Sibling Patterns in Schizophrenia

It has been hypothesized that siblings in different positions within the family constellation are subject to varying degrees of stress (*1, 2*). Owing to this factor, the first-born sibling is not infrequently presented as having significantly greater difficulties in adjustment than the later born (*3*). Since stress is believed to be an etiological variable in schizophrenia, attempts were made to establish the existence of a definite relationship between sibling position (especially that of the first-born) and the incidence of this disease in a large sample (*1*). This relationship has, however, never been satisfactorily established (*4*). In the majority of studies, families of all sizes, as well as families that are most probably incomplete—containing other psychotic siblings, siblings who have died, and so on—are included in the samples. Thus, the conclusions lack consistency, in part at least, because of shortcomings in statistical design or analysis (*5*). An attempt was made in the study discussed in this report to investigate the hypothesized relationship between sibling position and incidence of schizophrenia in such a way as to minimize the errors mentioned.

The data were collected during 1955 and 1956 at Warren State Hospital, Warren, Pennsylvania. The cases studied were restricted to schizophrenic patients with two normal siblings and were drawn from the following sources: the files of such patients present in the hospital for more than 2 years and the files of such patients discharged over a period of 15 years. The information recorded in each file included the age and the sex of the patient and of his siblings, so that ordinal position by sex could be determined. Families containing adopted children or stepchildren, twins, triplets, or siblings who had also been hospitalized for any mental disease were rejected. Also excluded were cases in which a sibling had died before the patient reached his 20th year, or in which the clinical diagnosis was primarily of mental deficiency or organic central nervous system disease. To insure inclusion of only completed families, only those cases were approved in which the youngest sibling was over 10 years of age.

These conditions were set in the hope that, if there were an ordinal positional effect, it would be most clearly demonstrated where only one of the three siblings developed schizophrenia. Patients with only two siblings were selected in order to limit and define ordinal positional effects and also to facilitate the evaluation of the role of the sex of the patient and siblings in the constellation.

Table 1 summarizes sibling constellations and sex distribution of 156 cases which met all criteria. Since, during the period covered by this study, the male first-admission rate to mental hospitals for schizophrenia was generally 15 percent lower than the female rate, an appropriate correction factor for sex incidence was introduced. Approximate expectancies for the case distribution, by sibling, were calculated for each constellation. The results are summarized in Table 2.

Chi-square tests were carried out for each constellation that appeared to depart substantially from expectation. None of these tests indicated statistically significant departures from expected incidence rates—that is, no ordinal position appears to carry specific vulnerability to schizophrenia within the three-sibling constellation.

Table 1. Schizophrenic index cases by sibling constellation. (M, male; F, female.)

Sibling constellation by sex			No. of representatives within each constellation and ordinal position			
Ordinal position						
1st	2nd	3rd	Total cases	1st	2nd	3rd
M	M	M	12	6	3	3
M	M	F	20	5	6	9
M	F	M	23	3	9	11
F	M	M	17	5	7	5
F	F	M	24	12	7	5
F	M	F	30	13	5	12
M	F	F	18	6	4	8
F	F	F	12	5	5	2
Totals			156	55	46	55

Table 2. Corrected anticipated incidence, by sibling constellation. (The figures in this table were computed across, separately for each constellation. Totals were obtained by addition.)

Sibling constellation			Breakdown by patient			
Ordinal position			Total cases	Ordinal position		
1st	2nd	3rd		1st	2nd	3rd
M	M	M	12.0	4.0	4.0	4.0
M	M	F	20.0	6.3	6.3	7.4
M	F	M	22.9	7.2	8.5	7.2
F	M	M	17.1	6.3	5.4	5.4
F	F	M	24.0	8.4	8.4	7.2
F	M	F	29.9	10.5	8.9	10.5
M	F	F	18.0	5.4	6.3	6.3
F	F	F	12.0	4.0	4.0	4.0
Totals			155.9	52.1	51.8	52.0

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Persistent Patterns of Wakefulness in the Pretrigeminal Midpontine Preparation

It is well established that wakefulness and its electroencephalographic correlate, low-voltage, fast activity, are maintained by a tonic barrage of impulses arising in the brain-stem reticular formation (*1, 2*; also *3*). Behavioral and electroencephalographic sleep patterns are precipitated when the midbrain reticular formation is widely injured but the classical sensory paths are spared; conversely, interruption of the latter pathways at the midbrain level, with the medially placed reticular formation left intact, does not modify alert behavior and waking electroencephalographic patterns (*2*).

The problem of finding what is the lowest level of brain-stem transection which still permits synchronized electro-

encephalographic patterns throughout the neocortex is of considerable importance, as is that of determining the critical amount of reticular formation which has to remain connected to the cerebrum in order to maintain vigilance. Working with acute preparations, Rossi and Zirondoli (*4*) showed that electroencephalographic sleep patterns were elicited when the transection was slightly rostral to the origin of the trigeminal roots (pretrigeminal section); more caudal lesions, in which all or part of the trigeminal afferent fibers were left intact (posttrigeminal section), were followed by waking electroencephalographic patterns. Later Roger, Rossi, and Zirondoli (*5*) contributed experiments suggesting that the different electroencephalographic patterns displayed by the two types of preparations were dependent, respectively, on the maintenance or the elimination of the tonic flow of afferent trigeminal impulses. However, new data and a revised interpretation are provided by the experiments reported here (*6*).

Under ether anesthesia and with aseptic techniques, cats carrying screw electrodes implanted in the skull were subjected to complete electrolytic transection of the brain stem at the pontine level. In all instances, and as controlled by serial histological examination, the transection was such as to interrupt all connections between the trigeminal nerves and the cerebrum (pretrigeminal section). All animals showed spontaneous respiration and decerebrate rigidity. Our observations always started immediately after completion of the experimental procedures, and most preparations were followed for long periods of time—that is, up to 9 days after the pontine transection. The electroencephalogram was recorded on an ink-writer from frontal, parietal, and occipital areas of both hemispheres. The behavioral tests were limited to observations of spontaneous and provoked ocular movements and changes in pupillary diameter, the third and fourth pairs of cranial nerves being the only motor pathways leaving the central nervous system rostral to the transection.

When the transection was performed through the middle part of the pons [pretrigeminal midpontine preparation (Fig. 1*A*)], the electroencephalographic patterns consisted of low-voltage, fast rhythms, similar to those characteristic of alert behavior in the normal cat. A peculiar feature was their persistence throughout the survival time, with only infrequent and short-lasting interruptions by sleep patterns (characterized by high-voltage, slow waves). Hourly electroencephalographic examination, for not less than 24 consecutive hours, of the same cats before and after midpontine transection brought out some striking differences. While the normal intact cats, when isolated in a quiet environment, would display low-voltage, fast electroencephalographic activity for not more than 20 to 50 percent of the total recording time, a waking electroencephalographic pattern persisted in the midpontine preparations for at least 70, and frequently 90, percent of the total time of recording, in spite of the complete absence of any intentional stimulation.

Separate controls showed that the low-voltage, fast rhythms corresponded to the usual electroencephalographic patterns of wakefulness. The possibility that there was abnormal flattening due to depression or deterioration of cortical neurons was disproved by the following evidence: (i) The arterial pressure ranged from 120 to 140 mm-Hg; (ii) no cerebral edema was present; (iii) cortical excitability was good, as demonstrated by the response of the visual area to photic stimuli and to topical application of 0.1-percent strychnine; and (iv) spindle bursts and slow waves could be reversibly induced by small amounts of pentobarbital. Furthermore, the low-voltage, fast activity was usually accompanied by behavioral correlates suggestive of wakefulness. As a matter of fact the midpontine preparation was able to follow with vertical eye movements an object entering its visual field and sometimes reacted with pupillary dilatation to an emotional stimulus, such as the presentation of a dog or a mouse. Although it may be doubtful that the eye movements observed in our experiments were a sign of conscious behavior, it should be stated that such eye movements were absent whenever electroencephalographic sleep patterns were being recorded. Hence, our data provide convincing evidence that the normal sleep-wakefulness rhythm, or at least its electroencephalographic correlate, is definitely altered by a midpontine transection and replaced by an enduring state of vigilance. However, there is no evidence suggesting a parallel increase in the intensity of alertness.

An opposite alteration of the sleep-wakefulness rhythm was induced by slightly more rostral transections of the pons [pretrigeminal rostropontine preparations (Fig. 1*B*)], which were followed by lasting patterns (up to 7 days) of electroencephalographic synchrony, associated with the usual ocular signs of sleep (such as myosis and lack of purposeful eye movements). These lesions probably correspond to Rossi and Zirondoli's "pretrigeminal" transections.

One important conclusion must be emphasized. Of the two preparations (the "rostropontine" and the "midpontine pretrigeminal" cats, both connected to sensory receptors through the first two cranial nerves only), the former displays a permanently synchronized electroencephalogram, whereas the latter shows a clear-cut desynchronization. Thus, the critical factor is the injury or the integrity of a small amount of nervous tissue lying in the rostral part of the pons.

The shift in the normal sleep-wakefulness rhythm toward a state of endur-

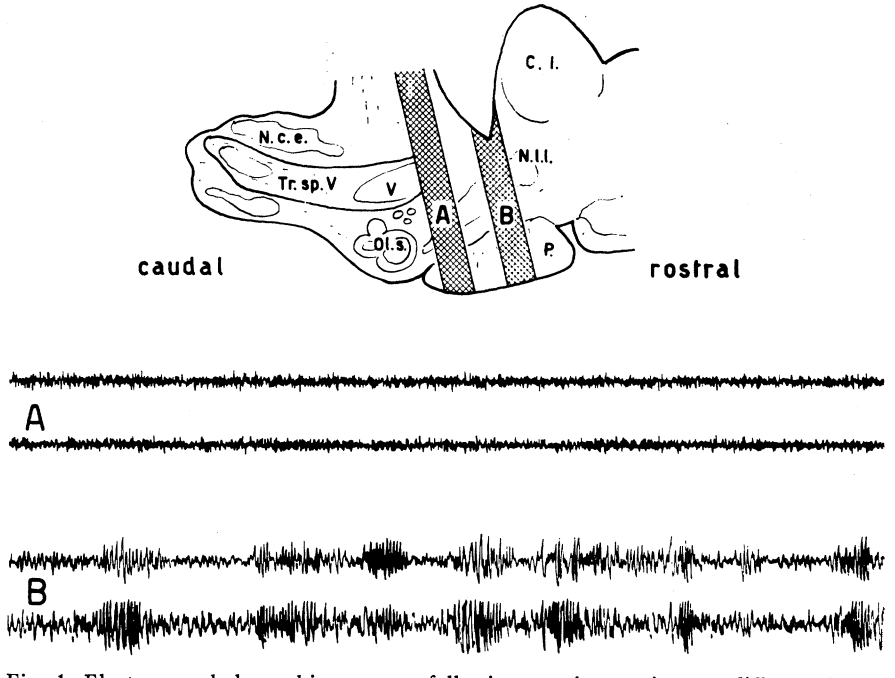

Fig. 1. Electroencephalographic patterns following pontine sections at different levels. In a sagittal view of the brain stem of a cat are schematically reproduced the levels of midpontine (*A*) and rostropontine (*B*) transections. Samples of the corresponding electroencephalographic patterns (recorded from right and left frontal areas, respectively) appear below the diagram. *C.i.*, inferior colliculus; *N.c.e.*, nucleus cuneatus externus; *N.l.l.*, nucleus of lateral lemniscus; *Ol.s.*, superior olive; *P.*, brachia pontis; *Tr.sp.V.*, spinal tract of trigeminal nerve; *V.*, pontine trigeminal sensory nucleus.

ing wakefulness which seems to be characteristic of the midpontine preparation deserves more attention, and its mechanisms are being presently investigated (7). Suffice it to say here that the behavioral and electroencephalographic patterns of the "midpontine" animal do not appear to result from hypoventilation and consequent hypercapnia, as demonstrated by blood gas measurement before and after appropriate brain-stem transection (7). A synchronizing, or possibly sleep-inducing, influence exerted by some structure in the caudal brain stem can be tentatively envisaged, and its existence will be tested experimentally. This might provide a new interpretation of Roger, Rossi, and Zirondoli's finding (5) that trigeminal deafferentation precipitates electroencephalographic sleep patterns in the *encéphale isolé* cat.

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Delayed Deaths in Sublethally X-rayed F_1 Hybrid Mice Injected with Parental Strain Spleen Cells

Essentially permanent protection against death from radiation exposure (that is, protection for a large fraction of the normal life span) is afforded in mice subjected to amounts of x-irradiation that would otherwise be lethal, by the injection of normal bone marrow cells taken from isologous mouse donors (mice of the same inbred strain). Following the injection of hematopoietic cells from homologous donors (mice of a different genetic strain), protection against radiation death is either greatly decreased (1) or is of only temporary duration, and the phenomenon of "late" or "homologous deaths" during the fourth week and later becomes evident (2). During the course of studies (3) on the role of the lymphoid tissues in this "homologous disease" (4), it was observed that the injection of normal parental strain spleen cells into nonirradiated, or into sublethally x-irradiated, F_1 hybrid mice resulted in delayed deaths (5).

Ten-month-old male mice (strain C57L × A, F_1 hybrids) were the recipients. The donors of the spleens were 10- to 25-week-old mice of the A strain. Nonirradiated LAF_1 mice, and also mice exposed to a sublethal radiation dose [500 r of 250-kvp (peak) x-rays] received a single intraperitoneal injection of A-strain spleen cells, as homogenate, in Tyrode's solution containing 4 mg of penicillin. The results are summarized in Table 1. It is evident that the injection of A-strain spleen cells leads to delayed deaths—in mice irradiated with 500 r during the second, third, and fourth weeks and in nonirradiated mice, at 3 to 8 weeks. The lethal effect in the nonirradiated mice appeared to be dependent in part on the size of the spleen cell inoculum—the larger the number of cells injected, the earlier the deaths. The general appearance of these mice (Fig. 1) is reminiscent of that of irradiated mice with homologous disease following injection of homologous bone marrow; debilitation, body-weight loss, and atrophic spleen and thymus were noted. The lethal effect could not be duplicated by the injection of LAF_1 spleen cells into other LAF_1 mice or into A-strain mice.

It seems plausible that the above-described phenomenon is in the nature of a reaction against the host—possibly the homograft type of reaction (6)—of injected spleen cells capable of producing immunoreaction. Since A-strain mice are known to have the specific histocompatibility antigen (designated *H-2*^{a}) at the *H-2* gene locus (7), and since C57L mice are known to have a different specific antigen (*H-2*^{b}), it is evident that LAF_1 mice contain both antigens and, therefore, that A-strain spleen cells are not "foreign" antigenically to the immunological apparatus of LAF_1 mice. On the other hand, the tissues of the LAF_1 host contain an antigen (*H-2*^{b}) that is "foreign" to the A-strain spleen cells injected

Fig. 1. Typical "homologous disease" in mouse of strain LAF_1 previously subjected to sublethal dose (500 r) of x-irradiation, 35 days after injection of 12×10^6 nucleated cells from A-strain mice.

into their midst. Under these circumstances, immunological reactivity can take place only in one direction, and we see, in effect, the "rejection" of the host tissues by the injected A-strain spleen cells.

The similarities between the above phenomenon and that of "homologous disease" in x-irradiated mice (at LD_{100} doses) injected with homologous bone marrow cells is perhaps more than fortuitous. It is suggested that this latter syndrome may be a consequence, at least in part, of transfer of cells in the injected bone marrow suspension, capable (or potentially capable) of producing immunoreaction. According to this view, attempts to remove or inactivate such cells in the donor bone marrow could conceivably reduce the potential hazard of homologous reactions following the administration of nonisologous marrow as therapy for acute radiation sickness.

Note added in proof. It has been found (8) that the lethal effect of injected parental spleen cells is not duplicated by the injection of A-strain spleen cells lysed in distilled water, nor by injection of 40 mg of A-strain liver as a homogenate in Tyrode's solution. Thymus cells have been found to be much less active than cells from spleen. Thus 12×10^6 nucleated thymus cells (from

Table 1. Lethal effect of injected spleen cells from A-strain mice in normal and irradiated LAF_1 mice. Mice were injected a few hours after irradiation unless otherwise indicated; the number of test animals is shown in parentheses.

No. or wt of A-strain spleen cells injected	Radiation dose to recipient (r)	Mortality	
		No.	Days after irradiation
6.5×10^6	500 r	5 (5)	9, 10, 10, 12, 12
3.2×10^6	500 r	4 (4)	12, 12, 12, 28
16×10^6	500 r	1 (1)	12
(85 mg)	500 r	7 (7)	14, 17, 19, 19, 25, 26, 26
(82 mg)*	500 r	6 (6)	24, 26, 27, 31, 31, 20
6.5×10^6	None	1 (5)	55
16.4×10^6	None	5 (5)	24, 27, 28, 42, 42
33×10^6	None	4 (4)	17, 20, 20, 20

* Injected 6 days after irradiation.