Lesch-Nyhan disease is an inborn error of purine metabolism that has caught the imagination of a number of physicians and scientists. Initial excitement was relevant to the facts that a well defined defect in a single enzyme represented not only the first molecular disorder of purine metabolism to be recognized, but the first biochemical explanation for at least a subset of patients with symptoms of gout and the other effects of hyperuricemia. However, even casual observation of patients with this disease provides a much larger sphere of interest in terms of potential chemical understanding of cerebral function. From the beginning we were impressed by the idea that this was an opportunity to define the manner in which a distinct abnormality in biochemistry could lead to stereotyped patterns of neurologic disease and abnormal behavior. The disease was described over 30 years ago (1). The promise is still there. Many questions have been answered, but many remain to be elucidated.

Lesch-Nyhan disease is caused by deficient activity of the enzyme hypoxanthine–guanine phosphoribosyltransferase (HPRT) (2). This enzyme normally catalyzes the conversion of hypoxanthine and guanine to their respective nucleotides, inosinic acid (IMP) and guanlyc acid (GMP). This leads to enormous overproduction of purine nucleotides via de novo synthesis and accumualtion of uric acid. The logical results of this metabolic abnormality are hyperuricemia, uricosuria, tophaceous gout, and urate nephropathy. In addition to these manifestations, mutations in the HPRT gene lead to a variable spectrum of neurologic and behavioral phenotypes. In the classical Lesch-Nyhan syndrome patients have striking neurologic, cognitive, and behavioral abnormalities, including self-injurious behavior. Hyperuricmic variants display only gout or renal disease and have no neurological abnormalities. The neurological variants present an intermediate picture in which there are motor and neurological abnormalities, but no abnormal behavior. Enormous progress has been made in definition of the various phenotypes and the management of those aspects of disease that are caused by the accumulation of uric acid. Progress has also been impressive in the biochemical definition of the overproduction of purine by the de novo pathway and by evidence of hypoxanthine excess, especially in the central nervous system. Biochemical progress has also been evident in recognition of the enzyme defect in HPRT, and in the molecular biology of the gene and definition of the nature of mutation. We can expect continued progress in each of these areas. On the other hand, much remains to be learned. The relationship of the neurological and behavioral features of the disease has been elusive. Without a clear understanding of fundamental mechanisms, meaningful interventions into these important manifestations of disease have not been developed. It is now hoped that with the advent of powerful new tools for research, understandings of these interrelations will emerge, along with better ways to care for patients.

Lesch-Nyhan disease is a model system for the elucidation of relationships between cognitive development, neurologic function, and behavior and the biochemistry of the brain. Implicit is the idea that if we could really understand how these linkages occur, there would be broad implications for neurobiology. The disease provides a considerable target for the development of treatment of manifestations for which there is now little control. The classic patients display a neurologic picture that is similar to that of cerebral palsy. Muscle tone and deep tendon reflexes are increased, and there are abnormal movements such as chorea and athetosis, as well as dystonia. None of these patients has learned to walk and most require assistance in sitting. The usual appearance of a patient with this disease is in a narrow form-fitting wheelchair supported by a seat belt and a belt around the chest that permits the patient to participate in the world around him. Most patients display considerably more cognitive ability than the motor defect would imply. Most have speech, and a few have even had normal intelligence based on testing. At least one of our patients has succeeded in a normal school curriculum. Two patients have graduated from high school. The testing of intelligence is so complicated by the behavior of these patients that most testing is doubtless inaccurate. A patient who, when presented with written words or images on pages, cannot resist an urge to tear them out of the book or throw them on the floor or at the examiner makes for a difficult test object. These behavioral features of the disease are uniform in the classic disease. The best known of these manifestations is the self-injurious behavior; the most common of these behaviors is biting, which leads to loss of tissue around the lip and partial amputation of the tongue. Those who do not bite themselves tend to indulge in other self-injurious behaviors, such as head-banging or bruising the chin on a hard surface. These patients have normal pain sensation and regularly display evidence of this when they injure themselves. They sleep poorly and often keep the entire family awake until methods are developed for protection against mutilation when family members are asleep. Patients also have aggressive behavior directed against others, limited largely by the limitation imposed by the motor defect. Most patients vomit, and there have been complicating esophageal ulcers or anemia from chronic blood loss, as well as acute hemorrhage. This also tends to get incorporated into behavior as a form of aggression.
Neuropathogenesis

The manner in which the abnormality in purine metabolism causes the neurologic and behavioral characteristics of the classic disease has not been established, but there is a variety of evidence that this has to do with an abnormality in neurotransmitter balance. A relationship to serotonin was first suggested by studies of aggressive murine behavior in animals with significantly lowered contents of serotonin in the brain. The administration of 5-hydroxytryptophan, an immediate precursor of serotonin, statistically significantly reduced this aggressive behavior (3). In Lesch-Nyhan patients the excretion of 5-hydroxy-indoleacetic acid in the urine (4) was significantly increased. This might mean that the amounts of serotonin in the brain were low. The administration of 5-hydroxytryptophan and carbipride in conjunction with imipramine to increase levels of serotonin (5) abolished the self-injurious behavior. This was a very rewarding result, although it was disappointing in that it was always temporary. In general, the effects lasted only a few weeks and could not be reobtained by a further administration of the compounds.

Evidence for abnormality in dopamine neurotransmitter function has come from positron emission tomography (PET), in which ligands that bind to dopamine-related proteins in the brain have been used. The earliest studies used compounds that bound to dopamine D1 or D2 receptors in the basal ganglia. These studies provided nice pictures in which the appearance of the basal ganglia was highlighted. However, quantitative data did not reveal important differences in these receptors in Lesch-Nyhan patients versus controls. Ernst et al. (6) studied this system by the administration of $^{18}$F-dopa, which permits external imaging by PET and provides a measure of the activity of the dopa decarboxylase enzyme and hence of neuronal dopamine activity. They found a striking decrease in Lesch-Nyhan patients compared to controls.

The most compelling evidence from PET scanning has come from work of Wong et al. (7), who used the ligand $^{11}$C]WIN 35,428, which binds specifically to dopamine transporters. In these studies of 6 patients, there was as much as a 75% reduction of dopamine transporter in putamen and as much as 63% in caudate compared to 10 control individuals and 3 patients with Rett syndrome. These data are consistent with a reduced density of dopamine containing neurons or terminals. These investigators also studied volumetric magnetic resonance imaging in the same individuals and found that caudate volume was reduced by 30%. Correction for volume reduction gave a figure for an even greater decrease in the caudate-to-cerebellum ratio of binding to dopamine transporters. These studies are strong evidence for alteration in dopaminergic systems in the Lesch-Nyhan disease.

These data are consistent with the pioneering work on neurotransmitters reported by Lloyd et al. in 1981 (8). These investigators studied the brains postmortem of three patients with the Lesch-Nyhan disease who, like previously autopsied patients, displayed no morphological abnormalities. Control material was obtained postmortem from the brains of age-matched patients who had no evidence of neurologic disease (n = 8). Studies of neurotransmitter biochemistry revealed that dopaminergic function in the caudate, putamen, nucleus accumbens, and external pallidum was significantly lower in patients than in controls. It was impressive that significant differences could be obtained in a series in which the number of patients was as low as three, giving credence to the significance of these findings. Values in the patient ranged from 10 to 30% of the control values. The low levels included those of dopamine itself, homovanillic acid (HVA), dihydroxyphenylalanine decarboxylase, and tyrosine hydroxylase. The deficits in dopamine function were not as severe as those seen in Parkinson disease, but they were significantly different from controls.

In the same study, data on norepinephrine and serotonin function were not significantly different in the brains of the patients. The activity of dopamine β-hydroxylase was not decreased in the hypothalamus, and that is significant because alterations in this enzyme have previously been reported in the plasma of some patients. The levels of serotonin were slightly increased and significantly so in the putamen. 5-Hydroxyindolacetic acid was also elevated there, as well as in the pallidum, so these data were consistent with our findings in the urine of patients with this disease. The data on serotonin and norepinephrine highlight the specificity of the observations on dopaminergic function.

Similarly, we studied the concentrations of HVA in the cerebrospinal fluid in a patient with this disease and found that the level was low (9). A more elaborate study was reported by Silverstein et al. (10). They pointed out that concentrations in cerebrospinal fluid of HVA and 5-hydroxyindolacetic acid undergo age-related changes. There is a rapid fall in the first 3 years of life and then a more gradual fall through adolescence. Accordingly, they did serial measurements of cerebrospinal fluid HVA in 4 patients over a 5-year period with an age range of 1.5–17 years, and they compared these data with age-related data on 94 controls. The values for the Lesch-Nyhan patients were lower than the mean for age in 18 of 19 samples tested, and 10 samples fell below the range found in controls.

The hypothesis that dopamine is related to self-injurious behavior received support by the development of a rat model by Breeze et al. (11). They used 6-hydroxydopamine (6-OHDA), which destroys catecholamine-containing neurons in the brain. Treatment of adult animals makes them sensitive to a number of behaviors on the administration of dopa or a dopa agonist. Treatment of newborn animals leads to self-injurious behavior in response to a dopa agonist. This change in sensitivity was a long-lasting effect of neonatal treatment with 6-OHDA. As long as that compound was given in the neonatal period, the dopa agonist could be given even in adulthood and the self-injurious response was observed. In one series, 0 of 20 control animals exhibited dopa-induced self-injurious behavior. Similarly, 0 of 18 animals given 6-OHDA as adults, and 39 of 60 treated in the neonatal period with 6-OHDA, exhibited self-injurious behavior, a highly significant difference. There were also dose-effect relationships. In the neonatally treated animals, the greater the dose of dopa or dopa agonist, the greater the percentage of animals exhibiting self-injurious behavior.

Breeze et al. (11) conducted pharmacological studies in which D2 or mixed D1–D2 receptor antagonists such as haloperidol and flupentixol had some effect in blocking the self-injurious response to dopa. On the other hand, there was virtually complete inhibition of this response when the D1 antagonist SCH-23390 was used. Unfortunately, to date none of the D1 or D2 antagonists that have been used in Lesch-Nyhan patients have been effective in the management of their self-injurious behavior.

Other Disease Models

The basal ganglia are increasingly recognized as a target for the adverse effects of metabolic disease. Haas et al. (12) reported experience with an 8-year-old girl with propionic acidemia who was in excellent metabolic control, and was in hospital after receiving intensive treatment for pancreatitis such that her levels of the abnormal metabolites in the urine were lower than they had ever been. Nevertheless, as she was being prepared for discharge she became suddenly aphasic, experienced complete infarction of her basal ganglia, and died within a few days. A review of our our only other patient on whom an autopsy had been done after death from propionic acidemia revealed lesions in the basal ganglia in which there was neuronal loss.

More recently, we reported (13) on two other patients in whom propionic acidemia had a more indolent presentation than in the
usual patient (the usual patient has acute life-threatening episodes of ketoacidosis that at least call attention to the disease). These patients instead presented first neurologically. On first examination, one of the patients appeared to be a typical Lesch-Nyhan patient. He was wheelchair-bound and had a combination of athetoid and dystonic movements that were typical of his basal ganglia disease. However, he had no abnormalities in behavior and his metabolic disease appeared to be static at that time. We had not seen the second patient, although a diagnosis of propionic academia was made for the first time after the age of 20. Our first encounter with the second patient was a blood sample that was sent to the laboratory for HPRT analysis because he not only had a diagnosis of athetoid cerebral palsy, but he had destructively bitten his lower lip. The HPRT was normal, and we suggested sending blood and urine for further metabolic studies. Further studies found methylcitrate and the other organic acids typical of propionic academia, and enzymatic analysis revealed a severe deficiency of propionyl CoA carboxylase.

In seeking models for abnormalities in dopaminergic systems we have begun to look at patients with abnormalities in biotin synthetin system (14). Patients with these abnormalities first became recognized with the programs of neonatal screening for phenylketonuria. It became apparent that there was a subset of patients uncovered by neonatal screening programs that, despite excellent compliance with the diet and normal levels of phenylalanine after treatment, went on to develop severe mental retardation. A number of these disorders reflect various steps in the synthesis of tetrahydrobiotin or BH4, which is the essential cofactor of the phenylalanine hydroxylase reaction (14). The importance from the dopamine point of view is that BH4 is also the cofactor for the tyrosine hydroxylase reaction in the synthesis of dopa, and, hence, dopamine. In the first step of this reaction, the guanosine triphosphate (GTP) reaction is severely deficient in patients homozygous for mutations in this gene; they have the typical so-called malignant hyperphenylalaninemia resulting from abnormalities in biotin synthetin. Other patients have since been identified that have clinical generalized dystonia that is inherited in autosomal dominant fashion and is responsive to low doses of dopa (15). Patients with this syndrome have mutations on one of their two genes on chromosome 14q. Many males in affected families are asymptomatic even though they carry the mutation, whereas females tend to develop clinical dystonia. An intermediate syndrome has recently been discovered in families with dopa-responsive dystonia in which children who are heterozygous for two different mutations in the cyclohydrolyase gene have a syndrome markedly dystonic and somewhat responsive to dopa intermediate between the classic autosomal recessive cyclohydrolyase deficiency and the dopa-responsive dystonia. These patients seem to do better when treated with tetrahydrobiotin as well as with dopa.

A relationship between deficiency of HPRT and its potential shortages of IMP and GMP and its di- and tri-nucleotides could be through a requirement for GTP in signal transduction through the dopamine receptor-agonist interaction (16–18). Alternatively, there could be defective synthesis of tetrahydrobiotin, as in the GTP cyclohydrolyase deficiency dopa-responsive dystonia, leading to a shortage of dopamine in the basal ganglia.

In summary, there is substantial evidence relevant to dopamine and the Lesch-Nyhan disease. I am hopeful that with time we will be able to make the appropriate connections between neurotransmitter interrelations and mutation in the *HPRT* gene. I am hopeful that all of this will lead to a more effective means of treatment in Lesch-Nyhan disease.