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Behavioral Phenotypes in Organic Genetic Disease

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Introduction

It is my pleasure to open this first plenary session of the Society for Pediatric Research. I would like to express my appreciation for the privilege of having served this year as your President and to address to you a few remarks. I shall discuss with you some of the things that I have recently been interested in.

Basic to all of our work has been the conviction that you can learn things from the careful observation and study of patients. A major goal is the elucidation of things that will be of benefit in the diagnosis and management of the patients studied and others. Further, I believe that there is considerable evidence that the study of clinical problems can yield information of fundamental biologic importance. Garrod's enunciation of the one-gene one-enzyme hypothesis out of experience with patients with alkaptonuria is the classical case in point. There are other examples. This presentation is not an attempt to match these. Rather, I would like to consider with you some of our patients and some of the things that they have taught us.

Inborn Errors of Purine Metabolism

Figure 1 illustrates a disorder that has come to be known as the Lesch-Nyhan syndrome [5]. The little boy shown has had a condition that is of interest to investigators in a wide variety of disciplines. The condition has provided work for scholars in many different walks of life: clinicians, biochemists, behavioral scientists, somatic cell geneticists, and others.

The child had a number of features of the disease. He was retarded. His IQ was less than 50. He had the characteristic features of spasticity, the upgoing toe, and the athetoid posturing. These children have ever present restraints instituted to protect themselves from themselves, from self-mutilation.

A close look at Figure 1 reveals self-mutilation about the lower lip, but the process is more subtle than in some of our patients. You also see his bright eyes and cheerful face and get some idea of what a nice guy he was. It is this kind of appearance that has made most persons who have worked with these children feel that they are more intelligent than their IQ scores or their severe motor defect would suggest. These patients do communicate, and they relate strongly to people.

Study of pedigrees such as those that we published in the first issue of *Pediatric Research* [8] told us quite a lot about the genetics of the disorder. It became clear that this is a disease of the male and that it is always transmitted through the female. We concluded that the gene was on the X chromosome, and that it expressed itself as a recessive.

The primary product of the mutant gene is in the activity of an enzyme which was once known as inosinic acid pyrophosphorylase. It is now known as HGPRT, for hypoxanthine guanine phosphoribosyl transferase. It catalyzes the addition of the ribose phosphate from phosphoribosyl pyrophosphate (PRPP) to hypoxanthine, or to guanine to form their respective nucleotides, inosinic acid or guanylic acid.

Figure 2 illustrates the activity of HGPRT in the erythroctyes of patients and controls. The enzyme is active in every cell of the body. It is readily measurable in red cells. In the patients, the values obtained cannot be distinguished from zero. The bar designated *G-L* represents a different problem: a partial defect in patients without cerebral dysfunction reported recently [4]. The zero value in the patients with the Lesch-Nyhan syndrome made us wonder about the nature of the defect. We now have evidence that there is an enzyme even in the erythrocyte [1], so we feel that there is a structural gene mutation.

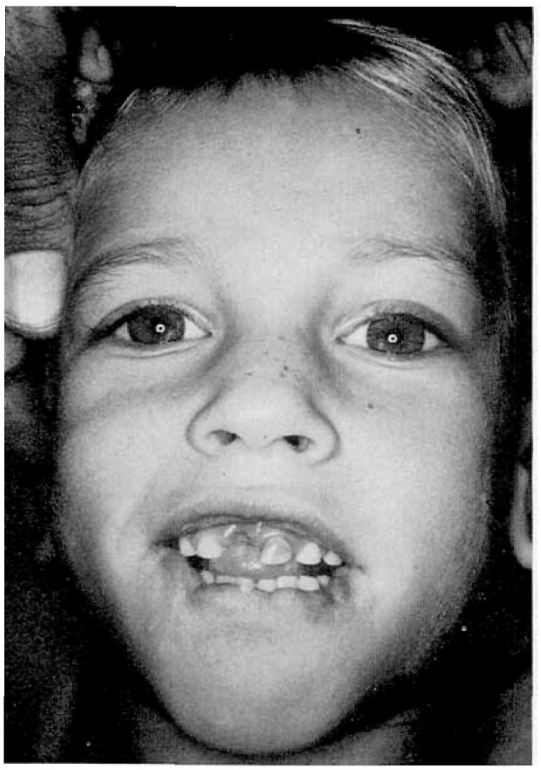

Fig. 1. MJ, a 6-year-old boy with the Lesch-Nyhan syndrome.

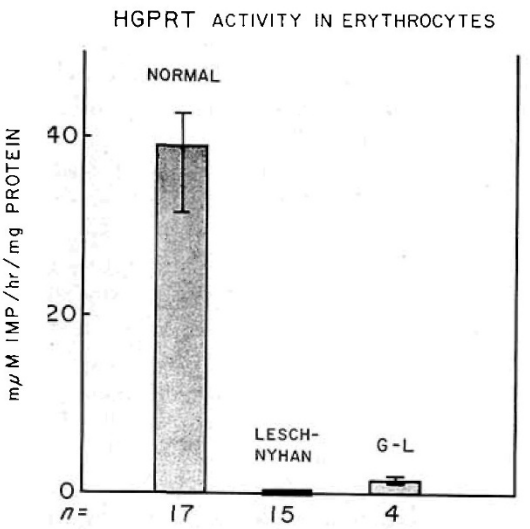

Fig. 2. Activity of hypoxanthine guanine phosphoribosyl transferase in erythrocytes of patients and control subjects.

Genetic Analysis of HGPRT Deficiency: Implication for the Expression of Genes on the X Chromosome in the Female

Fibroblasts grown in cell culture were first cloned by Migeon *et al.* [6]. In the presence of HGPRT, tritiated guanine is incorporated first into guanine monophosphate (GMP) and then into RNA, which permits the autoradiography of the cell. It is then possible to look at or to photograph the cells in the phase microscope to identify the cells, and to look at or photograph the cells in the bright field where only cells with positive grains can be seen. Thus a clone of HGPRT-positive cells from the mother of a patient is visible both ways. A negative clone from the same lady looks like all of the cells in a homozygote: in the phase microscope, one can see the cells, whereas in the absence of HGPRT the nucleic acids are not labeled, and thus in the bright field one sees right through them. These studies established that in this condition the Lyon hypothesis holds in the sense that the heterozygous carrier of the gene has two populations of cells.

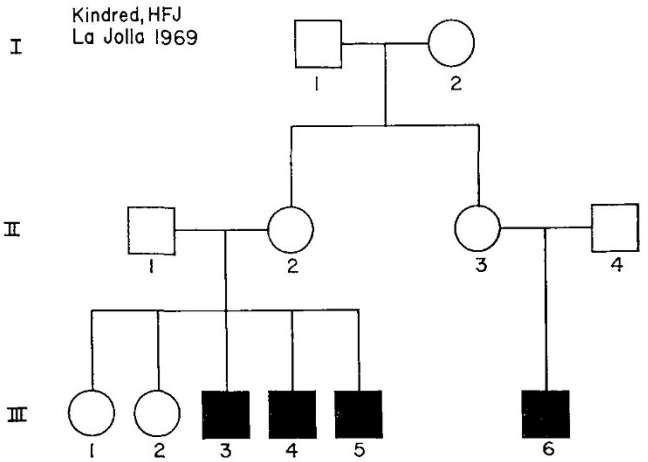

Fig. 3. Pedigree of a family in which glucose-6-phosphate dehydrogenase *types A* and *B* were found, as well as hypoxanthine guanine phosphoribosyl transferase deficiency. The black squares designate boys with the Lesch-Nyhan syndrome. Reprinted with permission from the Proceedings of the National Academy of Sciences [7].

Table I. Activity of hypoxanthine guanine phosphoribosyl transferase in erythrocytes (RBC)

Subject	mμmoles/hr/μliter RBC
I_2	39.1
II_2	38.3
II_3	39.7
III_1	37.0
III_2	40.6
III_3	0.0
III_4	0.0
III_5	0.0
III_6	0.0
Control mean	39.1

Some more information on this subject was provided by a family whom we have studied with Drs. Marks and Keele in Dallas [7]. We thought that the family might be of particular interest because they were black. Virtually all of the patients previously encountered had been white, and we had not previously encountered any patients with glucose-6-phosphate dehydrogenase (Glc-6-PD) variants. A partial pedigree of this family is shown in Figure 3. There have been four involved boys in *generation III*. Data on the activity of HGPRT in the erythrocytes in this family are shown in Table I. In this method, controls cluster closely around a mean of 39 mμmoles/hr/μliter of packed erythroctyes. In the patients the activity was zero. The females in this family were all normal. Not only the two siblings III_1 and III_2, but the two heterozygous mothers II_2 and II_3, as well as their mother, I_2, were completely normal. This is what we have found in a large series of carriers of the gene. They are virtually always normal.

Now, if the inactivation of the X chromosome were a random process as specified by the Lyon hypothesis, we would expect the mean activity of the enzyme in a series of mothers of deficient males to approximate 50%, but it does not.

The method that we have employed to study this problem involves separations of Glc-6-PD isozymes on disk gel [2]. Glc-6-PD *type A* migrates considerably more rapidly than Glc-6-PD *type B*, and the heterozygous *AB* situation is clearly identified. The kindred under study turned out to be meaningful because of the presence of two Glc-6-PD types as well as two HGPRT types. The grandfather I_1 was *type B*, and the grandmother I_2 was *type A*. Therefore, their daughters II_2 and II_3 would have the *AB* heterozygous genotype. A similar conclusion could be drawn from analysis of their children. The sons III_3, III_4 and III_5 were *types B, B,* and *A*, whereas the daughters were *types A* and *AB*. However, when we looked at the patterns for these ladies II_2 and II_3, their erythrocytes and their leukocytes were only of *type B*.

We have found clones of HGPRT minus fibroblasts after skin biopsy in these two women, confirming the genotype. In fact, in experiments in progress, these HGPRT minus clones have been Glc-6-PD *type A*. We concluded from these studies that the expressed phenotype might not always reflect the random inactivation specified by the Lyon hypothesis. In this family we have seen hemizygous expression in the heterozygote. This could reflect nonrandom inactivation or, more likely, selective pressures following inactivation.

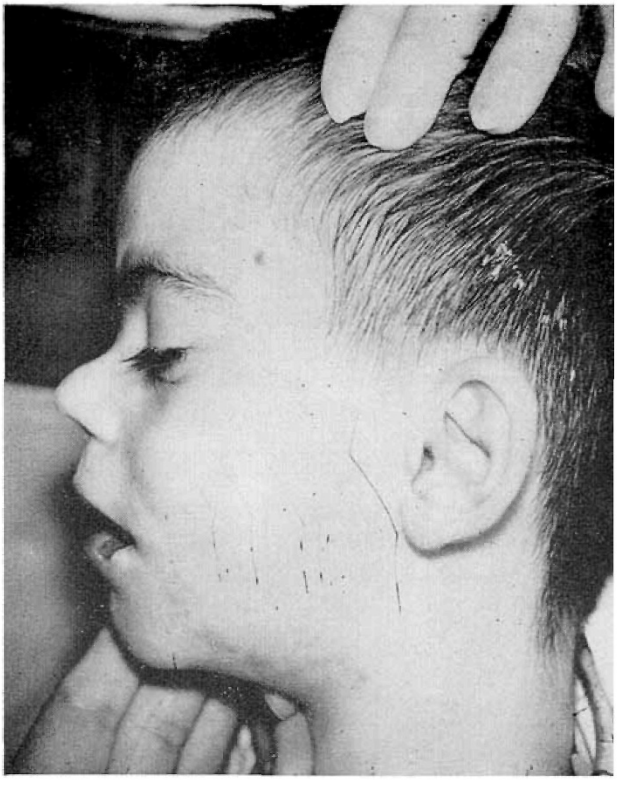

Fig. 4. JE, a 6-year-old boy with the Cornelia de Lange syndrome. He had recently bitten and lacerated his lower lip.

Self-Mutilation

This problem has led us along some other scientific directions. Experience has taught us that in this condition the degree of self-mutilation can be extreme. Obviously, it would be of some interest to have an animal model for this. Rats treated in our laboratories can regularly be made to mutilate. This effect can be produced by the administration of 1,3,7-methylxanthine, which a chemist will recognize as caffeine. Other rats have been injected with the 1,3-methyl derivative, which we as clinicians know as theophylline and which produces self-mutilation even more regularly. We have been able to do this with mice and rabbits, as well as with rats. These observations and those on the patients are consistent with the hypothesis that at least some forms of behavior are chemically determined.

Self-Mutilation in the de Lange Syndrome

Figure 4 introduces another extrapolation. An interest in something like self-mutilation generates the referral of patients who mutilate. Many, of course, turn out to have nothing wrong with their chemistry, at least that

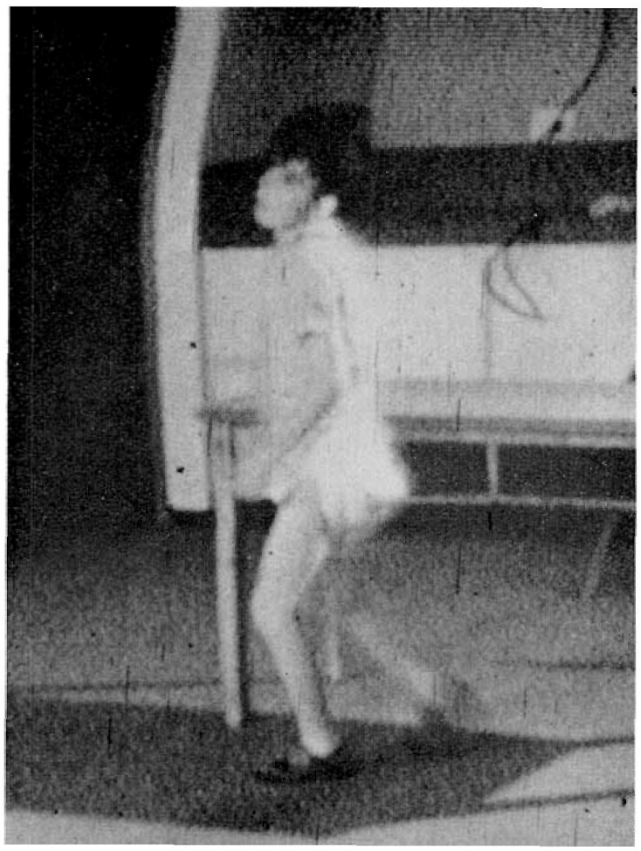

Fig. 5. JE, shown in the course of a characteristic turning movement.

we can find. This patient was studied by Dr. Carol Shear and me and was recently reported [9]. He had the syndrome described by Cornelia de Lange. His low hairline, long eyelashes, and synophrys were particularly striking. His other morphologic characteristics were typical. He is shown at the age of 6 years. By 4 years of age he had developed some self-mutilative habits. He picked at his chest, learned to dislocate his hips at will, and began biting his fingers. One day he produced the laceration illustrated on his lower lip by biting. He kept working on this, ultimately producing a permanent scar of the lower lip.

Of course, one child with self-mutilation certainly does not establish it as a characteristic of a syndrome. We decided that it was worth reporting when we saw a similar child with Drs. Brian Kirman and Jan Stern in England. He had been known to have the de Lange syndrome for many years. At 3 years of age he began picking at his face. He would assume a characteristic posture with one hand picking his cheek and the other over his head more or less stroking or pulling at the crown of his hair. At 4 years of age he began biting his lower lip. A distinct lesion resulted before the front teeth were removed.

In order to pursue this further, Drs. Yvonne Bryson and Nadia Sakati and I recently undertook a survey of patients at the Fairview State Hospital. We found four patients with self-mutilation and the de Lange syndrome. These patients, who engaged in a variety of persistent, individualized, self-mutilating behavior, will be reported. Their addition to our series increases the significance of the association.

Other Aspects of Behavior in the de Lange Syndrome

These experiences with self-mutilating behavior in the Cornelia de Lange syndrome led us to consider more fully the overall behavior of children with the syndrome. We felt that it was in many ways characteristic or stereotypic. We found it very hard to describe all this in words, and, therefore, we have put together a series of film strips in order to demonstrate and to study some of the things that we have been considering and some of the associations that we have made.

When I say *we*, I would like to say that all of our studies of children with the de Lange syndrome have been carried out with Dr. Carol Shear of the University of Miami. She has done a major amount of the work with the film. The patients filmed have been followed by Dr. Shear for a number of years. It is important to comment that the children whom we selected for this study, while all severely retarded, were living at home and most were in unusually supporting family situations, so that when we talk about behavior, we are not talking about institutionalization. It is our operating hypothesis that the behavior is endogenous, not exogenous. We feel that these children have a pattern of unusual behavior that is unique to them. Stereotypic patterns of behavior that occur in syndromic fashion in sizable numbers of individuals provide the possibility that there is a concrete explanation and that it is discoverable. In these children, there are so many anatomic abnormalities, from changes in hair and bones to dermatoglyphics, that it is a reasonable hypothesis that their behavior is determined by an abnormal neuroanatomy and that that would be discoverable, possibly neurophysiologically, ultimately anatomically. First, it will be important to document and to analyze the behavioral syndrome. Recordings of the behavior of the children were made on two different occasions at the Mailman Center, using videotape. We have ed-

ited some three hours of continuous recording to about 15 minutes of film strip.

Circling Behavior

The text that follows has been edited from our comments on the film strip. The first patient shown was the patient illustrated in Figure 4. He clearly demonstrated the clinical characteristics of the de Lange syndrome. He was photographed in what was a characteristic behavior for him and for the others whom we have studied (Fig. 5). He was constantly circling, turning, or whirling. This round and round behavior was stereotyped. We have filmed another, somewhat younger, patient with the syndrome who was also observed to be turning constantly. It seems to us that either the patients are trying to stimulate their vestibular systems or there is an abnormal stimulus to behavior in the vestibular system or in its neural connections. This aspect of the problem has led us to think about animal models.

Whirling Mice

One of these models is mice with turning behavior, such as those studied by Dr. McNutt in San Antonio. These animals have a genetically determined disorder, and therefore one might expect, as in the patients that we have looked at, that there might be an anatomic lesion. In the mouse, the disorder segregates as an autosomal recessive character. These mice are constantly whirling around, turning, jumping, and doing reverse somersaults. The involved mice have a developmental defect in their vestibular system that is detectable as early as the 10th day of fetal life. The rhinencephalon is also unusual in shape, and Dr. McNutt is exploring the neuropathology.

Hand Posturing

Older films of our first patient, taken 2 years previously, also demonstrated his turning behavior. The patients are not particular about which side they turn to; they go clockwise and counterclockwise. This patient also illustrated another aspect of behavior in this syndrome. Hand posturing is frequently seen in these children. In this patient, the hand to the ear was an often repeated stereotyped movement. There were other persons in the room at the time that we made this particular strip, and yet the patient made no contact with any of them. This is another characteristic that we illustrate further a little later.

Figure 6 illustrates the youngest of the three patients that we have studied. It is a little harder to see him in the black and white print as a patient with the syndrome, because his skin and hair are so fair, but he did have synophrys, and he really was quite hirsute though blond. He was demonstrating the abnormal posturing of the hands. This boy could sit for hours looking at his hand in a variety of positions. He would switch from one hand to the other. Occasionally, he quickly slapped himself on the face. He also slapped himself on the knee. This patient, until a few months previously, had not demonstrated any tendency toward self-mutilation, but I think that this has been changing. It was fascinating to watch him study his hand. The significance of this kind of hand posturing is certainly not clear, but you have to see it to appreciate it. The position of his fingers was very precisely repeated day in and day out. It is hard for me to escape the idea that the behavioral patterns that we have been seeing in these children are endogenous, that in some way they are coming from within. They are just a slice of the overall behavior of the child, but gradually we are coming to appreciate the components. Ultimately we would like to build a visual dictionary. These children all seem self-programmed. These stereotyped patterns of unusual behavior could reflect the presence of structural defects in the central nervous system, just as there are structural defects in the hair, the bones, and the dermatoglyphics. In this way, we are thinking about stereotypic behavior that is anatomically or neurophysiologically induced.

Isolation-Reared Monkeys

Another way to look at behavior that has similarities is to study isolation-reared monkeys. A series of such monkeys was raised at Hazelton Laboratories in Falls Church, Virginia, for the National Institute of Child Health and Human Development. The monkeys were isolation-reared in wire cages, each one by himself, but in the parent colony room so that they could see the other animals. Inputs to the senses of smell, vision, and hearing should, under these circumstances, be relatively normal. Most of the time these animals just sit in the corner of the cage, occasionally rocking, but not much else. We found the hand posturing of one of these monkeys provocative (Fig. 7). His placing of his hand over his head was certainly reminiscent of what we saw in *CJ* and was just what we had seen in the boy in England. It is also quite reminiscent of what one sees in catatonic schizophrenia. When one of these monkeys is picked up, another phenomenon is visible.

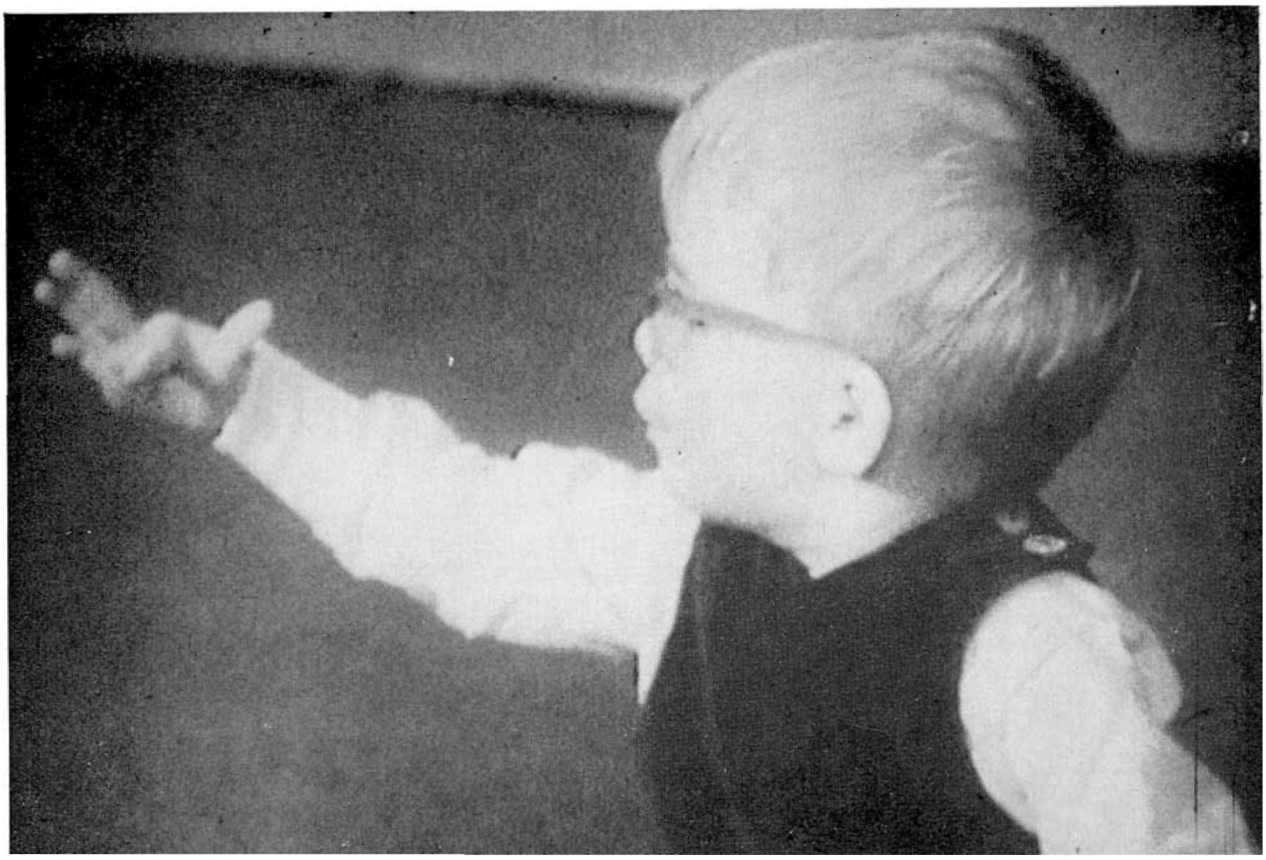

Fig. 6. CJ, a boy with the de Lange syndrome, illustrating hand posturing, a behavioral stereotype.

The monkey becomes upset. He screams in alarm and usually urinates and defecates. These animals are all hyperreactive to touching. What should be a comforting, pleasureful stimulus has, for them, become an aversive stimulus. This reaction suggests the possibility of denervation sensitivity. The usual rewarding mechanisms are dysfunctional. These animals prefer to sit in the cage, endlessly rocking and making very little contact. There are probably some lessons in this behavior concerning human sensuality and affection, and the influence of early deprivation.

Responses to Kinesthetic Stimulation

Another of our patients was a very hyperactive child. On the day that we filmed him, he repeatedly pushed over furniture. He was completely resistant to attempts to restrain him or to keep him in one place. He had a complete lack of contact with the examiner or with anybody who had taken care of him. He was like that all of the day that we were filming. We put him in a swivel chair at the suggestion of Dr. James Prescott (NICHD), who felt that there might be a relation between the whirling behavior that we have shown before and a need for sensory stimulation of the cerebellum or the vestibular apparatus. We were skeptical, but we put the patient in the chair, and manually we rapidly rotated the chair and the boy. To our surprise he quieted down. He then proceeded, through nonverbal communication, to ask me to whirl him again. None of these patients whom we have studied had any speech. He indulged in touching behavior which was quite unusual for him. He looked back, asking without being able to verbalize it, and rocked to suggest moving the chair; he then got out of the chair, pushed it around toward the examiner, and whirled it around. That appeared to be pretty specific communication. That was the first attempt at communication with another individual that I had ever seen from that little boy. In the face of these persistent requests, we did rotate him again. He became calm, quiet, and sleepy. The restful scene was dramatically different from the hyperactive, irritable, unconsolable child that we had seen just moments before. A next step, obviously, is to

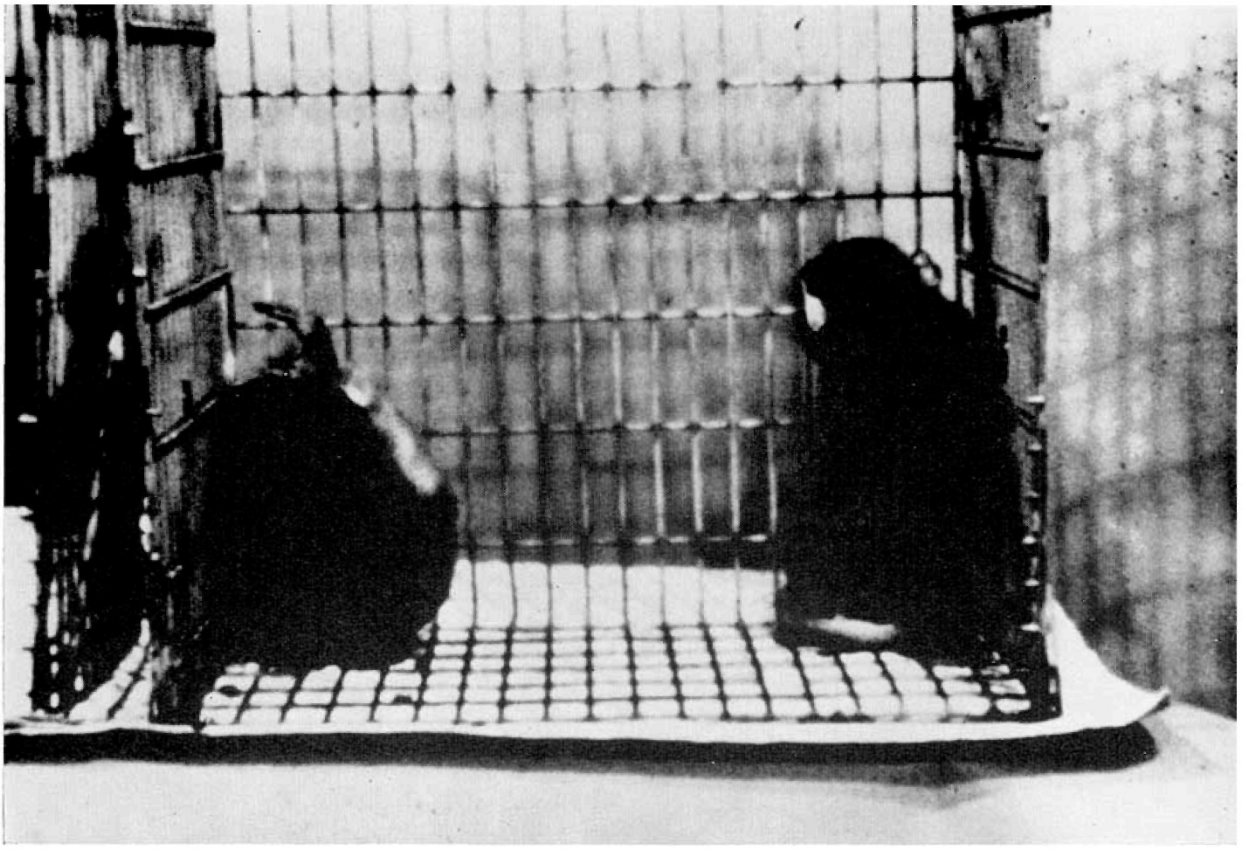

Fig. 7. Isolation-reared monkeys. The monkey on the left illustrates interesting hand posturing. The photograph was kindly provided by Dr. James Prescott.

extend this kind of observation into the neurophysiologic or electrophysiologic correlates of this behavior. We have thought to undertake a study of cortical-evoked responses, particularly to vestibular stimulation. This could be done with computer averaging. It would be of interest to control the study with parallel exploration of visual, auditory, and other evoked responses.

We tested rotation in the other patients. In our first patient, the response was not quite so dramatic, because this boy was not hyperactive; but a distinct change was observed, and he, too, returned to the chair when removed from it. Although not hyperactive, this boy had always been very hard to work with. He was a very difficult child from the point of view of the mother. He had never shown any recognition that his mother was any different from anybody else, nor did he show any recognition of others who have cared for him.

Possibly relevant experience is that provided by the isolation-reared monkeys studied by Drs. Mason and Berkson at the Delta Regional Primate Center in New Orleans. Each monkey was raised in isolation, but with a fuzzy maternal surrogate. The surrogate was made by putting a fuzzy rug over a Clorox bottle. There was a pie pan beneath. There were two different experimental conditions. In one, the surrogate was moving. It moved freely in all horizontal directions, and up and down about 6 inches, using a cam-operated system. A pattern of daily movement of the surrogate has continued through the life of the monkey to date. For the other experimental subjects, the identical cloth surrogate was employed, but, in this case, the surrogate had been bolted to the floor of the cage so that it never moved. The difference between these two groups of monkeys was striking. The monkey with the stationary surrogate was a typical isolation-reared monkey, much like the Harlow monkeys or those that we discussed before. He was afraid of the examiner. He hid behind his cloth surrogate. He spent most of his day sitting in a corner. On the other hand, the monkey raised with the moving surrogate showed no

Fig. 8. JE, shown as he moved about the walls of the room in autistic fashion.

fear of handling nor of the examiner. He moved around pretty much like a normal monkey. These observations have, of course, some link to fetal development. In the uterus the only likely stimulation is the motion of the mother, so that the fetus gets whole body moving stimulation which has had its counterpart in the rocking chair or the moving cradle in the nursery. In our culture there has been a dramatic decrease in this kind of whole body stimulation.

Autistic Types of Behavior

Another aspect of behavior in the children is what one might consider autistic types of behavior. We have mentioned earlier a lack of response to the human. These children have never been cuddly or warm, nor have they ever related in any way to people. In Figure 8, the patient is shown circling around the room and touching the wall in a manner seen often in children with infantile autism. I do not want to make the point that these children have infantile autism. I do not believe that they do, but they do not relate very well. When we put all three patients in the room together, each one operated in his own self-programmed manner. The presence of someone else, either another patient, a mother, or an observer, was never acknowledged. We wondered how they kept from bumping into each other or into the furniture. They simply do not relate.

Aggression

We were also interested in studying a series of films representing Harlow monkeys. These monkeys were originally raised by Dr. Harlow and photographed in Dr. Berman's laboratory in Brooklyn, New York. As the isolation-reared monkey gets older, he begins to look and act a lot more like an ordinary monkey. You see differences when they begin to socialize. In one sequence, the monkeys were separated by a piece of wood which was later taken away. They looked like normal monkeys as they crawled up and down the wall. Once they realized that there were two in one cage, they looked each other over, but they did not seem to be different from other monkeys. All this changed when they touched. When one touched the other it became apparent that these were really very different monkeys. They all were extraordinarily aggressive. Once those monkeys touched, they fought with ferocity.

Commentary

A fuller treatment of isolation-reared monkeys, along with quite a number of other things that are relevant to human infants, can be seen in a film entitled "Rockabye Baby," which was recently put together by Time-Life, Inc., in consultation with Dr. Prescott.

We would like to make the point that there are some specific things about the behavior of the patient with the Cornelia de Lange syndrome. These things come under the heading of behavioral stereotypy. Stereotypy is, of course, common in retarded children. However, patterns observed in the de Lange syndrome are repeated sufficiently so that they have some specificity. I also think that there is no guarantee that, in this way, we have seen or recorded everything that is characteristic of the behavior of these children. I think that we may have just begun to catalogue their repertoire. It is difficult to come to grips with this type of thing. We are hopeful that we can begin to look at behavior

in a quantitative sense in collaboration with Dr. Paul Eckman at the University of California, San Francisco. Dr. Eckman does very interesting studies on nonverbal communication. Hopefully, we can look in a scientific way, and we might then be able to say that this is the behavioral stereotype of the patient with the de Lange syndrome, and that a suitable number of control individuals do or do not respond in the same way.

I have indicated above that our idea is that the de Lange patient has so many very striking structural abnormalities, involving things as subtle as the dermatoglyphs or as general as the overall size of the patient, that, if there is a behavioral pattern that is characteristic of the syndrome, the likelihood is that this behavior pattern is anatomically directed. Possibly, we can get a handle on the disordered anatomy by neurophysiologic studies or by very careful neuroanatomic study of autopsy material. I do not think that the isolation-reared monkey represents the same thing at all. However, I am struck with many behavioral similarities. These similarities might suggest that a process similar to what we see on a congenital structural basis in the de Lange syndrome could conceivably occur, and much more commonly, in response to sensory deprivation in monkey or in man.

Some very interesting studies that might have relevance have very recently been conducted by Drs. Cheek and Hill at Johns Hopkins in collaboration with Dr. Myers at the National Institute of Neurological Diseases and Stroke [3]. They studied placental insufficiency which was produced by experimental ligation of vessels in the placenta of rhesus monkeys. In these experiments, monkeys were operated upon at 110 days of the 165-day gestation. The uterus was opened and the fetus was removed; the vessels were then clamped so that there was a reduction of between 20 and 50% of the total mass of the placenta. The monkey was then reinserted into the uterus. At term, these monkeys were all small for dates. When Drs. Cheek and Hill looked at the chemical composition of the brain, they found that there was not much change in the cellularity of the cerebrum. In the cerebellum, on the other hand, the weight and the total DNA content were significantly reduced. Therefore, this type of intrauterine growth retardation led to a cellular deficit that was specific for the cerebellum. The cerebellum may be particularly sensitive to stress early in development.

In conclusion, we have come quite far afield from the molecular biology and cellular genetics that we began with. I hope that some of the associations and correlations that we have made are sufficiently meaningful to lead further to research.

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10. The author is pleased to acknowledge the important share of Dr. Carol Shear in this work; we have collaborated on all of the studies on children with the de Lange syndrome. The author is indebted to Dr. James Prescott for his advice and counsel and for making available to us his extensive collection of film on monkeys; to Hazelton Laboratories, TRW, Falls Church, Va., for their donation of the animals to the National Institute of Child Health and Human Development; and to Dr. W. McNutt for sharing with us his films of whirling mice and for discussing with us the results of his research in progress.

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12. Requests for reprints should be addressed to: William L. Nyhan, M.D., University of California San Diego, La Jolla, Calif. 92037 (USA).

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