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Behavior in the Lesch–Nyhan Syndrome[1]

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The Lesch–Nyhan syndrome is a heritable disorder of the metabolism of uric acid in which behavioral manifestations are prominent and among the most provocative. The mutated or variant gene that determines this disorder is carried on the X chromosome. The disease is expressed exclusively in males. The molecular expression of the abnormal gene is in the completely defective activity of the enzyme hypoxanthine guanine phosphoribosyl transferase. As a result these patients overproduce uric acid and may develop early in life many of the clinical findings we associate with gout. They have in addition a variety of neurological abnormalities including mental retardation, spastic cerebral palsy, and involuntary, choreoathetoid movements. Involved patients have unusual, compulsive, aggressive behavior. Its most prominent but by no means exclusive feature is self-mutilation. The central feature in the management of this behavior is physical restraint. A number of practical procedures have been learned which facilitate the care and feeding of these patients. Promising new findings suggest that behavioral modification using extinction techniques and pharmacologic methods utilizing agents designed to increase the effective cerebral content of serotonin may each have a place in the management of behavior in this syndrome.

INTRODUCTION

The Lesch–Nyhan syndrome (Lesch & Nyhan, 1964) is an inborn error of purine metabolism in which abnormal behavior is a major manifestation.

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The disorder is determined by a gene on the X chromosome and affects only males. The primary product of the abnormal gene is a variant enzyme, hypoxanthine guanine phosphoribosyl transferase (Seegmiller, Rosenbloom, & Kelley, 1967; Sweetman & Nyhan, 1972). This enzyme, which is present in every cell in the body, normally converts hypoxanthine and guanine to their respective nucleotides, inosinic acid and guanylic acid. In patients with the Lesch–Nyhan syndrome the activity of this enzyme is completely lacking. The metabolic consequences of this defect are an enormous overproduction of uric acid and accumulation of large amounts of uric acid in body fluids. Hypoxanthine also accumulates, particularly in the cerebrospinal fluid (Sweetman, 1968) where concentrations of uric acid are never high. Uric acid is not formed in the central nervous system and it is effectively excluded by the blood–brain barrier.

As a result of their uric acid excess, these patients may develop any of the manifestations of gout. They may have arthritis tophi, renal stone disease, and nephropathy (Nyhan, 1968, 1973, 1974; Howard & Walzak, 1967). Urate nephropathy may lead to renal failure. This was the rule, usually with death in childhood, until the advent of treatment with allopurinol (Sweetman & Nyhan, 1967; Balis, Krakoff, Berman, & Dancis, 1967). These patients also have a variety of abnormalities that are clearly unrelated to the presence of large amounts of uric acid in body fluids. A severe degree of mental retardation is one of the cardinal features of the disease. IQs are usually below 50 and none learn to walk. On the other hand, we have regularly felt that most of these patients were more intelligent than test scores indicated. Tests of IQ were certainly not developed with children like these in mind. The neurological defect makes it difficult for these children to perform adequately. Writing is out of the question. Furthermore, the behavior disorder imposes a virtually unique problem for adequate testing. All of these children have bright, understanding eyes. They relate unusually well to people and they are usually felt by those closest to them to understand everything that is said to them. They all learn speech, and some communicate quite well. A few of our patients have been thought by parents, teachers, or psychologists to be functioning at a normal level of intelligence. One patient has been reported in whom performance of selected psychological tests was within normal limits (Scherzer & Ilson, 1969).

All of the patients have cerebral palsy and display a very marked choreoathetosis. Increase in muscle tone may be the earliest neurological manifestation. Abnormal movements usually begin by 8 to 12 months of age. They are increased by tension or excitement. Opisthotonic or extensor spasms of the trunk are characteristic. Speech is notably dysarthric. Athetoid dysphagia is another problem. These patients are difficult to feed.

They vomit frequently. In a crowded State hospital, or elsewhere, these features can lead to aspiration or to inanition, either of which may be fatal. Convulsive seizures are seen occasionally, but not uniformly in this syndrome.

Among the inborn errors of metabolism, this disease is relatively common. In collections of patients with mental retardation it is our experience to find this disease second in frequency to phenylketonuria and more common than other heritable metabolic diseases.

The abnormal behavior (Lesch & Nyhan, 1964; Nyhan, 1968) of patients with the Lesch–Nyhan syndrome is generally first manifest with the eruption of teeth. Patients begin biting themselves, and self-mutilation through biting continues as the single most unsettling feature of the disease to parents and others responsible for the care of these children (Lesch & Nyhan, 1964; Nyhan, 1972a; Reed & Fish, 1966; Hoefnagel, 1965). The biting is ferocious. Partial amputations of fingers are common. There have also been some who have produced a partial amputation of the tongue. Most patients have lost a considerable amount of tissue about the lips. The hallmark of this syndrome is a distinct absence of tissue about the upper or lower lip (Figure 1). In some patients there is destruction of both. It is rare to see a patient with this disease in whom there is not permanent damage to the lips, unless the primary teeth have been removed early. As they grow and develop, this behavior becomes more varied. These children find other ways of self-mutilating, such as picking with their fingers, scalding in hot water, and catching themselves in braces employed for cerebral palsy or in the spokes of a wheelchair. They will bite others but this is limited by the motor defect.

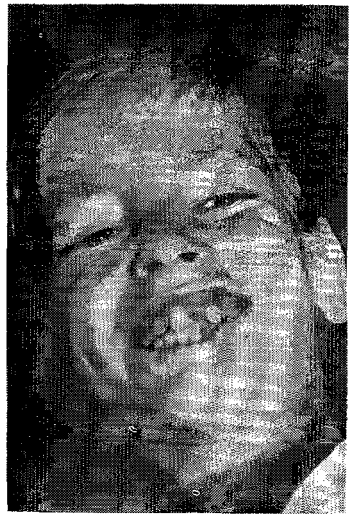

Fig. 1. A patient with the Lesch–Nyhan syndrome, illustrating the characteristic loss of tissue about the lips.

In working with handicapped children it is clear that many of them have highly specific patterns of behavior. We have proposed the idea that there are behavioral phenotypes (Nyhan, 1972b) or syndromes just as there are patterns of somatic expression. It is furthermore clear that it is the child's behavior rather than his IQ or motor capacities that determines whether he must be institutionalized. Among deviant behaviors, self-mutilative behavior is one of the most difficult to live with. Most patients with the Lesch–Nyhan syndrome are ultimately admitted to institution, although they are otherwise quite engaging children.

Self-Mutilative Behavior in Pediatric Patients

The differential diagnosis of self-mutilation in childhood is not large. We have reported self-mutilation in the DeLange syndrome (Shear, Nyhan, Kirman, & Stern, 1971; Bryson, Sakati, Nyhan, & Fish, 1971). Children with the DeLange syndrome have a behavioral phenotype (Johnson, Nyhan, Shear, Ekman, & Friesen, 1976) in which quite a number of behaviors are seen regularly in the syndrome. Aversive, self-stimulatory behavior appears to be an integral component of this phenotype. Some of the children acquire malformations of the lip indistinguishable from those of patients with the Lesch–Nyhan syndrome. However, the mutilation is much less severe than in the Lesch–Nyhan syndrome; loss of tissue is rare and seems almost accidental. The behavior is readily extinguished, using aversive operant methods which are never effective in the Lesch–Nyhan syndrome. At the same time the behavior of the patient with the DeLange syndrome may lead to serious consequences. We followed one patient with the DeLange syndrome who shortly after beginning to self-mutilate died in an episode that was interpreted as suicide. Another was murdered by another retarded child shortly after being admitted to a state institution (Johnson et al., 1976). Self-mutilative activity is also seen in children with sensory neuropathies. The pattern in these children is quite different. The trauma is clearly accidental. These patients begin to look like pugilists. They have many unrecognized fractures. They have trophic changes or burns which result in the loss of the ends of fingers or toes. The nasal septum is particularly subject to traumatic loss. Patients with dysautonomia may also have self-mutilation. In these patients the problem appears also to result from abnormalities in innervation, although they may have abnormalities in other aspects of behavior. Autistic children and children with nonspecific mental retardation may have self-mutilative behavior, especially after long institutionalization. The pattern of mutilation in these patients is usually quite different from that of the Lesch–Nyhan syndrome. Head banging is

its most common form. Hitting is next, and picking and biting are much less common. The activity tends to be chronic and low grade. It therefore leads not to losses of tissue but to hypertrophies in the area of trauma. The cauliflower ear is a common example. Such a patient may develop partial or complete blindness due to trauma to an eye, but serious consequence of the behavior is the exception rather than the rule. In sum, self-mutilation is seen in a variety of children with mental retardation but it is rare. When examined closely this behavior almost never resembles that of the patient with the Lesch–Nyhan syndrome.

Behavior of the Patient with the Lesch–Nyhan Syndrome

The self-mutilative behavior of the patient with the Lesch–Nyhan syndrome is remarkable for its effectiveness in producing loss of tissue. In no other type of patient is self-aversive behavior so dramatic or so effectively mutilative. Amputations of digits often include the entire bone of a phalanx. One of our patients now has an acquired cleft of the palate. It is also remarkable for its lightninglike rapidity. When one of these patients gets out of restraints, the hand goes instantly to the mouth. The hand may be quicker than the eye if the eye is not trained through experience with these patients, and one quick trip to the mouth can produce a considerable amount of damage. It is a source of continued surprise that patients so athetoid, who have so much difficulty controlling the simplest hand movements, can so quickly and so accurately get the hand to the mouth and bite or lacerate it on a tooth.

Sensory modalities are all intact in these patients. They definitely perceive pain. They do not want to bite themselves and scream in pain when they do. These are unusually engaging children. When they are restrained securely, they are relaxed and good-humored, and they smile easily. They tend to look quite a bit alike. Athetoid children in general resemble each other, but these children are reminiscent of the principal character of the ballet "Petroushka" with their admixture of good humor and tragedy, unusual posturing, and the usual mittenlike coverings on their hands.

When protective coverings or restraints are removed, the patient's personality undergoes a dramatic change. He appears terrified. He screams, I think, for help, to protect him against himself. Older patients are sometimes able to get help, to get them back in restraints before they damage themselves. A corollary of this involves sleeping behavior. We have frequently obtained the history that a child with this syndrome has never slept properly since the time his teeth came in. Neither had the family, because he screamed all night. We interpreted this as a call for help and protection against himself. Patients restrained securely, with all four extremities tied

for sleep, sleep very well. Parents have sometimes had to be convinced of this by an overnight admission to hospital. However it is done, teaching parents or guardians to restrain the patient securely in bed obliterates this problem of sleeping behavior.

It is paradoxical that the self-mutilative behavior is uncontrollable, but nevertheless very much within the patient's consciousness. Furthermore, it changes with time; as a patient gets older he gets better at finding ways, especially enlisting the help of others in protecting him against himself. We have thought that the basic urge that drives him to mutilate is a chemical consequence of the disease, while the various methods that individual patients learn to attempt control are like the modulations any of us employ in civilizing primitive behavioral impulses.

Mutilation in these patients does not come only from biting. They may pick at a wound or work on it with their tongues. A tooth may be combined with a hard surface or even a bed sheet to injure an interposed lip. Patients may find hot water faucets and burn themselves. One patient burned himself in a dry ice acetone bath left unattended by an investigator in a clinical research center. The extensor spasms of the trunk in which the head is thrown back forcibly may lead to injury if the head meets a hard surface.

More often this extension behavior injures someone else. Nurses and others caring for these children learn to be careful when they are behind them. The back of the head is hard and it is thrown back with considerable force. Patients are less effective with other outer-directed aggressive behavior, but it is clear that the behavior of these children is not simply self-mutilative. It is a generally compulsive aggressiveness that the patient cannot control. He is as remorseful if he succeeds in hurting another as when he hurts himself, but he cannot help continuing to pursue it. They do bite, but the unwary must be very close for this to be effective, and those that get very close to these patients quickly become wary. They hit with their hands and kick with their feet. Attendants are better off with plastic glasses so that they do not break when they are knocked off. One of our patients was visited at Christmas by his mother, whom he had not seen for some months as she lived in another state. When he saw her come in the room he was overjoyed. Nevertheless, he promptly threw a truck he had received as a present across the room at her and lacerated her ankle. Some of these patients spit at people. They all vomit, and certainly this is not all self-induced; possibly not even much of it is, but some of it appears at least semivoluntary. They do seem to vomit situationally. Some have vomited on others, especially those feeding them. Some of our older patients have developed aggressive patterns of behavior with sexual overtones, pinching or grabbing the bottoms or the genitalia of those that come near them.

Verbal forms of aggression develop in most of them. Four-letter Anglo-Saxon expressions are commonly used, especially in the presence of those that seem upset by them. One of our patients developed more subtle forms of aggression, telling for instance his mother, as she left to drive somewhere, that he hoped she'd get in an accident and die. This boy lived at home and loved his mother more than anyone else in the world. It was she who received the worst of his behavior. Another patient we observed was expert at turning one of the nurses in the unit against another. He manufactured things to tell one, saying that another had said this about her. Nurses experienced with this patient learned never to believe the things he attributed to another staff member.

The behavior of these patients is a striking and provocative element in the syndrome. It is the first instance in which a stereotyped pattern of human behavior has been associated with a distinct biochemical abnormality. Understanding of mechanism could contribute to an understanding of behavior and its biochemical basis.

Day-to-Day Management and Nursing Care

Over the years we have learned a number of things about the care and feeding of these children that may be useful to parents or others responsible for their care. Feeding is a problem. Many have mouths made inefficient by mutilation or the removal of teeth. Swallowing is inefficient and they vomit frequently. Consequently, some degree of inanition is the usual situation. We have admitted to hospital some patients in whom this was the chief complaint. Most patients with the syndrome have a retardation of linear growth and the bone age, but the defect in weight gain is always greater. The reasons for this are not clear, and endocrinologic evaluation is negative (Skyler, Neelon, Arnold, Kelley, & Lebovitz, 1974). We have felt that the etiology is nutritional. One argument for this hypothesis is the fact that those children who have grown and developed best have been those who have lived at home and who had the best nutrition.

We have been very successful in improving the nutrition of even some very advanced cases who were skin and bones at the start. For such a patient we have emphasized small, frequent, high-caloric liquid feedings. Milk, to which egg or ice cream is added, makes an excellent between-meals and bedtime supplement. We refeed within one hour for vomiting. Few of these patients can do much chewing, so that solids should be mashed up very soft and contain no chunks on which to choke. It is not necessary to use purees. We have used spoons exclusively, avoiding knives and forks, which may be dangerous. The food is placed well back on the tongue. Paper or plastic

cups are preferable to glass, which patients can break even with their teeth. Syringe feeding of liquids or medications may be useful. It is ideal to have one person, or a very few, feed the patient so that each becomes accustomed to the routine. Eating is one of the few real pleasures these children can enjoy. It is worth devoting some effort to making mealtime pleasant, arranging the food attractively, and serving things that he likes.

It is preferable to have these patients up in a chair most of the day. This permits them to use many of their muscles, and to participate in the environment. They like to be where the action is, whether it is the kitchen or playroom at home or the nurses' station. They enjoy television, radio, and recordings. Most will ultimately profit by an individually built chair. It is well to start with an ordinary wheelchair, the smaller and narrower the better, and learn what works with an individual patient before embarking on something elaborate. The organization of restraints in the chair is important. These patients cannot sit up unless tied in securely. Once in place they can do a lot, including playing with toys and getting themselves around.

Cloth diapers provide the mainstay for restraints and it is possible to function quite well, especially in hospital, with nothing more complex than cloth diapers. They are ideally tied rather than pinned. Pins come apart more easily, and they can be dangerous. The chair is gradually built up with diapers, one around each thigh and fastened to the poles on the back of the chair. The forearms are tied to the back of the chair, leaving the hands free. There is a tie around the chest. The ties around the arms are brought under

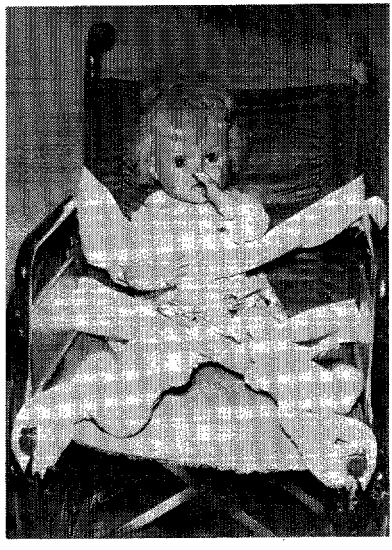

Fig. 2. Pattern of restraint using ordinary cloth diapers and an ordinary wheelchair, permitting a patient with the Lesch–Nyhan syndrome to be up and about.

Fig. 3. Patient with the syndrome in a specially designed wheelchair, small and narrow enough to fit him. The integral central bar on the seat and the seat belt above were enough to keep him upright in the chair. He was illustrating with his right hand his ability to move the chair.

this and tied to the back of the chair. Any hard surface is padded. The principle is illustrated in Figure 2 with an ordinary wheelchair. Figure 3 illustrates a patient in a specially constructed wheelchair with a built-in seat belt and a central bar in the seat, which were enough to keep this boy upright in the chair. Figure 4 illustrates a more elaborate individually constructed stationary chair. A much more elaborate chair was designed by Letts and Hobson (1975) which is removable from the wheeled frame, permitting service as a car seat. A clear plastic arm and hand enclosure reminiscent of the side of an isolette has portholes from which the child cannot withdraw his arms because the back of the chair prevents extension of the humeri. Objects can be place in the enclosure permitting the patient to use his hands and arms to manipulate them without fear of getting a hand to the mouth.

In Figures 3 and 4 the patient's hands are shown free, permitting their use in locomotion, play, or learning. This illustrates the utility of elbow restraints which prevent flexion of the elbow, making it impossible for a hand to get to the mouth. These restraints are the most valuable in permitting a child maximum use of his hands. Two forms are shown. The simplest, in Figure 4, can be made using cloth diapers, wooden tongue depressors, and adhesive tape. The manufacture of one of these restraints is shown in Figure 5. Patients of ours have had similar devices fashioned of leather with

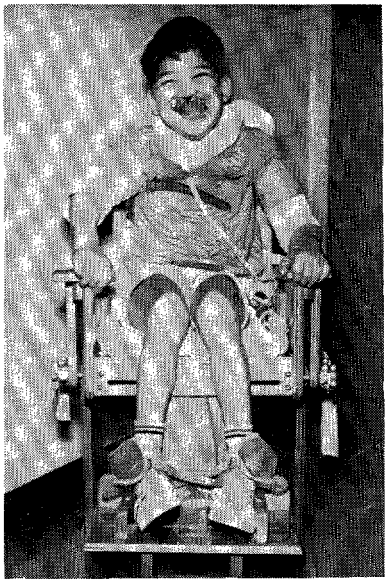

Fig. 4. Patient in a more elaborate specially built stationary chair. This patient could get himself to a standing position using this chair. A desk-top-type work table could be added in front. One of our patients who wore leg braces had a specially constructed wooden stand table at which he could stand and work or play.

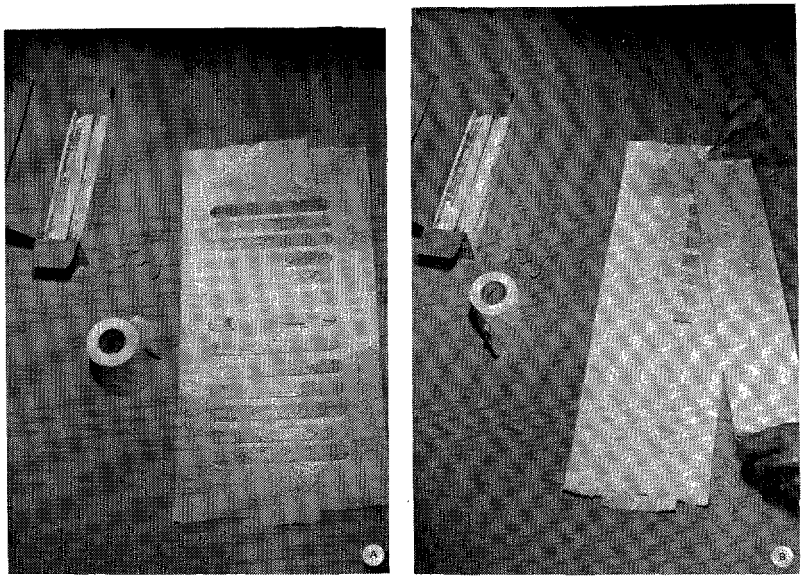

Fig. 5. The fashioning of elbow restraints. In 5A the cloth diaper is folded to the appropriate size and taped, and the tongue depressors are placed in a row. In 5B the diaper is folded over and taped with wide adhesive tape. The restraint is then placed around the elbow and taped circumferentially to itself.

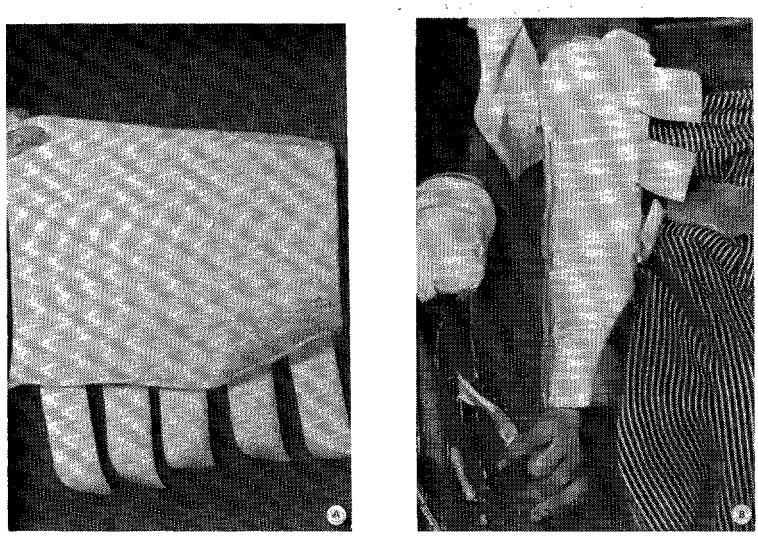

Fig. 6. Cloth and plastic elbow restraint. A—open. B—partially attached to illustrate the method of closure.

intrinsic staves and a zipper closure. We have employed plastic elbow splints (Figure 3) made on order for individual patients.[3] A close-up is shown in Figure 6.

Most patients cannot be maintained continuously in elbow restraints or they begin to develop abrasions at the edges. This can become a form of self-mutilation. Therefore, it is useful to alternate them with some form of mitten. Quite a variety is effective in individual children. Again, the simplest and most effective can be fashioned from cloth diapers (Figure 7). These are tough and withstand the most vigorous efforts of the child. We have used actual boxing gloves and they are highly effective, but they are airless and lead to maceration. Any heavy cloth mitten will usually do nicely. Some children need only rather thin cotton mittens, or even socks, more as a reminder than true protection, but effective in some. Most are highly specific about a finger or two, which are repeatedly damaged and sometimes covering only the dangerous finger suffices. Plastic hair rollers have been used with success. These individual variations among children are reminiscent of variations in behavior among normal children. Among our patients with this syndrome some are basically very gentle people, on whom, as it were, an irresistible impulse has been grafted. These are the ones for whom thin mittens suffice. There is a spectrum of behavior in the syndrome, as there is among normal individuals.

[3]In San Diego these may be obtained from Abbey Rents, 2110 El Cajon Boulevard, San Diego, California, Attention: Mr. Ron Morton.

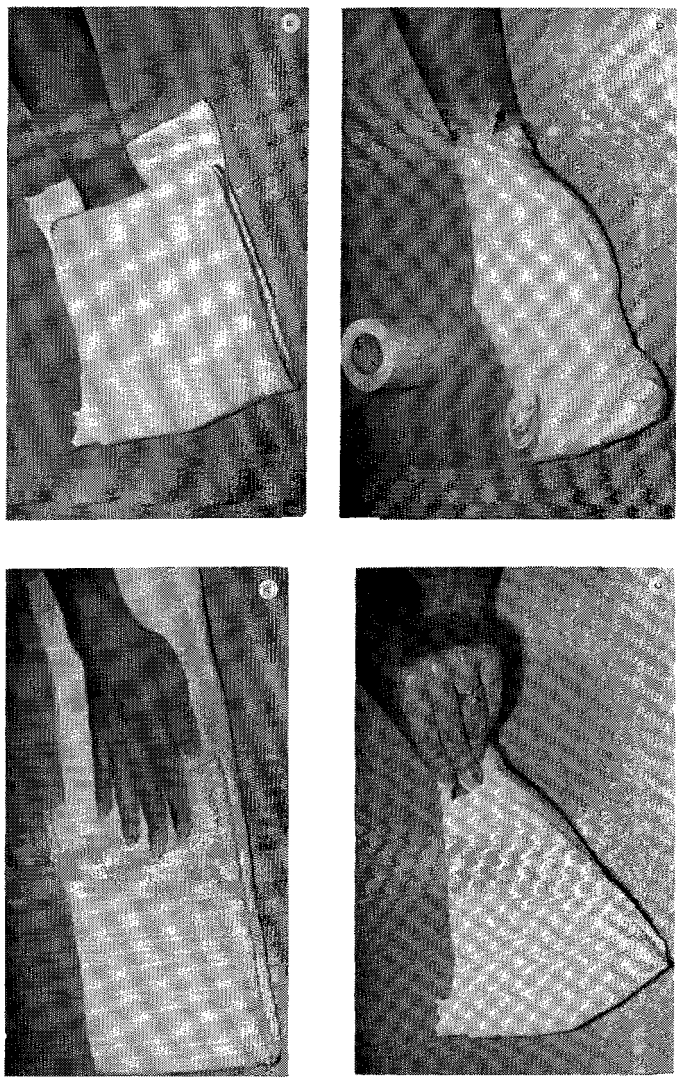

Fig. 7. Cloth mittens fashioned from diapers and adhesive tape. A—Folded diaper with hand in place. B—Cloth is folded over to enclose the hand. C—Sides are drawn in to make a mitten. D—Adhesive tape completes the closure.

At night most patients are best tied with all four extremities to the bed using heavy diapers. A jacket restraint or tieback vest[4] is often very useful for restraint in bed. This can also be used in the chair.

We have tried and discarded helmets. Most of our patients have not enjoyed being on the floor. Bathing usually requires two people. A large sink may be easier on their backs than the usual bathtub. In any case, the spigots should be covered to protect against direct injury or turning on the water at an inopportune time. For the attendant who can maintain a sense of humor, these are interesting children to care for. They provide considerably more feedback than virtually any child with a similar degree of physical and mental handicap.

Behavior Modification

Self-mutilative behavior in mentally retarded patients has been considered a learned response and as such subject to unlearning with suitable techniques of behavioral modification. In many retarded patients this type of behavior has been thought to reflect an attention-getting device. This has seemed less reasonable in patients with the Lesch–Nyhan syndrome, but there are elements of this in the behavior. Mild aversive techniques, including mild shock with a prod, have been very effective in, for instance, patients with the Delange syndrome. They have been totally ineffective in the Lesch–Nyhan syndrome. Most observers have found the behavior to worsen with aversive techniques. We have encountered patients who have been subjected to extreme aversive techniques, such as slapping, hitting, and locking alone in a dark room, never with any shred of improvement. Most institutions which have removed restraints in programs of behavioral modification have ended up with extreme examples of mutilation that were very upsetting for the family and the staff, and, of course, the patient. This approach to behavior modification is known as extinction. It is generally considered to be undesirable in the management of self-mutilation. Increase in the rate of deviant behavior in the early stages of such a program is characteristic. Severe losses of tissue and blindness have been observed under these circumstances in mentally retarded, self-mutilative patients (Duker, 1975). Nevertheless, it has generally been observed in patients with the Lesch–Nyhan syndrome that mutilative behavior increases under some circumstances. Some conditions appear to reinforce it. These include the responses of parents, attendants, nurses, and others to the behavior and its attendant pain, blood, and horror. The crying of the child in response to his

[4]Posey Company, 39 South Santa Anita Avenue, Pasadena, California.

pain elicits responses which are reinforcing. The sight of the patient's injured part, or of his own blood, may be perversely reinforcing.

Extinction therapy in which the patient was ignored when he bit without restraints was reported to be successful in a patient with the Lesch–Nyhan syndrome reported by Duker (1975). Extinction was combined with removal to a new environment, and the rate of biting behavior was documented to decrease. This patient also was a head banger and the therapy failed to decrease that behavior; instead it increased. The report is not a convincing success. However, a similar extinction in biting behavior was documented in a number of patients by Anderson, Herrmann, Alpert, and Dancis (1975), whose technique was to turn away when the patient went to bite himself. These investigators reported an increase in biting behavior with aversive stimulation, so that there was a distinct difference in response to extinction therapy. We have recently studied a patient who was the product of an independent program of extinction therapy conceived for him by the staff at the Arizona Training Program in Tucson, Arizona. There is no question that biting of the hands was not a problem for this boy, and it was of considerable advantage to him not to have his hands restrained. His primary teeth had been removed prior to the start of this program. He developed a single lower tooth and proceeded to lacerate his lower lip. This tooth was removed to prevent disfigurement, for he continually worked at the area. Furthermore, he slept only fitfully at night until he was restrained for sleep.

The results obtained to date are mildly encouraging. They indicate that the behavior is subject to some modification. On the other hand, it is clearly not a complete therapy, and there may even be displacement from an area of abnormal behavior improved to one that develops or worsens. The approach merits intensive further investigation.

Chemical Approaches to the Modification of Behavior

Understanding of the molecular feature of the Lesch–Nyhan syndrome and its metabolic consequences led to highly effective therapy for those aspects of the disease that are directly related to uric acid. Treatment with allopurinol which inhibits xanthine oxidase regularly lowers the concentrations of uric acid in the blood and urine. It is in this way possible to prevent arthritis tophi, renal stones, and fatal nephropathy. This treatment has not influenced the neurologic, cerebral, or behavioral manifestations of the disease. These observations, along with the fact that a number of patients have now been treated with allopurinol from birth and never had significant elevations of uric acid (Marks, Baum, Keele, Kay, & MacFarlen, 1968), indicate clearly that the cerebral and behavioral aspects of this

disease are not a consequence of elevated concentrations of uric acid.

In a recent communication from Japan (Mizuno & Yugari, 1974) the oral administration of L-5-hydroxytryptophan was associated with a marked reduction in the rate of self-mutilative behavior in patients with the Lesch–Nyhan syndrome. Four patients were treated with 1–8 mg of hydroxytryptophan per kg of body weight per day for 36 weeks. It was said that mutilation ceased within 1–3 days of the initiation of treatment. There were no adverse effects. Mutilation reappeared within 12–15 hours of the discontinuation of treatment.

There is information from a variety of other sources which provides a rationale for serotonergic influences in self-mutilative behavior. Self-mutilation has been induced in rats and rabbits by the administration of caffeine or theophylline (Boyd, Dolman, Knight, & Sheppard, 1965; Morgan, Schneiderman, & Nyhan, 1970). Aggressive behavior has been observed in experimental animals following the administration of psychotomimetic drugs (Valzelli, 1967). In rats aggression has been studied in an assay, the end point of which is the killing of a mouse introduced into the cage. Some rats are spontaneously muricidal. Aggressiveness may also be induced by the production of lesions that transsect the olfactory pathways. In studies in which serotonin turnover was blocked by monoamine oxidase inhibitors such as pargyline, analysis of the content of serotonin in the brain was significantly lower in aggressive animals than in normal animals (Valzelli, 1967). Increased aggressive behavior was reported in rats given p-chlorophenylalanine which inhibits the synthesis of serotonin (Dichiara, Camba, & Spano, 1971). The administration of 5-hydroxytryptophan, which is the immediate precursor of serotonin, to rats made highly muricidal by olfactory bulbotomy significantly reduced this aggressive behavior (Dichiara et al., 1971). A dose of 30 mg/kg was employed. Rats selected for their muricidal behavior were found to lose this in response to treatment with 200 mg/kg of 5-hydroxytryptophan (Kulkarni & Bocknik, 1973). The data provide a background for the use of measures calculated to increase the cerebral content of serotonin in an approach to the management of patients with self-mutilation.

Recent experience with the use of 5-hydroxytryptophan in man indicates that large amounts may be administered with safety. Its combination with a peripheral aromatic amino acid decarboxylase inhibitor is pharmacologically rational. Like dopamine, 5-hydroxytryptamine cannot enter the brain directly. Rather the free acid, 5-hydroxytryptophan, crosses into the brain where it is converted to serotonin. Yet, in the presence of an active decarboxylase, most hydroxytryptophan administered is converted peripherally to serotonin and thus lost to the central nervous system. Carbidopa (MK-486) is a highly effective inhibitor of the decarboxylase and it does not cross the blood–brain barrier. Thus it is a peripheral decarboxylase inhib-

itor. It has been used predominantly, along with dopa, in the treatment of Parkinson's disease. Wyatt and colleagues (Wyatt, Vaughan, Galanter, Kaplan, & Green, 1972; Wyatt, Kaplan, & Vaughan, 1973; Wyatt & Gillin, 1974) have employed 5-hydroxytryptophan in the management of patients with schizophrenia. These investigators gave 5-hydroxytryptophan along with carbidopa in doses up to 6 g and 150 mg per day, respectively. If the dose of hydroxytryptophan was increased slowly, side effects were minimal or absent. Rapid increase in dosage or abrupt discontinuation of 5-hydroxytryptophan produced side effects, including nausea, vomiting, diarrhea, diaphoresis, and mild diastolic hypotension. Two patients had grand mal seizures on abrupt withdrawal of the drug. Coleman (1971) has treated a large series of infants with Down's syndrome with 5-hydroxytryptophan. She has reported doses of 1–10 mg/kg even from the first days of life. As many as 15% of these infants developed seizures resembling infantile spasms. The electroencephalogram was that of hypsarrhythmia.

A positive effect of pharmacologic therapy on self-mutilative behavior in patients with the Lesch–Nyhan syndrome would be readily apparent. The patient usually cannot be released from restraint even for seconds without biting himself. The rapidity and ferocity with which biting takes place are difficult to overemphasize. This inhibits quantitation, for one tends to hold the patient after restraints are removed, and the data may reflect the frequency of release by the attendant rather than patient-generated rates. We have therefore undertaken to obtain quantitative behavioral data using timed videotape recordings of facial expression and body movement under standardized conditions. This provides hard copy records for scoring behavior. It permits independent scorers or coders, and reexamination from time to time in analyses using the VIDR system of Ekman and Friesen (1969).

It is clear from results to date that the administration of 5-hydroxytryptophan can lead to a modification in behavior. A successfully treated patient is able in the presence of the drug to tolerate being without restraint for short periods of time. Two hours is about maximal, and someone must be with the patient at all times when the restraints are off. The patient usually prefers to hold something to immobilize himself while restraints are off. Thus we have seen an effect from treatment. However, the results are considerably less encouraging than the Japanese workers implied (Mizuno & Yugari, 1974). Furthermore, we have observed any therapeutic effect at all in only one patient treated with 5-hydroxytryptophan alone. Much of the hydroxytryptophan administered is decarboxylated. A major portion appears in the urine as 5-hydroxyindoleacetic acid, and increasing the dose does not reliably increase the effect.

For these reasons we have turned our attention to the decarboxylase inhibitor. We have now had experience with a small number of patients

treated with carbidopa and hydroxytryptophan. The results are considerably more interesting. A therapeutic effect is regularly achievable. Periods up to 8 hours have been readily tolerated without restraint. The patient has been observed under conditions in which he thought he was alone without any biting behavior. It is not inconsistent that most patients do not respond to 5-hydroxytryptophan alone while most seem to respond to 5-hydroxytryptophan when it is combined with a peripheral decarboxylase inhibitor. Only the dicarboxylic acid 5-hydroxytryptophan can cross the blood–brain barrier. Our data on urinary 5-hydroxyindoleacetic acid indicate that in the absence of the decarboxylase inhibitor very little 5-hydroxytryptophan must get into the central nervous system. Our results are preliminary. It is already apparent that tolerance develops rapidly to these regimens of treatment. Nevertheless, the results are encouraging. They indicate that the problem is researchable and that the behavior is subject to chemical modification. It is possible that combinations of pharmacologic and psychologic approaches to treatment might be combined to create a therapeutic environment for these patients.

REFERENCES

Anderson, L. T., Herrmann, L., Alpert, M., & Dancis, J. Elimination of self-mutilation in Lesch–Nyhan disease (Abstr.). *Pediatric Research,* 1975, *9,* 257.

Balis, M. E., Krakoff, I. H., Berman, P. H., & Dancis, J. Urinary metabolites in congenital hyperuricosuria. *Science,* 1967, *156,* 1122-1123.

Boyd, E. M., Dolman, M., Knight, L. M., & Sheppard, E. P. The chronic oral toxicity of caffeine. *Canadian Journal of Physiologic Pharmacology,* 1965, *43,* 995.

Bryson, Y., Sakati, N., Nyhan, W. L., & Fish, C. H. Self-mutilative behavior in the Cornelia de Lange syndrome. *American Journal of Mental Deficiency,* 1971, *76,* 319-324.

Coleman, M. Infantile spasms associated with 5-hydroxytryptophan administration in patients with Down's syndrome. *Neurology,* 1971, *21,* 911-919.

Dichiara, G., Camba, R., & Spano, P. F. Evidence for inhibition by brain serotonin of mouse killing behaviour in rats. *Nature,* 1971, *233,* 272.

Duker, P. Behaviour control of self-biting in a Lesch-Nyhan patient. *Journal of Mental Deficiency Research,* 1975, *19,* 11-19.

Ekman, P., & Friesen, W. A tool for the analysis of motion picture film or videotape. *American Psychologist,* 1969, *24,* 240-243.

Hoefnagel, D. The syndrome of athetoid cerebral palsy, mental deficiency, self-mutilation and hyperuricemia. *Journal of Mental Deficiency Research,* 1965, *9,* 69-74.

Howard, R. S., & Walzak, M. P. A new cause for uric acid stones in childhood. *Journal of Urology,* 1967, *98,* 639-642.

Johnson, H. G., Nyhan, W. L., Shear, C., Ekman, P., & Friesen, W. A behavioral phenotype in the DeLange syndrome. Pediatric Research, *10,* 1976.

Kulkarni, R. G. R., & Bocknik, S. E. Muricidal block induced by 5-hydroxytryptophan in the rat. *Archives Internationales de Pharmacodynamie et de Therapie,* 1973, *201,* 308-313.

Lesch, M., & Nyhan, W. L. A familial disorder of uric acid metabolism and central nervous system function. *American Journal of Medicine,* 1964, *36,* 561-570.

Letts, R. M., & Hobson, D. A. Special devices as aids in the management of child self-mutilation in the Lesch–Nyhan syndrome. *Pediatrics,* 1975, *55,* 853-855.

Marks, J. F., Baum, J., Keele, D. K., Kay, J. L., & MacFarlen, A. Lesch–Nyhan syndrome treated from the early neonatal period. *Pediatrics,* 1968, *42,* 357-359.

Mizuno, T.-I., & Yugari, Y., Self-mutilation in the Lesch–Nyhan syndrome. *Lancet,* 1974, *1,* 761.

Morgan, L. L., Schneiderman, N., & Nyhan, W. L. Theophylline: Induction of self-biting in rabbits. *Psychonomic Science,* 1970, *19,* 37-38.

Nyhan, W. L. Introduction, clinical and genetic features. In J. H. Bland (Ed.), *Seminars on the Lesch–Nyhan syndrome. Federal Proceedings,* 1968, *27,* 1027-1033.

Nyhan, W. L. Clinical features of the Lesch–Nyhan syndrome. *Archives of Internal Medicine,* 1972, *130,* 186-192. (a)

Nyhan, W. L. Behavioral phenotypes in organic genetic disease. Presidential address to the Society for Pediatric Research, May 1, 1971. *Pediatric Research,* 1972, *6,* 1-9. (b)

Nyhan, W. L. The Lesch–Nyhan syndrome. In W. P. Creger (Ed.), *Annual Reviews, Annual Review of Medicine,* 1973, *24,* 41-60.

Nyhan, W. L. The Lesch–Nyhan syndrome. In J. Hamburger, J. Crosnier, & M. H. Maxwell (Eds.), *Advances in nephrology* (Vol. 3). Chicago: Yearbook Medical Publishers, 1974. Pp. 59-70.

Reed, W. B., & Fish, C. H., Hyperuricemia with self-mutilation and choreoathetosis. *Archives of Dermatology,* 1966, *94,* 194-195.

Scherzer, A. L., & Ilson, J. B. Normal intelligence in the Lesch–Nyhan syndrome. *Pediatrics,* 1969, *44,* 116-120.

Seegmiller, J. E., Rosenbloom, F. M., & Kelley, W. N. Enzyme defect associated with a sex-linked human neurological disorder and excessive purine synthesis. *Science,* 1967, *155,* 1682.

Shear, C. S., Nyhan, W. L., Kirman, B. H., & Stern, J. Self-mutilative behavior as a feature of the de Lange syndrome. *Journal of Pediatrics,* 1971, *78,* 506-509.

Skyler, J. S., Neelon, F. A., Arnold, W. J., Kelley, W. N., & Lebovitz, H. E. Growth retardation in the Lesch–Nyhan syndrome. *Acta Endocrinologica,* 1974, *75,* 3-10.

Sweetman, L. Urinary and CSF oxypurine levels and allopurinol metabolism in the Lesch–Nyhan syndrome. *Federal Proceedings,* 1968, *27,* 1055-1059.

Sweetman, L., & Nyhan, W. L. Excretion of hypoxanthine and xanthine in a genetic disease of purine metabolism. *Nature,* 1967, *215,* 859-860.

Sweetman, L., & Nyhan, W. L. Further studies of the enzyme composition of mutant cells in X-linked uric aciduria. *Archives of Internal Medicine,* 1972, *130,* 214-220.

Valzelli, L. Drugs and aggressiveness. *Advances in Pharmacology,* 1967, *5,* 79-108.

Wyatt, R. J., & Gillin, J. C. The development of tolerance to and dependence on endogenous neurotransmitters. In A. J. Mandell (Ed.), *Neurobiological mechanisms of adaptation and behavior,* New York: Raven Press, 1974.

Wyatt, R. J., Kaplan, J., & Vaughan, T. Tolerance and dependence to serotonin, a speculation. *Archives of General Psychiatry* 1973, *29,* 597-599.

Wyatt, R., Vaughan, T., Galanter, M., Kaplan, J., & Green, R. Behavioral changes of chronic schizophrenic patients given L-5-hydroxytryptophan. *Science,* 1972, *177,* 1124-1126.