Vestibular Disorder and Space Utilization by Monkeys

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In an earlier paper (Riopelle and Hubbard, 1977) we reported on the behavior of monkeys whose mothers were deprived of manganese during pregnancy. Their performance on behavioral tests during the first two months of life was entirely within normal limits for most tasks but their clasping response to a ventrally placed cylinder was extraordinarily vigorous and their righting response, which required release from clasping, inadequate. Their persistent clinging probably reflected an insecurity or uncertainty regarding their bodily orientation in space. It is likely that the insecurity was caused by a defect in the vestibular system that was produced by the manganese deficiency.

Manganese deficiency in pregnant mice and rats prevents the formation of otoconia in the utricle and saccule in the fetuses. Such animals are ataxic, they show impaired righting reflexes, and they do not orient properly in water (Hurley, Everson, and Geiger, 1958; Erway, Hurley, and Fraser, 1-966; Erway, Hurley, and Fraser, 1970). The canals, the utricle, and the saccule respond to linear and angular acceleration, and they transduce orientationally generated mechanical energy into a nerve code which is transmitted to various higher centers in the brain. Any defect, either at the receptor site, along the transmission line, or at the receiving stations would distort the message. Either otoconial absence or nerve injury would produce functional defect.

Whereas otoconial defects produce receptor inadequacy, nerve incompetence can be produced through either surgical or chemical means. A number of drugs derived from the Actinomycetes are toxic to the inner-ear receptors and the eighth cranial nerve. One of them, the antibiotic, streptomycin, once useful for tuberculosis therapy,

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is especially toxic to the vestibular portion of the nerve. Many other drugs also attack the eighth nerve, but they are most damaging to the auditory portion of the nerve (Goodman and Cilman, 1955; Hinshaw and Feldman, 1945).

The possible role of the vestibular system in behavior disorders has been recognized since Schilder (1933). Never the most popular theory of the etiology of disorders such as autism and schizophrenia, defective vestibular function has nevertheless been noted repeatedly in such patients (Ritvo et al., 1969; Ornitz, 1970). Moreover, in light of the widely recognized necessity of early sensory stimulation for the normal development of associated central mechanisms to which receptors project, the diffuseness of vestibular projections should, when abnormal, cause us to expect development failure in diverse parts of the brain. Rather direct confirmation of the importance of defective otoconia (the calcite crystals in the inner ear which, because of their mass, serve to initiate the translation of linear acceleration and head tilt into neural codes) was seen in mice behavior. Some "pallid" mice mutants suffer agenesis of otoconia. They do not swim properly, they are ataxic, they cling excessively to an unstable support, they suffer loss of spatial orientation, and they show increased emotionality (Erwayetal., 1970).

Further evidence comes from the reported considerable balance dysfunction in persons who had been arrested for "skyjacking." These individuals resisted balance testing, had difficulty pivoting about slowly, and swayed when their eyes were closed. Some were late in beginning to walk, others had recurring dreams about flying, yet feared high places. Numerous other psychiatric symptoms were present, of course; nevertheless the prominence of balance-related symptoms was remarkably unlike that seen in other psychiatric populations (Hubbard, 1971). From this experience has evolved the hypothesis that persistent vestibular defect is likely to have deleterious effects on personality and on the exploitation of available space which far exceeds simple imbalance. The hypothesis gains further plausibility when we consider the turbulent, if not violent, responses of humans to an unstable footing, or to vertical oscillation as in a boat, or spinning as on a slow centrifuge. Pallor, pilomotor erection, goose pimples, nausea, fear, even terror, are easily produced in these and related circumstances.

The present study was designed to examine the possibility that such informational distortion if persistent would induce compensatory accomodational changes in behavior, particularly those activities which relate to the way in which animals deploy themselves in space (avoid heights, hide behind objects) when they are alone or when they are in the presence of another animal.

METHOD

Subjects

The subjects were nine male and five female rhesus monkeys between 1.2 and 4.0 years of age. They were assembled into three groups as follows: (a) two males had received 115 or 128 intramuscular injections of the ototoxic drug streptomycin sulfate (beginning at 20 mg/kg and increasing to 120 or 150 mg/kg) during a six month period which began at 24 or 60 days after birth, (b) four other males and two females whose mothers during both pregnancy and early postnatal life had been fed a diet containing neither manganese nor zinc, and (c) three more males and two other females whose mothers were not deprived during pregnancy and who themselves were fed a diet containing normal amounts of manganese and zinc. They served as controls.

Apparatus

A wire divider created a room within a room that was approximately 5 m long, 3 m wide, and 4 m high and served as the observation room. A wire screen near one end of the room and perpendicular to its major axis made another, slightly smaller room which contained the monkeys. Several devices, arranged to provide different heights for perching and climbing, were situated within the monkeys' portion of the room; included were a water trough 1 m wide, 3.3 m long, and .5 m deep; a triangular shelf 2 m long and .3 m wide placed 2 m above the trough; a rope 2 m long hanging from a pipe near the ceiling. Two stanchions, one in each distant corner from the wire screen provided perches at three height levels (1.8, .8, and .1 m). One stanchion was equipped with a vertical wire screen on its bottom portion and the other with a broad plank extending parallel to the rear wall at a height of .9 m and also with a short piece of rope hanging from the middle level; a ramp terminating onto a 3 m high standard was also present.

A closed-circuit television camera was placed in the observation room. The camera was pointed toward a mirror on the entrance door to achieve a wide-angle view of the monkeys' portion of the room. It was connected to a video recorder and television monitor located in an adjacent room.

Procedure

The animals were observed once while alone and twice while paired with another animal, once each with the animal next older and next younger. (Of course, the oldest and the youngest were observed only once in the social situation). Either condition was initiated by taking one or two animals from their home cage to the experimental room in a transfer cage. They were introduced into the testing chamber through a guillotine door. When the room was secured, the video camera was turned on and the door to the entire experimental room was closed, leaving the monkey(s) alone. They were then allowed time to become familiar with and to adjust to the experimental room and to each other; usually this took between 15 and 45 minutes. The television monitor and the video recorder in the adjacent room were turned on and observations began after the adjustment period.

The monkeys' behavior was recorded on video tape for 15 minutes. Emphasis in the analysis of the recording was placed on space utilization and on the emotional behavior. Two observers noted different classes of behavior, while an audio cassette tape recorder, connected to the video recorder, announced in order numbers from 1 to 60 once every 15 seconds. Each such interval served as the unit of observation. The observer, recording on a prepared data sheet, noted the first occurrence of any of the following behaviors: (a) Top, Middle, or Low Stanchion: the monkey was located at one height of the tall stands at the beginning of 15 sec. observational interval. His height was scored, (b) Top or Middle Ramp: the monkey was on the ramp or its attached stand, (c) Tank Edge or Water the monkey was on the rim of the tank or in the water, (d) Front Wire: the monkey was clinging to the front wire partition, (e) Floor the monkey was on the floor, (f) Rope: the monkey grasped onto or climbed the rope, (g) Pipe: the monkey climbed onto or along the pipe running near the ceiling, (h) Plank: the monkey walked or jumped on the cantilever plank extending horizontally from one of the stands, (i) Not In View: if the monkey was not visible during an interval, he was scored in this category.

The video tape was scored once for the Alone condition and it was scored twice for the Paired condition, once for each animal. The results with at least one entry in each category were analyzed by one-way analyses of variance with separate analyses performed for the alone and the paired condition.

RESULTS

Figure 1 shows the time spent in each category as a percentage of the time the monkeys were visible along with the percentage of total time they were not in view. Behavior patterns differed among the three groups. The streptomycin-treated monkeys spent most of the time off the floor and in the high places of the playroom (top stand and middle stand, Fig. 1), in both the Alone and the Paired condition. Also, they were the only ones that climbed along the pipe near the ceiling. The No Mn-Zn monkeys when alone were out of view most of the time, usually hiding behind the tank. When they were visible to the camera, they spent

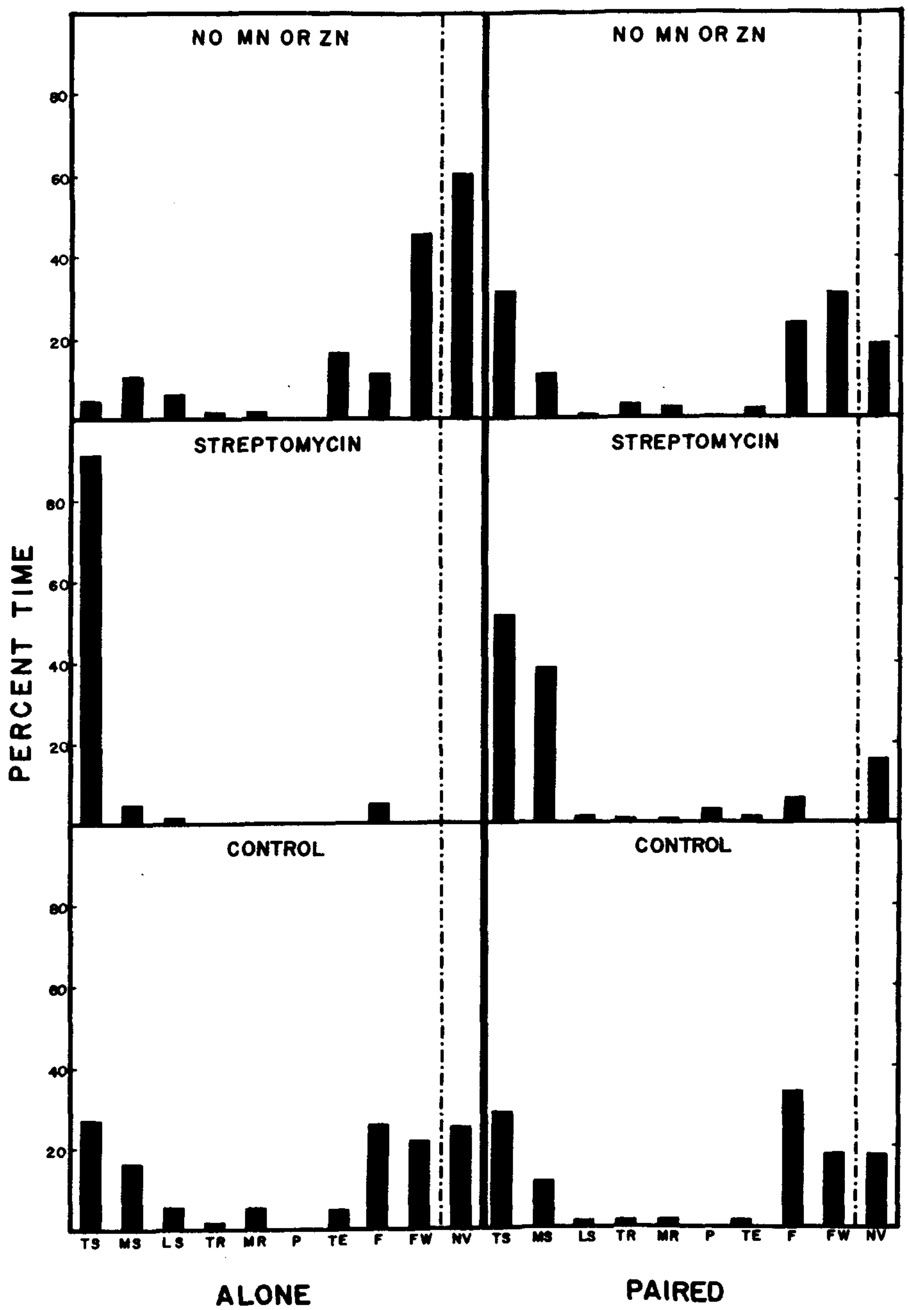

Figure 1

Percentage of time spent in different sites of the experimental room by monkeys deprived of manganese and zinc or subjected to repeated injections of streptomycin sulphate and by control monkeys. Both experimental procedures cause damage to the vestibular mechanism.

most of the time clinging to the front wire. When paired, the No Mn-Zn monkeys became more visible than when alone, and they spent less time on the front wire and more time on the top stand than they did when alone. The control monkeys' patterns of behavior were similar under either the alone or the paired conditions. They spent most of their time on the floor, top stand, and front wire. The control monkeys were visible most of the time.

When analyses of variance were performed by categories, significant group differences were found in four categories. In the Alone condition, significant Fs were obtained for Top Stanchion and Not In View. In the Paired condition, significant Fs were obtained for Middle Stanchion and Pipe. The streptomycin-treated monkeys spent the most time of any group in all of the above categories except for Not In View. The tests of significance confirmed that the streptomycin-treated monkeys spent more time occupying the higher places of their room; on the top of the stanchion, and on the pipe, than the other two groups did. The No Mn-Zn monkeys spent significantly more time out of view than did the other groups. No significant differences were obtained for any of the other categories. The use of space varied according to the developmental regime the monkeys had been subjected to, with the streptomycin monkeys spending more time in higher places than did either the No Mn-Zn or the control monkeys.

DISCUSSION

Empirical evidence, some of it "hard" and some "soft", is slowly accumulating which documents that vestibular dysfunction has pervasive deleterious consequences to behavior, especially if it begins early in life. Changes have been noted in a variety of animal species, and presumptive data from humans are now fairly extensive. The reason is not hard to see, for the vestibular system is far more than a receptor mechanism. Because of its numerous and diverse projections and connections it actively participates in the integration of visual, somatic, auditory, and olfactory inputs and in skeleto-muscular and viscero-muscular responses.

We know as yet very little about the precise way in which general behavior is changed by early vestibular defect. We have earlier shown that monkeys made Mn-deficient in utero (by depriving the mother) cling excessively to objects pressed against their ventrum (Riopelle and Hubbard). Similar tendencies are evident in pallid mice with otoconial defect (Douglas etal., 1975). Bilaterally labyrinthectomized squirrel monkeys, Saimiri sciureus acted similarly when placed in a gravity-free environment (Johnson, Money, and Graybiel, 1965).

We now show that monkeys deploy themselves differently in a complex spatial environment if they are deprived of Mn or are given streptomycin than they would it they were normal. Specification of the character of the changes will be difficult considering the complexity of the behavior studied. Such a specification is far beyond the aspiration of the present study. It is likely, however, that timidity and labile emotionality will be prominent in the description.

It should be noted that all animals behaved in apparently normal fashion: without these quantitative data, one would be hard pressed to identify the animals of the different groups. Clearly, the changes are subtle. (We, of course, would have equal difficulty in identifying skyjackers in advance of their deeds.) In light of the accumulating data relative to vestibular involvement in diverse complex behavior, further attention should be directed toward elaborating its role in emotion-related behavior.

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To The Editor

An excellent and a very useful observation was reported by Robertson and Metz (1979) which stated that aspirin is an inhibitor of prostaglandin E1 (PGEl). Most proteolytic enzymes, especially bromelain, are also known to inhibit PGE1 (Taussig et al, 1975). Proteolytic enzyme supplementation has been shown to improve insulin handling in diabetic patients (Graham, 1977).

Our observation is that maturity-onset diabetes mellitus is glucose interference rather than intolerance. We believe that in a majority of diabetes mellitus cases there are inflammation-evoking substances such as foods, chemicals and inhalants in the environment which can be isolated by provocative test exposure and they evoke a rise in PGE1 or other substances which suppress insulin release. These insulin inhibitors could be carbohydrates, fats, chemicals (Capurro, 1970) (such as petrochemical hydrocarbons, formaldehyde and so forth), allergic or allergic-like reactions to cats, dogs, molds, weeds, bacterial or fungi species and so forth.

We have recently conducted a few provocative food tests on four patients. After a four to five day fast (or kept on infrequently used foods), single food testing was conducted on each patient. In all cases, blood sugar was measured one hour post-meal. A single food which resulted in higher than 160 mg percent blood sugar post-meal was again refed either overnight (P.P.) or three hours later but after 10 to 30 minutes post-bromelain (200-500 mg total) ingestion. In both instances, blood sugar and insulin levels were analyzed by Ames Eye tone and RIA methods respectively. Their blood sugar and insulin results are shown in Table 1. In all cases, 200 or 500 mg of bromelain lowered significantly one hour post-meal blood sugars and in three out of four cases, one hour post-bromelain insulin values increased (Table 1). According to Randolph (1976), a reexposure to a reactive substance immediately sets out an acute reaction; however, we have observed in all cases lowering of blood sugar values which clearly indicated a very significant suppression of high blood sugar reaction ($P<0.014$) most probably due to the inhibition of PGEl.

These preliminary studies indicate that reactive foods which cause high blood sugar (chemical diabetes) with an associated inhibition of insulin secretion may be mediated

TABLE 1
EFFECT OF BROMELAIN ON BLOOD SUGAR AND INSULIN

Patient	Food Tested	Time Interval Between Refeeding	Amount of Bromelain (mg)	One Hour Post Meal Blood Sugar (mg%)*		Insulin uU/ml		
						Fasting Normal<50	One Hour Post Meal	
				Before Bromelain	1 hr Post Bromelain		Before Bromelain	Post Bromelain
P.P.	......		....	.....	....	28	....	....
P.P.	Dates		....	170	....	....	107	....
P.P.	Dates	Overnight	200	.....	90	...	....	29
J.W.	......		....	.....	....	24	....	....
J.W.	Oranges		....	175	....	...	77	....
J.W.	Oranges	Overnight	200	....	150	...	....	104
H.S.	......		....	....	....	29	....	....
H.S.	Potato		....	200	....	...	152	....
H.S.	Potato	3 hrs.	200	....	150	...	...	332
K.F.	......		....	80	....	53 (premeal)	....	....
K.F.	Raisins		....	240	....	...	54	...
K.F.	Raisins	3 hrs.	500	....	125	...	...	86
K.F.	Banana		....	180	....	...	....	....
K.F.	Banana	3 hrs.	500	....	110	...	....	....

*P<.014 (two-tailed)

through the release of prostaglandin E1. However, this chemical diabetic stage is apparently reversed by the proteolytic enzyme, bromelain. In one case (P.P.), the post-bromelain insulin value was found to be lower than pre-bromelain exposure. This interesting and unexpected result indicates a biochemical anomaly the reason for which is unclear to us.

We believe that all "so-called" diabetic patients should be treated with an ecologic survey of their reactivity to foods, chemicals and inhalants, then their nutritional needs should be supplemented such as B6, vitamin C, chromium and so forth, which are demonstrated in the laboratory to be deficient, along with bicarbonate and pancreatic enzymes. Such a treatment is very individualized as compared to the generalized treatment now practiced by many physicians.

More studies along these lines should be conducted in order to understand more fully the causes of the diabetes meliitus disease process.

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To The Editor

This is to provide additional information and statistical analysis which strengthen the paper, **Vitamins: The Get-Smart Pills?** (Maseck, 1980).

Mr. Maseck has sent me the label of the supplement used and the following information by letter:

1. Two supplement tablets were given daily, for five days per week, resulting in the following average daily supplementary intakes: vitamin A palmitate 5714 I.U., irradiated ergosterol (vitamin D2) 571 I.U., thiamin mononitrate 1.43 mg, riboflavin 1.71 mg, pyridoxine HCI 2.86 mg, cobal-amin 2.86 meg, vitamin C (not mentioned in the paper) 107 mg, and niacinamide 14.3 mg. The honey-sweetened tablets (Thompson HoneyBee Multi-vitamin Tablets, Chew-able) contained no other 'concentrated foods.'

2. "The school psychologist who did all the testing and marking had no idea which children took vitamins and which took candies."

3. Student helpers "stayed while each child ate his pills or candies [two M&M's] to make sure there were no 'trades.'" Although the pills and candies were distinguishable, and the parents were informed which group their child was in when they gave consent for the experiment, Mr. Maseck emphasized to the children before starting that he "had no idea what the results would be. I am fairly certain that they did not know or care what a vitamin is." Also, "I couldn't remember from one day to the next which child was in which group."

Hence the experiment: (1) most importantly, was based on blind procedures for reading, spelling, and picture vocabulary IQ testing, (2) was controlled regarding administration of an oral preparation, and (3) may have partially avoided the possibility of biasing expectations by the subjects or by those in contact with them.

Statistical analysis of the test data in the paper's Tables A to C gives the result that the reported superior gains in the supplemented group are statistically significant for two of the three tests (See Table 1).

TABLE 1

MEAN GAINS FOR SUBJECTS AND CONTROLS, WITH STANDARD ERRORS OF THE MEAN AND STATISTICAL SIGNIFICANCE OF DIFFERENCES BETWEEN MEANS.

Measurement	Subjects Mean Gain	Controls Mean Cain	P*
Reading progress, mo.	4.40±0.60	1.63±0.87	<0.01
Spelling progress, mo.	6.9 ±2.2	5.1 ±1.8	n.s.
Peabody picture vocabulary IQ	4.8 ±2.3.	-1.9±2.1	<0.05

'Probability of null hypothesis, by 1-tailed t-test; n.s., not significant (f*3).15)

Using additional information supplied by Mr. Maseck (that there were 472 pupil days represented by both groups in his Table D), and correcting for absences, I made chi-square statistical tests on the most objective behaviors listed in Table D. These indicate that the large differences found in the supplemented group regarding absences, tardiness, leaving the room, and leaving seats are all statistically significant (P=0.01 or less).

In summary, Maseck's experiment with a supplement containing modest amounts of eight vitamins included valuable features not apparent from the original report, and statistical analysis shows that objective measures of intellectual performance and behavior showed improvements which are reliably superior in the supplemented group. These valuable results warrant attention and further exploration.

I thank Mr. Maseck for his full cooperation and for reviewing these comments. He indicates that further information is presented in his thesis, "An Experimental Study of the Effect of Supplementary Vitamins on the Learning Ability and Behavior of Children" (1971), available from Library Photodupli-cation Service, California State University, 6000 J Street, Sacramento, CA 95819.

Reference:

MASECK, D.: Vitamins: The Get-Smart Pills? J. of Orthomolecular Psychiatry 9: 58^5,1980.

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To The Editor:

Doctor Hoffer's Editorial, Volume Nine, Number One, is most interesting and informative and is the first time that I have seen suggested in writing or verbally how, by using other nutrients, that one could increase the utilization of other vitamins, minerals, etc.

The need to improve the utilization of vitamin B3 was most interesting by the use of Isoleucine.

In my own practice, previously in Canada and the United States, but presently in Great Britain, the need to supply patients with mega-doses of vitamin B3, amongst other vitamins, does present a considerable financial burden to the patient; more so when he freely receives drug prescriptions at no charge — though this has recently changed, but only minimally.

My own research with some colleagues has concentrated around vitamin B3 and vitamin C in particular. In a few pilot studies we found that by giving B3 in mega-dosages along with B3 potentised in a homeopathic form, e.g. 6X or 12X, that the need for B3 was thereby reduced.

In our work with vitamin C in high oral dosages we have recently experimented by combining the ascorbic acid with a mineral compound in homeopathic form and have found an increase in vitamin content of the urine by 60 percent.

We would be interested to know if there are any other studies to improve the utilization of the vitamins with amino acids as suggested by Hoffer or in our own case, by the homeopathic use of the same element and/or a mineral element.

In conclusion I would welcome a further article by Hoffer and others on mega-amino acid therapy as there has been a dearth of this in the literature.

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