations. Moreover, the work of Chaudhari and Hahn offers an important new direction for research on this problem.

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REFERENCES

BLEULER, E. (1950) *Dementia Praecox or the Group of Schizophrenias* (Translated by ZINKIN, J.). International Universities Press, New York.

BORBELY, A. A. (1982) Sleep/wake-dependent and circadian aspects of sleep regulation. Paper presented at the Sixth European Congress on Sleep Research, Zurich, Switzerland.

BORBELY, A. A., BAUMANN, F., BRANDEIS, D., STRAUCH, I. and LEHMANN, D. (1981) Sleep deprivation: effect on sleep stages and EEG power density in man. *Electroenceph. clin. Neurophysiol.* **51**, 483–493.

CHANGEUX, J.-P. and DANCHIN, A. (1976) Selective stabilization of developing synapses as a mechanism for the specification of neuronal networks. *Nature* **264**, 705–712.

CHAUDHARI, N. and HAHN, W. E. (1983) Genetic expression in the developing brain. *Science* **220**, 924–928.

CONEL, J. L. (1939–1963) *The Post-Natal Development of the Human Cerebral Cortex*, Vols I–V. Harvard University Press, Cambridge, MA.

COURCHESNE, E. (1977) Event-related brain potentials: comparison between children and adults. *Science* **197**, 589–592.

COWAN, W. M. (1973) Neuronal death as a regulative mechanism in the control of cell number in the nervous system. In *Development and Aging in the Nervous System* (Edited by ROCKSTEIN, M.), pp. 19–41. Academic Press, New York.

CRAGG, B. G. (1975) The density of synapses and neurons in normal, mentally defective and ageing human brains. *Brain* **98**, 81–90.

DOBBING, J. and SANDS, J. (1973) Quantitative growth and development of human brain. *Arch. dis. Child.* **48**, 757–767.

DREYFUS-BRUSAC, C., SAMSON, D., BLANC, C. et MONOD, N. (1958) L'electroencephalogramme de l'enfant normal de moins de 3 ans. *Etudes neonatal* **7**, 143–175.

ELUL, R. (1972) The genesis of the EEG. In *International Review of Neurobiology*, Vol. 15 (Edited by PFEIFFER, C. C. and SMYTHIES, J. R.), pp. 228–272. Academic Press, New York.

EVARTS, E. V. (1971) Feedback and corollary discharge: a merging of the concepts. *Neurosci. Res. Prog. Bull.* **9**, 86–112.

FEINBERG, I. (1974) Changes in sleep cycle patterns with age. *J. psychiat. Res.* **10**, 283–306.

FEINBERG, I. (1976) Functional implications of changes in sleep physiology with age. In *Neurobiology of Aging* (Edited by GERSHON, S. and TERRY, R. D.). Raven Press, New York.

FEINBERG, I. (1978) Efference copy and corollary discharge: implications for thinking and its disorders. *Schizophrenia Bull.* **4**, 636–640.

FEINBERG, I. (1982) Schizophrenia and late maturational brain changes in man. *Psychopharmac. Bull.* **18** (3), 29–31.

FEINBERG, I, and CARLSON, V. R. (1968) Sleep variables as a function of age in man. *Archs gen. Psychiat.* **18**, 239–250.

FEINBERG, I. and EVARTS, E. V. (1969) Changing concepts of the function of sleep: discovery of intense brain activity during sleep calls for revision of hypotheses as to its function. *Biol. Psychiat.* **1**, 331–348.

FEINBERG, I. and FLOYD, T. C. (1982) The regulation of human sleep: clues from its phenomenology. *Hum. Neurobiol.* **1**, 185–194.

FEINBERG, I. and HIATT, J. F. (1978) Sleep patterns in schizophrenia: a selective review. In *Sleep Disorders: Diagnosis and Treatment* (Edited by WILLIAMS, R. L. and KARACAN, I.), pp. 205–231. John Wiley, New York.

FEINBERG, I., HIBI, S. and CARLSON, V. R. (1977) Changes in the EEG amplitude during sleep with age. In *Aging Brain and Senile Dementia* (Edited by NANDY, K. and SHERWIN, I.), pp. 85–98. Plenum Press, New York.

FEINBERG, I., KORESKO, R. L. and HELLER, N. (1967) EEG sleep patterns as a function of normal and pathological aging in man. *J. psychiat. Res.* **5**, 107–144.

FEINBERG, I. and LAYCOCK, F. (1964) The ability of blindfolded children to use landmarks to locate a target. *Child devel.* **35**, 547–558.

FREYHAN, H. A., WOODFORD, R. B. and KETY, S. S. (1951) Cerebral blood flow and metabolism in psychoses of senility. *J. nerv. ment. Dis.* **113**, 449–456.

GOODIN, D. S., SQUIRES, K. C., HENDERSON, B. H. and STARR, A. (1978) Age-related variations in evoked potentials to auditory stimuli in normal human subjects. *Electroenceph. clin. neurophysiol.* **44**, 447–458.

HAMBURGER, V. and OPPENHEIM, R. W. (1982) Naturally occurring neuronal death in vertebrates. *Neurosci. Commentaries* **1** (2), 39–55.

HÖKFELT, T., JOHANSSON, O, LJUNGDAHL, Å., LUNDBERG, J. M. and SCHULTZBERG, M. (1980) Peptidergic neurones. *Nature* **284**, 515–521.

HUTTENLOCHER, P. R. (1979) Synaptic density in human frontal cortex—developmental changes and effects of aging. *Brain Res.* **163**, 195–205.

HUTTENLOCHER, P. R., DE COURTEN, C., GAREY, L. J. and VAN DER LOOS, H. (1982) Synaptogenesis in human visual cortex—evidence for synapse elimination during normal development. *Neurosci. Lett.* **33**, 247–252.

INNOCENTI, G. M. (1981) Growth and reshaping of axons in the establishment of visual callosal connections. *Science* **212**, 824–827.

IVY, G. O. and KILLACKEY, H. P. (1982) Ontogenetic changes in the projections of neocortical neurons. *J. Neurosci.* **2** (6), 735–743.

JACKSON, J. H. (1958) *Selected Writings*, Vol. I (Edited by TAYLOR, J.). Basic Books, New York.

KASAMATSU, T. and PETTIGREW, J. D. (1976) Depletion of brain catecholamines: failure of ocular dominance shift after monocular occlusion in kittens. *Science* **194**, 206–209.

KETY, S. S. (1956) Human cerebral blood flow and oxygen consumption as related to aging. *Assoc. Res. nerv. ment. Dis.* **35**, 31–45.

KETY, S. S. and SCHMIDT, C. F. (1948) The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedure and normal values. *J. clin. Invest.* **27**, 476–484.

LASSEN, N. A., FEINBERG, I. and LANE, M. H. (1960) Bilateral studies of cerebral oxygen uptake in young and aged normal subjects and in patients with organic dementia. *J. clin. Invest.* **39**, 491–500.

MAY, J. (1931) The dementia praecox—schizophrenia problem. *Am. J. Psychiat.* **88**, 401–466.

MORUZZI, G. (1966) The functional significance of sleep with particular regard to the brain mechanisms of underlying consciousness. In *Brain and Conscious Experience* (Edited by ECCLES, J. C.), pp. 345–388. Springer, New York.

O'LEARY, D. D. M., STANFIELD, B. B. and COWAN, W. M. (1981) Evidence that the early postnatal restriction of the cells of origin of the callosal projection is due to the elimination of axonal collaterals rather than to the death of neurons. *Devl Brain Res.* **1**, 607–617.

PARMALEE, A. H., JR., WENNER, W. H., AKIYAMA, Y., STERN, E. and FLESCHER, J. (1967). Electroencephalography and brain maturation. In *Regional Development of the Brain in Early Life* (Edited by MINKOWSKI, A.). Blackwell, Oxford.

PETTIGREW, J. D. and KASAMATSU, T. (1978) Local perfusion of noradrenaline maintains visual cortex plasticity. *Nature* **271**, 761–763.

PURVES, D. (1980) Neuronal competition. *Nature* **287**, 585–586.

PURVES, D. and LICHTMAN, J. W. (1980) Elimination of synapses in the developing nervous system. *Science* **210**, 153–157.

SATZ. P. and BULLARD-BATES, C. (1981) Acquired aphasia in children. In *Acquired Aphasia* (Edited by SARNO, M. T.), pp. 399–426. Academic Press, New York.

TRUMAN, J. W. and SCHWARTZ, L. M. (1982) Insect systems for the study of programmed neuronal death. *Neurosci. Commentaries* **1** (2), 66–72.

WILLIAMS, R. L., KARACAN, I. and HURSCH, C. J. (1974) *Electroencephalography (EEG) of Human Sleep: Clinical Applications.* John Wiley, New York.