Otolith Formation and Trace Elements:

A Theory of Schizophrenic Behavior

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Introduction

It seems only axiomatic to assume that schizophrenic behavior includes a multiplicity of patterns, as well as numerous contributing factors. Underlying any social factors which may trigger psychotic acts of behavior, there may often be some basic physiological factors as well. I sense that the current pendulum of thought about schizophrenia has swung almost entirely toward the search for a primary biochemical lesion within the brain itself. Indeed, whatever the basic cause(s) may be, one can expect to find certain biochemical or neurophysiological changes within the brain. However, despite numerous and hopeful discoveries of these sorts, we seem to be no closer to understanding the diversity of chemical, neurophysiological, or behavioral patterns in so-called psychotic individuals. It is, therefore, in the absence of any commanding evidence in these directions that my own interests in the development of the vestibular apparatus and its function in physiological equilibrium have been directed toward these age-old problems of psychological and emotional balance.

To establish a basis for these ideas, I will (1) review some of the literature which indicates some vestibular dysfunction in schizophrenic and autistic patients, (2) present some evidence for interrelationships of somatosensory deprivation and activity and behaviors stimulatory to the vestibular system, and (3) present some preliminary activity data for mice with and without normal otolith formation. In summary, it appears that any organism may develop a rather different repertoire of behavioral patterns if it lacks a normally efficient sensory system as important as the vestibular apparatus, or if this system is not adequately stimulated during critical periods of brain development. Our work might be relevant to these phenomena since we are studying congenital defects of the otoliths, the gravity receptors of the vestibular portion of the inner ear.

For biologists who have been trained to think only of five major senses, it may be necessary to develop the rationale for considering that vestibular function may be so important. Although most

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biologists know of the semicircular canals and otoliths, I fear that most persons think of these structures as relatively less important than, for example, the closely associated cochlea. However, it is well established that the vestibular apparatus is far more ancient phylogenetically than is the cochlea. All vertebrates and many invertebrates possess some sort of statolith, or gravity receptor.

Ontogenetically, it is interesting to note that vestibular function appears earlier than any other major sensory perception, except for oral tactile function as has been demonstrated in several vertebrates (Gottlieb,1971). Physiologically, the vestibular apparatus is stimulated by every movement of the head of that organism. Electrophysiologically, a continuous volley of neural impulses is transmitted from the end organs, the cristae and maculae, to the vestibular nucleus and thence to the cerebellum where the information is monitored. Only when movement of the head produces changes in the frequency of these continuous discharges (Goldberg and Fernandez, 1971), does it elicit an appropriate response, for example, counter-rolling and nystagmic movements of the eyes, or changes in muscle tonus. For the most part, of course, these are reflex reactions below the level of conscious awareness. They occur during wakefulness and in sleep. Only when the stimuli are intense enough, or when there is disharmony between the input from the two ears, do we become keenly aware of the effects of the vestibular system. For example, in the first condition, many persons are susceptible to motion sickness if they are unable to control their own repetitive stimulation by movement; in the second case, persons in whom one ear is more severely damaged than the other by trauma or disease are unable to tolerate sudden movements without acute periods of dizziness or nausea. Regardless of these facts, our coordinated movement is highly dependent upon the sensory input from the vestibular system.

Vestibular Dysfunction in Schizophrenia

There is an extensive body of literature suggesting a relationship between schizophrenia and vestibular function. Schilder (1933) provided the theoretical basis for such a relationship in which he related numerous behavioral and psychological characteristics to a vestibular impairment. Although he lacked convincing neurophysiological evidence, such information has been accumulated by at least 11 laboratories during the past 50 years (Ornitz, 1970). Most of this evidence has been based upon a reduced eye nystagmus in response to a variety of stimuli, including caloric, rotational, optokinetic, and galvanic stimulation.

In spite of Schilder's theoretical considerations of the role of otoliths, it must be emphasized that nearly all of the subsequent investigators have ignored or dismissed the possible involvement of otoliths as a primary factor in schizophrenia. The reasons for this are somewhat understandable since none of the well-defined symptoms (ataxia, falling, spontaneous nystagmus, nausea, etc.) normally associated with labyrinthine defects are evident and since there is so much variability in vestibular response among schizophrenics, even from one testing to the next (Colbert et al., 1959). Nevertheless, these ideas seem to be worth pursuing in light of more recent understanding of the otolithic organs.

The simplest clinical test for vestibular function has been the application of hot or cold water in the external ear canal, the so-called caloric stimulus. This stimulus presumably sets up convexion currents within the endolymph, inducing nystagmic movements of the eyes which are observable directly or recordable by electronystagmography. Most otologists assume that such currents stimulate one or more cristae, depending on the position of the head. A number of investigators have demonstrated that schizophrenics exhibit a reduction in number, frequency, and/or duration of nystagmus after caloric stimulation (Angyal and Blackman, 1940, and

Fitzgerald and Stengel, 1945, for additional earlier studies). Fitzgerald and Stengel (1945) carefully measured the caloric response following hot and cold stimulation of both ears. They found abnormal patterns of nystagmus in 23 of the 50 cases of schizophrenia. Moreover, nine of the 27 schizophrenics whose patterns were within normal limits on the first testing exhibited an abnormal pattern on subsequent testing.

The caloric stimulation was also used to determine its effect on a locomotor task performed by normals and schizophrenic subjects (Angyal and Sherman, 1942). Although all subjects were blindfolded and asked to mark time without changing their position or direction, the controls actually exhibited a greater degree of movement and rotation than did schizophrenics. Caloric stimulation of the ear opposite to the basal direction of rotation for that subject caused him to reverse his direction until the effects of the caloric stimulation diminished. Their analyses indicated that schizophrenics exhibited a shorter and less intense response to the caloric stimulation.

Nystagmus has also been observed in normals and schizophrenics after they were stopped suddenly from rotation in a Barany chair. Schizophrenics exhibited a reduction or absence of nystagmus under these conditions, and they seldom experienced any dizziness or nausea (Angyal and Blackman, 1940; Pollack and Krieger, 1958). Leach (1960) re-examined the effects of rotational stimulation, measuring nystagmus during the periods of angular acceleration and deceleration of the chair. He tested 96 normal subjects and 75 schizophrenics, each during three rates of angular acceleration and deceleration. He found that schizophrenics exhibited a longer latency 'period before nystagmus was evident and a shorter duration of nystagmus after coasting to a stop. During both acceleration and deceleration, the schizophrenics exhibited fewer nystagmic beats. Perhaps the most significant contribution of this study was the indication that the results were different for the three different velocities of angular acceleration and deceleration. For all criteria in which schizophrenics differed from the normal subjects, the difference was greatest at the lower velocity. This is rather convincing evidence that schizophrenics are less perceptive of milder stimuli, or contrariwise, that they require greater stimulation to exhibit a more nearly normal response.

Ritvo et al. (1969) have found that post-rotational nystagmus also exhibited a shorter duration in autistic children. Although they claim an ability to use nystagmography to distinguish between function of cristae and maculae, they present no evidence regarding the relative role of these two organs in autism or schizophrenia. Ornitz (1970) attempted to explain the vestibular dysfunction of autistic children on the basis of a supposed deficiency in central integration. However, this is not incompatible with the present suggestion that the end-organ itself may be less than normally efficient, especially during early stages of development. Similarly, MacCulloch and Williams (1971) attempted to explain these and other phenomena found in schizophrenics on the basis of a supposed lesion, perhaps caused by birth trauma, in the midbrain tract in the region of the vestibular nuclei. Interestingly enough, they have demonstrated that schizophrenics exhibit a much greater variability in the electric potential of the heart beat. It is conceivable, however, that such findings could be related to an impaired vestibular function, the effect of which is then transferred to the autonomic nervous system.

Besides caloric and rotational stimulation, schizophrenics have also been studied during optokinetic stimulation (Pollack and Krieger, 1958). Whereas normal subjects could move their eyes to follow a revolving pattern of stripes, schizophrenics could not dissociate head and eye movements. Even when requested to keep their head forward,

they would end up looking over their shoulder in the direction of movement of the revolving drum. These investigators even suggested that schizophrenics may exhibit "defective righting reflexes."

Galvanic stimulation has also been applied to the area of the temporal bone of normal and schizophrenic subjects (Dzendolet, 1963; Dzendolet and Moore, 1965). They did not know which cells were affected by the electric stimulation (0.5-4.0 cps), but they assumed that it may have selectively stimulated vestibular neurons. They found that head and eye nystagmus was significantly greater in schizophrenics for stimulation at 0.5 cps and that certain patterns of responsiveness over this range of stimulation were unique to schizophrenics. It is, of course, possible that this galvanic stimulation exerted its effect directly upon the cerebellum. It is interesting in this regard that Creak and Pampiglione (1969) found that 29 of 35 schizophrenics exhibited an abnormal EEC.

As for the effect of rotation on nystagmus there can be little doubt that the otoliths, as well as the cristae, are stimulated by angular acceleration. Although caloric stimulation has been assumed to cause its effect by producing convexion currents acting upon the cristae, it is also possible that the same currents, which necessarily flow over the utricular otolithic mass, could also stimulate the organ. Such an effect would be proportional to the size of the otolith, so that any reduced otolith which might be present in a schizophrenic subject would be less responsive to this stimulation. The same effect would be expected if stimulated by angular acceleration. Alternatively, the actual change in temperature, caused by caloric stimulation, of the neuroepithelial cells of the cristae and maculae may alter the continuous volley of signals sent from that ear, thus producing disharmony between input from the two ears.

In addition to such physiological data, Hubbard (1971) has presented considerable clinical evidence for an impaired vestibular function in schizophrenic patients. While analyzing the rise of the skyjacking phenomenon, he concluded that vestibular function was a major contributing factor in the development of behavior among such a select group of schizophrenics (skyjackers). He was impressed by the almost universal appearance of so-called crypto-vestibular signs, including persistent dreams of paralysis, flights of fantasy, body sensations of spatial disorganization, general incoordination in sports, and the necessity for excessive movement for a feeling of well-being.

Such clinical data, together with an appreciation for the development and function of the vestibular apparatus, led Hubbard (1971) to conclude that normal vestibular function is basic to establishment of spatial organization and emotional equilibrium. Moreover, it seems to him that gravity, the primary force to which the otoliths respond, is the most constant and reliable stimulus to which the organism must relate from birth until death.

Such clinical evidence is consistent with the physiological evidence suggesting some vestibular dysfunction in association with schizophrenia. Moreover the prominence of movement, real, verbalized, and/or fantasized, in schizophrenia, as well as the presence of stereotypic patterns of behavior among autistic children, supports my contention that to study patterns of total activity in mice with known vestibular defects is a valid means for pursuing these ideas experimentally.

With regard to otolith structure and function, the literature is replete with the notion that this part of the ear is as invariant as the formation of semicircular canals and cristae appear to be. However, otolith function is absolutely dependent upon the presence and density of the mass of otoconia. Recent studies, by techniques not requiring decalcification of these complex organic and calcium carbonate otoconia, have shown that they may be defective from embryonic development (Erway et al.,

1970, 1971; Erway and Mitchell, 1973; Purichia and Erway, 1972). Moreover, Lim (1973) has shown that there appears to be an elaborate mechanism for maintenance and turnover of otoconia within the adult ear. Johnsson (1971) and Johnsson and Hawkins (1972) have shown that significant losses of otoconia may occur in the human inner ear during the lifetime.

I postulate, therefore, that any genetic, nutritional, or other environmental factors which may affect the development or maintenance of otoliths may be a critical factor in one's sensory perception and brain development. Otoliths which are normally developed and adequately stimulated can provide an essential reference to that more or less constant field of gravity, and they also provide a valuable system for monitoring movements. Hence, otoliths appear to be essential for development of normal spatial perception.

Importance of Movement in Somatosensory Deprivation

The literature regarding somatosensory deprivation during critical ontogenetic periods of development has been reviewed by Prescott (1970). Among the numerous studies of so-called social deprivation, or isolation-rearing, of monkeys, motion-deprivation appears to be an important factor. Perhaps most convincing of all are the studies of Mason (1968) who reared monkeys in the manner of the classical Harlow monkeys. However, Mason provided a mechanically moving surrogate mother to which the youngster often clung for free rides and by which it was frequently stimulated by the randomness of movement of the surrogate. Unlike the usual Harlow monkeys which exhibit stereotypic patterns of behavior, these motion-stimulated isolates spent less time in contact with surrogate, more often moved about the cage, and were quicker to approach and to interact with people than were monkeys reared with stationary surrogates.

Prescott (1970) has also reviewed. anthropological evidence regarding child-rearing practices which relate to early motion stimulation and to precocious development of locomotor functions. Similarly, some experiments with regard to motion stimulation of premature infants has exhibited remarkable improvement in growth and well-being of such isolates (Neal, 1968).

As to what, if any, effect motion deprivation may have on the development of the brain itself, we may consider the studies of Essman (1971). He has reared mice in total isolation from 19 days after birth and has found marked changes in the nucleic acids and protein content of the brain. There is a vast body of literature suggesting that environmental enrichment causes significant increases in various parameters of brain development (Rosenzweig, 1972). What effect vestibular stimulation via locomotor activity might have on such development has hardly been considered.

It seems possible, therefore, that a deficiency of vestibular input, either for reasons of congenital defect or for lack of motion stimulation, may impair the early development and integrating capacities of the brain, especially that of the cerebellum. It is interesting to note that various sensory-deprivation conditions result in a morphologically detectable deficiency of interneuronal connections (Horn et al., 1973). These investigators were unable to explain the morphological differences solely in terms of visual sensory deprivation, but, ironically, they suggested that these differences might be due to differences in locomotor activity. I suggest that any locomotor activity will be monitored primarily by the vestibular apparatus, thus providing extensive stimulation and opportunity for development of the integrative functions of the brain. It is apparent from Prescott's reviews (1970, 1972) that the development and function of the vestibular-cerebellar axis is probably very critical to many other aspects of brain development.

Otolith Defects and Behavior in Mice

Our interests in otoliths first began with the so-called ataxic behavior of chicks, rats, and guinea pigs observed among progeny of manganese-deficient parents (Hurley, 1968). In addition, we were aware of similar behavioral defects among genetically mutant, pallid mice (Lyon, 1951). Knowing that the abnormal behavior in these mutant mice was due to an otolith abnormality, we demonstrated that the ataxia associated with manganese deficiency was also due to congenital otolith defects (Erway et al., 1966, 1970). Moreover, the otolith defect in pallid mice (Erway et al., 1971) and in pastel mink (Erway and Mitchell, 1973) could be prevented by manganese supplementation.

The manganese is required by the fetal mouse on or before the 15th day of gestation, immediately prior to the onset of formation of otoconial crystals. We have presented evidence that both manganese deficiency and the pallid gene affect the incorporation of radioactive sulfate into the otolith matrix which is composed of a mucopolysaccharide (Shrader et al., 1973). It is feasible that manganese becomes a rate-limiting cofactor for one or both of the enzymes associated with the biosynthesis of the mucopolysaccharide matrix, as has been demonstrated for a similar matrix in cartilage (Leach et al., 1969).

In addition to certain mutant genes and manganese, we have obtained evidence that zinc deficiency and drugs which affect carbonic anhydrase activity also cause otolith defects (Purichia and Erway, 1972). Zinc deficiency and dichlorophenamide affected otolith development even when fetuses were subjected to these treatments after the time at which otoliths were normally formed. This suggested that already formed otoconia may disintegrate, or decalcify, under these conditions which may presumably affect the pH of the endolymph. Carbonic anhydrase activity of the fetal and adult mouse ear is demonstrable, and it is inhibited by dichlorophenamide (Purichia, 1972).

Although both manganese and zinc appear to be essential for otolith development and/or maintenance, they exhibit different time-specific requirements, and they are presumably involved in these very different biochemical roles. Zinc deficiency and factors which may alter the availability of zinc are potentially significant contributors to changes in otolith integrity and function.

For the most part, our behavioral analyses have been restricted to relatively simple righting reflexes, testing whether or not the animals can maintain their balance in the water. This has provided a reliable diagnostic test for severe vestibular dysfunction, and it is well correlated with the reduction of otoconia within the utricle and saccule. However, morphologically detectable otolith defects often occur without any observable impairment in the swimming ability. A more detailed analysis of the swimming ability and otolith formation of another genetic mutant mouse, tilted head, has indicated that a few gigantic but strategically located crystals within the saccule are enough to enable some mice to maintain a vertical, "nose-up" position in the water (McGraw, 1973).

Regardless of the usefulness of the swimming test, we have begun to obtain data on more general patterns of behavior. In this regard, Lyon (1955) also observed that various mutant mice with otolith defects exhibited some rather stereotypic patterns of behavior, including head shaking, circling, and hyperactivity. We have observed the same phenomena in some of the pallid and tilted head mutant mice. Both of these genes affect otolith development, but they do so by different mechanisms.

In regard to the ontogenesis of righting reflexes, Gottlieb (1971) has pointed out that nothing is reported for mice, but 21-day-old fetal rats do exhibit head-righting and body-righting reflexes. Hurley and Everson (1959) demonstrated that young rats born to manganese-deficient mothers exhibited a delay in development of body-righting and

air-righting reflexes. Nevertheless, these manganese-deficient rats, which were later shown to exhibit otolith defects, did eventually develop righting reflexes, except when placed in the water (Hurley, 1968). The water environment apparently deprives the animal of adequate proprioceptive input.

Because of the argument that vestibular input is important to development of brain function, I wish to point out now that these manganese-deficient rats also exhibited an increased susceptibility to electroconvulsive shocks compared to normal rats (Hurley et al., 1963). It is feasible to consider that such vestibularly deprived animals failed to develop normal brain functions.

We have examined some righting reflexes and locomotor functions in the genetically mutant mice. The tilted head mice, which possess a few, gigantic otolithic crystals, exhibit a delay in body-righting and air-righting reflexes (McGraw, 1973). Likewise, the pallid mice exhibit a delay of several days in these righting reflexes (Anderson, 1973). More surprising, however, than the mere delay in development of righting reflexes, Anderson (1973) has shown that two-week-old pallid mice can barely cling to a fine wire mesh if the plane is inclined above 30 degrees, whereas their normal littermates can scamper up the plane even if it is inclined upwards of 70 degrees. However, by three weeks of age the pallid mice have also developed the skill to grasp and to climb the steep plane. It appears, therefore, that these pallid mice also exhibit a delay in the development of the locomotor coordination. Interestingly enough, one litter of pallid mice, which had been supplemented with manganese during gestation, exhibited no difficulty in climbing the plane at two weeks of age. Neither did they exhibit any delay in righting reflexes, nor any difficulty in swimming (Anderson, 1973).

Finally, I come to our current attempts to try to test the ideas presented above. We hope that our ability to manipulate otolith development by means of genes, manganese, zinc, and drugs, at least the sulfonamides, will enable us to determine how much of the variability in certain behaviors is related to the otoliths. To this end, I have devised a procedure for quantitating total activity of mice (any movement which will disturb an electromagnetic field generated by the Selective Activity Meter made by Columbus Instrument Co., Columbus, Ohio). This activity is recorded within the cage to which the mice are accustomed. The recordings are made for 24 hours or longer, and this can be repeated as often as desired. The data is printed out every six minutes and is available for any appropriate program of data processing and analysis. At present, the data is reduced to the number of motions/animal/six-minutes, and it is stored on computer disk files. It can be reduced to mean activity/12-hours/day and plotted on a much reduced histogram as indicated in Figure 1.

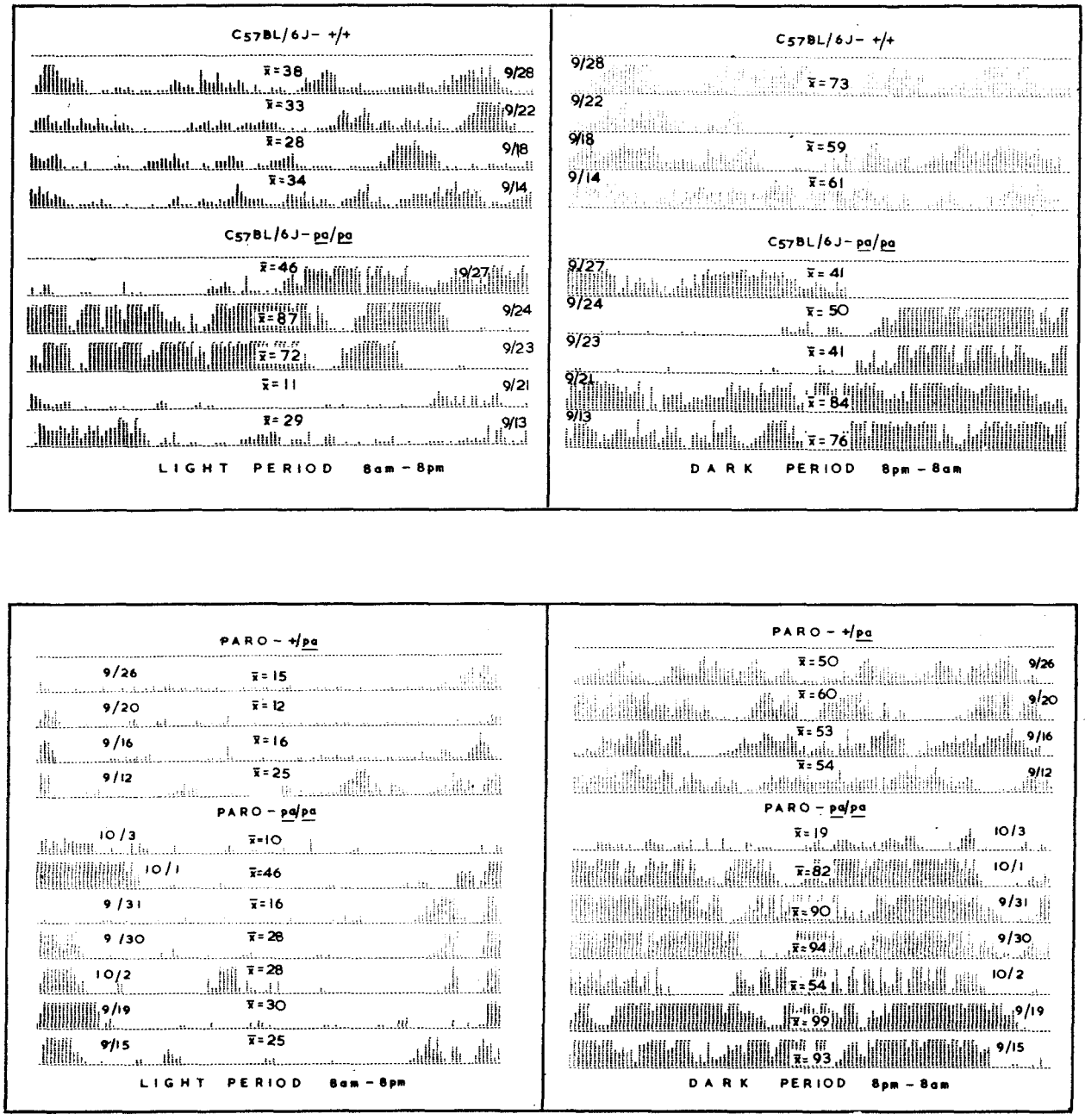
To illustrate the usefulness of this approach, we can make a genetic backcross (phenotypically normal heter-ozygotes, +/pa, crossed to mutant homozygotes, pa / pa) which will produce offspring in a 1:1 ratio of phenotypes like the parents. The heterozygous black offspring have normal otoliths, whereas the pallid mice, which have a dilute coat color and albino eyes, possess various degrees of otolith defects. These littermates are reared together until weaning age at about three weeks of age, and then the two genotypes may be separated for subsequent activity studies. The results which provided the basis of a preliminary report (Erway, 1973) are presented herein.

Four cages of female mice were used, including pallid and non-pallid mice from each of two different genetic inbred strains, C57BL/6J and one which we have called PARO simply because it contains the linked genes, pallid and rough. Each recording began at 8 a.m. for the date shown on the line, and it continued until 8 a.m. the next day when another cage was placed on the activity meter. The

lighting regime was set for 12:12, beginning with lights on at 8 a.m.

Twenty days worth of data has been reduced to as many lines in Figure 1. This representation enables the reader to appreciate some of the factors which contribute to the differences observed among these mice.

FIGURE 1



TOTAL ACTIVITY FOR TWO PALLID AND INBRED STRAINS OF MICE. Four cages of female mice were recorded for total activity during several 24-hour intervals for the dates indicated. Each column of the histograms represents a six-minute interval. Each character per column represents an average of 10 motions per animal, with the 12th character including all averages in excess of 120 motions per animal. The overall mean activity/animal/six minutes is shown separately for the light and dark periods.

1. **Diurnal pattern of behavior:** It is clear from the data, obtained from genetically normal mice of these two different inbred strains, that mice are, indeed, nocturnal animals, and that they exhibit approximately two to three times as much activity during the dark period as during the light period. If there is any significant difference between the control mice of these two inbred strains, it is that the PARO stock exhibits very little daytime activity. (The abrupt termination of data for 9/22 was due to technical failure.)

2. **Change in phase of activity:** In contrast to the relative uniformity of behavior among control mice, the two pallid groups exhibited considerable differences. The pallid mice of the C57BL/6J strain exhibited a marked variability among replicates, but this is most clearly accounted for by a phase shift in their pattern of activity. It is as though they had lost all sense of time, and they certainly did not remain entrained to the light-dark cycle as were the controls. Unfortunately, we could not determine from these data the actual phase of their activity since we did not have continuous recordings for more than two days at a time. We are obviously now planning to continuously record their activity for a week or more. Based upon these data alone, it is not clear whether or not the C57BL/6J pallid mice also exhibit more total activity than their controls.

3. **Increase in total activity:** Interestingly enough, pallid mice of the PARO inbred strain did not exhibit any marked shift of phase of activity. Instead, they exhibited nearly a 50 percent increase in total activity both day and night. For the first four or five replicates, these pallid mice exhibited a remarkably high and uniform pattern of nighttime activity. However, by 10/2 and especially by 10/3, their activity dropped extremely. The only suggestion of a phase shift in this pallid strain is noted by the height of activity during the first one to two hours after initiating the recorder for the day. Although cages were always changed at least 24 hours in advance of a recording, and extreme care was taken to gently move the new cage onto the recorder, approximately the width of the cage, these mice may have been more sensitive to that change, or to our presence, than any others appeared to be. This idea is supported by the observation that the pallid mice did not exhibit any such activity on 9/31 when no person entered the isolation room.

Clearly, there are many more factors than just otoliths which may contribute to the total activity of mice. We can see differences in patterns of activity in these two genetic strains. Moreover, the presence of the same mutant gene, pallid, within these two strains seems to produce two different effects, although I believe that both patterns may be a means of providing a compensatory stimulation for the same otolith deficiency. We have yet to test manganese-supplemented pallid mice to see if all or most of the differences in activity disappear. We are currently comparing the activity of normal, pallid, and tilted head mice, the genes for which are segregating in the same genetic stocks. The rather apparent hyperactivity of the tilted head mice can hardly be due to other effects of that gene, except on otoliths, since this gene has no pigment defect and does not respond to manganese supplementation as does the pallid genotype.

Summary

Arguments and some supportive evidence have been presented for considering that the vestibular sensor\ system, and especially the otoliths, may be uniquely important among all of the sensory organs in the development of normal, integrative functions of the brain, especially the cerebellum. On this basis, it is argued that any genetic or environmental factors which alter the normal development or maintenance of this elaborate, inertial-guidance system may affect the development of early locomotor functions. For example,

several mutations are known in experimental animals to cause congenital otolith defects. In addition, manganese and zinc are related to otolith development. Moreover, there is suggestive evidence that zinc deficiency, and drugs which may chelate zinc, may also affect the stability of otolith formation.

Development of righting reflexes and climbing ability is delayed in mice or rats with otolith defects. Moreover, adult pallid mice with otolith defects exhibit some altered patterns of total activity when tested for long periods of time within their own familiar cages.

On the basis of such morphological and physiological evidence for variability in otolith development in experimental animals, it is not unrealistic to assume that similar defects may occur during human development. It is worth noting that the less severe conditions which affect otolith development also permit a greater asymmetry between development of otoliths in the two ears. A complete absence of otoconia from both ears may be more tolerable to normal development than a disharmony of input from the two ears. Individuals can tolerate the absence of vestibular function in one or both ears, but apparent discordance of input from the two ears is almost unbearable in cases of injury or disease of an ear.

Even if the development of otoliths were normal, their usefulness as a source of spatial information would be proportional to the degree of stimulation received as that individual moves and interacts with its environment, especially during formative periods of development of brain function. In this regard, vestibular function may also be relevant to various forms of sensory deprivation in mice, monkeys, and man.

Although the other papers in this symposium give convincing evidence for a direct involvement of trace elements in brain function, I argue that it would be premature to ignore the possibility that trace elements might also affect the structure and function of the poorly understood vestibular organ. For example, it is feasible that the dramatically therapeutic effects of zinc and manganese supplementation on schizophrenic behavior (Pfeiffer and lliev, 1972) might also involve otolith function.

As global and unorthodox as these ideas regarding vestibular function may appear to be, I hope that this presentation may at least serve to focus our attention and research on some of the related problems in animal and human behavior, and perhaps even on certain psychological, social, and educational implications.

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