Review Article

Diagnosis and Treatment of the Lesch-Nyhan Syndrome

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Introduction

In 1964, Lesch and Nyhan [43] described two brothers with a disorder characterized by marked hyperuricemia, excessive uric acid production, choreoathetosis, striking mental and growth retardation, spasticity, and self-mutilation. Three years later, Seegmiller, Rosenbloom, and Kelley [64] described a virtually "complete" deficiency of an enzyme of purine metabolism, hypoxanthine-guanine phosphoribosyltransferase (EC. 2.4.2.8) (HGPRT) (some authors have used the nomenclature inosine monophosphate (IMP)-pyrophosphate phosphoribosyl transferase [5]) in erythrocyte lysates from three patients and in cultured skin fibroblasts from another patient with this disease, the Lesch-Nyhan syndrome. The enzyme defect was subsequently confirmed in other tissues from many similarly affected patients [30].

A number of patients have now been described who are hyperuricemic and produce excessive quantities of uric acid, but who have a "partial" rather than a "complete" deficiency of HGPRT [13, 34, 36, 38, 66]. These patients usually present with gouty arthritis or uric acid calculi, not with the devastating neurologic and behavioral features characteristic of the functionally complete enzyme defect [34]. These two diseases, both resulting from a deficiency of HGPRT, afflict a distinct segment of the hyperuricemic population. Both have now been well defined at the clinical and molecular level. The syndrome associated with a functionally complete deficiency of this enzyme is the subject of this review. This syndrome is of special interest in that it provides the first example of a specific enzyme

defect associated with a reproducible pattern of abnormal behavior.

Enzyme Defect

Hypoxanthine-guanine phosphoribosyltransferase catalyzes the conversion of hypoxanthine to inosinic acid and guanine to guanylic acid in the presence of phosphoribosylpyrophosphate (PP-ribose-P) [39, 40]. The natural purine base, xanthine, as well as several purine analogs, including 6-mercaptopurine, allopurinol, 8-azaguanine and 6-thioguanine, are also substrates for the enzyme [9, 42] (Fig. 1). The enzyme is activated by magnesium ions and is inhibited by the products of the reaction. Guanylic acid and its di- and triphosphates are much stronger inhibitors than inosinic or xanthylic acid [42].

Patients with the Lesch-Nyhan syndrome usually have no detectable HGPRT activity in erythrocytes or in tissues obtained at autopsy (Table I). Recently, one patient with the Lesch-Nyhan syndrome was found to have a mutant form of HGPRT with altered kinetic constants for both PP-ribose-P and the purine substrate [44] (Table II). Erythrocytes from this patient actually have normal HGPRT activity when assayed at very high concentrations of substrates; however, at the usual concentrations of substrates employed for the assay *in vitro* there is essentially no activity. It also seems likely, based on the actual intracellular concentration of these substrates, that this mutant enzyme exhibits little if any function *in vivo*. This particular mutant form of the enzyme is of particular interest because, unlike the normal enzyme, it seems to exhibit

sigmoidal kinetics with PP-ribose-P as the variable substrate (Fig. 2). Although levels of activity ranging from 0.2 to 5% of normal have recently been reported in several other patients with the classical syndrome, it is not clear whether the values observed are significantly above background in these particular studies or whether these also represent mutant forms of the enzyme with altered kinetic properties [49, 65]. Despite

Fig. 1. The reaction catalyzed by hypoxanthine-guanine phosphoribosyltransferase illustrated with hypoxanthine as substrate.

Table I. Specific activity of phosphoribosyltransferase of erythrocyte hemolysates from subjects with Lesch-Nyhan syndrome¹

Subjects	Phosphoribosyltransferase activity, nmoles/mg protein/hr		
	Hypoxanthine	Guanine	Adenine
Normal ²	103 $\pm$ 18	103 $\pm$ 21	31 $\pm$ 6
Patients with Lesch-Nyhan syndrome			
<i>JW</i>	<0.01	<0.004	58
<i>TS</i>	<0.01	<0.004	39
<i>DF</i>	<0.01	<0.004	53
<i>BM</i>	<0.01	<0.004	49
<i>MB</i>	<0.01	<0.004	56
<i>SM</i>	<0.01	<0.004	51
<i>FH</i>	<0.01	<0.004	94
<i>MW</i>	<0.01	<0.004	65
<i>JS</i>	<0.01	<0.004	71

¹ From Kelley [30].

² Mean $\pm$ sd for 32 subjects.

Table II. Comparison of the kinetic properties of the normal and a mutant hypoxanthine-guanine phosphoribosyltransferase enzyme

Cell	Enzyme source Type	Phosphoribosyltransferase activity, nmole/mg/hr		Apparent K_m			
				Mg PP-ribose-P ² , M		Guanine, M	Hypoxanthine, M
		Guanine	Hypoxanthine	Guanine	Hypoxanthine		
Erythrocyte	Normal	98 $\pm$ 14	97 $\pm$ 19 ³	2.5 $\times$ 10 ⁻⁴		5.0 $\times$ 10 ⁻⁶	1.7 $\times$ 10 ⁻⁵
	Mutant	8.2 (12.1) ⁴	33.7 (94.4)	3.2 $\times$ 10 ⁻³ ⁵	2.8 $\times$ 10 ⁻³ ⁵	4.8 $\times$ 10 ⁻⁵	1.8 $\times$ 10 ⁻⁴
Fibroblast	Normal	141 $\pm$ 17 ⁶		1.0 $\times$ 10 ⁻⁴			
	Mutant	10.4		2.0 $\times$ 10 ⁻³ ⁵			

¹ From McDonald and Kelley [44].

² PP-ribose-P: phosphoribosylpyrophosphate.

³ Mean $\pm$ sd in 119 subjects.

⁴ Numbers in parentheses represent V_{max} of the mutant enzyme for each purine substrate calculated from the Michaelis-Menten formula ($V_{max} = (K_m + S)/S$).

⁵ Values depict $S_{0.5}$ rather than K_m .

⁶ Mean $\pm$ sd in 13 normal cell strains.

Fig. 2. Effect of Mg phosphoribosylpyrophosphate (PRPP) concentration on guanosine monophosphate synthesis by normal and a mutant hypoxanthine-guanine phosphoribosyltransferase enzyme (from McDonald and Kelley [44]).

the absence of detectable enzyme activity in hemolysates from most patients with this disease, all examined so far appear to have a protein which exhibits cross reactivity (CRM+) with an antibody to the normal enzyme [2]. This indicates that the mutations responsible for the development of a functionally complete deficiency of this enzyme are usually, if not always, on the structural gene coding for the enzyme.

Fibroblasts cultured from many patients with the Lesch-Nyhan syndrome have detectable, although very low, levels of HGPRT activity [19, 35] (Table III). Detailed examination of the mutant enzyme in fibroblasts cultured from 10 patients with the Lesch-Nyhan syndrome revealed at least three different phenotypes (Table IV). These studies provide additional evidence that the mutations responsible for the development of this disease, at least in these 10 patients, are on the structural gene for the HGPRT enzyme. In addition, the mutations are probably not large deletions, frame

Table III. Phosphoribosyltransferase activity in fibroblasts cultured from hyperuricemic patients¹

Cell strain	No. of assays	Passage	Hypoxanthine-guanine phosphoribosyltransferase activity, nmoles/mg protein/hr	
			Mean	Range
Normal	13 ²	3-11	141±17 ³	95-190
Lesch-Nyhan syndrome				
121	17 ⁴	4-17	0.6	0.1-2.0
123	26	4-29	0.7	0.1-2.9
SM	4	13-24	1.0	0.1-2.4
JR	4	15-16	1.1	0.1-1.7
MW	3	13-17	1.3	0.1-2.0
182	9	5-16	0.6	0.1-3.0
193	8	5-13	11.0	5.4-15.2
197	9	7-11	2.0	0.9-6.1
198	10	4-8	2.7	1.4-3.6
199	10	4-7	2.9	1.9-4.9
200	10	4-9	4.0	0.1-9.0
"Partial" PRT ⁵ deficiency				
CN	2		11.0	
ES	2		26.0	

¹ Modified from Kelley and Meade [35].² Different cell strains.³ Standard deviation.⁴ Number of different preparations.⁵ PRT: phosphoribosyltransferase.Table IV. Genetic heterogeneity of hypoxanthine-guanine phosphoribosyltransferase deficiency in fibroblasts derived from patients with Lesch-Nyhan syndrome¹

	Product inhibition ²	Thermal stability	Prototype (cell strain)
Normal	+	+	
Mutant			
Type 1	+	+	193
Type 2	+	-	182, 197, 198, 199
Type 3	-	-	121

¹ From Kelley and Meade [35].² +: normal; -: abnormal.

shifts, or nonsense mutations, but are most likely point mutations causing a change in a single amino acid. It is clear from the study of the mutant forms of the enzyme in fibroblasts that a striking degree of genetic heterogeneity exists in the mutations leading to the Lesch-Nyhan syndrome. Antisera against erythrocyte HGPRT have recently been prepared and used to demonstrate the presence of normal amounts of immunologically identifiable but catalytically incompetent enzyme in erythrocytes obtained from five patients with the Lesch-Nyhan syndrome [59].

An increase in the activity of a closely related en-

zyme, adenine phosphoribosyltransferase (APRT) (EC. 2.4.2.7), which catalyzes the synthesis of adenylic acid from adenine in the presence of PP-ribose-P, was consistently observed in erythrocytes from patients with a complete deficiency of HGPRT [30, 64]. In many of the patients with a partial deficiency of HGPRT, the specific activity of erythrocyte APRT is also greater than normal. Greene *et al.* [24] have recently demonstrated that PP-ribose-P stabilizes purified APRT *in vitro*. In addition, free PP-ribose-P levels are increased in erythrocytes from patients lacking HGPRT who exhibit increased erythrocyte APRT [18, 24]. Greene and colleagues [24] have suggested that increased PP-ribose-P levels stabilize the APRT enzyme *in vivo* and that this leads to a diminished rate of degradation of the enzyme and thus to the increased specific activity. Although Greene *et al.* [24] and Rubin and co-workers [58] reported that APRT was more stable in circulating erythrocytes from patients with the Lesch-Nyhan syndrome than in those from normal subjects, this apparently is not true of cultured fibroblasts, although PP-ribose-P levels are increased in this type of cell as well [31].

Pathogenesis of Excessive Uric Acid Production

There are several possible mechanisms by which a deficiency of HGPRT could lead to excessive purine synthesis. The deficiency of this enzyme, which catalyzes the conversion of guanine to guanosine monophosphate (GMP) and hypoxanthine to IMP, might lead to an increase in purine synthesis *de novo* by virtue of a decreased synthesis of either IMP or GMP, inasmuch as these nucleotides are normally important inhibitors of purine biosynthesis *de novo*. Attempts to measure intracellular levels of GMP and IMP have been of only limited value, partly because of the very low intracellular concentration of these compounds under normal conditions [57].

An elevated intracellular concentration of PP-ribose-P has been demonstrated in erythrocytes [18, 25] and in cultured fibroblasts [57] obtained from patients with both the "partial" and "complete" enzyme defect (Table V). Furthermore, the elevated concentration of PP-ribose-P in fibroblasts has been shown to be the result of decreased utilization of the compound rather than increased synthesis [57]. An increased concentration of PP-ribose-P could increase purine biosynthesis *de novo* by providing more substrate for the presumed limiting step of this pathway, PP-ribose-P amidotransferase. The increased synthesis of purines observed in

patients with *type I* glycogen storage disease, which is due to a deficiency of glucose-6-phosphatase, has also been attributed on theoretical grounds to an increased concentration of PP-ribose-P [1, 27, 37]. In order for an increased concentration of PP-ribose-P to increase purine synthesis *de novo* in either of these conditions, however, the normal concentration of PP-ribose-P would need to be substantially less than that required for saturation of the enzyme. The concentration of PP-ribose-P in normal human erythrocytes ranges from 1 to 5×10^{-6} M, which is substantially less than the K_m for PP-ribose-P amidotransferase in mammalian adenocarcinoma cells (4.7×10^{-4} M) [26]. The Michaelis constants for this enzyme in normal human tissue, however, are not known, and the intracellular concentration of PP-ribose-P has been established only for mature erythrocytes. Data recently obtained from a study of the effects of orotic acid on purine synthesis in man as well as in cultured human cells, provide strong evidence that intracellular levels of PP-ribose-P are normally important in the regulation of purine biosynthesis *de novo* [32, 33]. From these considerations, it seems likely that increased levels of PP-ribose-P are at least partly responsible for the increased purine biosynthesis *de novo* in patients who have either "complete" or "partial" PRT deficiency.

Function of Hypoxanthine-Guanine Phosphoribosyltransferase in Relation to the Neurologic Defect

Identification of the normal function of HGPRT in brain is essential for a thorough understanding of the Lesch-Nyhan syndrome. The study of this question is made more difficult by the high probability that this enzyme has different functions in different cells, and by the observation that its loss is not at all detrimental to some cells.

One approach to understanding the disease is to ask what are the sources of the purine base substrates of HGPRT. There is little information regarding the supply of these purines to brain via the blood, but their concentrations in plasma are known to be quite low. Similarly, little is known about the metabolism of the nucleotides formed upon the breakdown of messenger RNA in brain. A third possibility is that purine bases may be derived from soluble purine ribonucleotides and in part reutilized via HGPRT. This has recently been studied in Ehrlich ascites tumor cells incubated *in vitro* [11].

When Ehrlich ascites tumor cells were incubated with glucose and 100 μ M adenine- 14 C, 14% of the radi-

Table V. Erythrocyte phosphoribosylpyrophosphate (PP-ribose-P) levels in hemizygotes and heterozygotes for "complete" phosphoribosyltransferase deficiency¹

	Erythrocyte PP-ribose-P, nmole/ml
Normal	4.4 ± 1.8
Hypoxanthine-guanine phosphoribosyltransferase deficiency	
Hemizygote	
ES	39.4
JK	20.5
WE	49.5
Heterozygote	
MS	6.5
ME	4.5
HK	1.5

¹ From Fox and Kelley [18].

oactive nucleotides formed were dephosphorylated in 90 min. When hypoxanthine- 14 C was used, 64% of the radioactive nucleotides formed were dephosphorylated in the same period. At least part of the hypoxanthine and guanine so produced would be available for re-use via HGPRT under appropriate conditions. The dephosphorylation of purine ribonucleotides, the first step in their conversion to hypoxanthine and guanine, is regulated in tumor cells by factors that are not yet understood. It is not even certain which enzyme(s) accomplish this dephosphorylation; several nucleotidases as well as several nonspecific phosphatases are all possibilities. Xanthosine monophosphate and IMP are dephosphorylated more readily than are adenosine monophosphate and GMP, but the basis for this difference is not known. Although dephosphorylation is generally believed to be inhibited by nucleoside triphosphates, under some conditions nucleoside monophosphates accumulate to quite high concentrations precisely when adenosine triphosphate concentrations are quite low. Clearly the whole question of nucleotide dephosphorylation and its regulation requires much more study.

The applicability of these studies of Ehrlich ascites tumor cells to the brain is uncertain; indeed, purine metabolism in this tissue has been studied by only a few investigators [61].

Some recent work, however, has shown that the maximum activity of adenine phosphoribosyltransferase in brain slices incubated *in vitro* was about 40% of the total activity measured in extracts of brain. The activity of hypoxanthine phosphoribosyltransferase in slices was about 2% of that measured in extracts, and that of guanine phosphoribosyltransferase was only 0.4% of that measured in extracts.

Preliminary studies suggest that one factor which regulates the activity of HGPRT in brain slices is the availability of PP-ribose-P. The rate of nucleotide synthesis from both adenine and guanine can be about doubled by the addition of guanosine, which can readily provide ribose 5-phosphate. The guanine which is also formed is rapidly and extensively deaminated, and this raises a serious question about the intracellular availability of guanine for HGPRT.

In contrast to the above-mentioned results of studies with Ehrlich ascites tumor cells, radioactive purine nucleotides formed upon incubation of brain slices with adenine- ^{14}C or hypoxanthine- ^{14}C were quite stable. Less than 0.5% of nucleotides formed from adenine were dephosphorylated, whereas dephosphorylation occurred in about 2% of nucleotides synthesized from hypoxanthine. Whether this low rate of dephosphorylation is true of brain cells *in vivo* is currently under investigation.

The rate of conversion of adenine nucleotides synthesized in brain slices from adenine- ^{14}C to guanine nucleotides is very slow ($< 0.5\%$ in 90 min, compared with 10% in Ehrlich ascites tumor cells), and the conversion of hypoxanthine- ^{14}C to guanine nucleotides is also less than 20% of that in Ehrlich ascites tumor cells. These results again suggest the potential importance of HGPRT activity in brain, but the question still remains, where does the guanine come from?

Although a beginning has been made in the attempt to understand the functions of HGPRT in brain and the basis of the pathology of the Lesch-Nyhan syndrome, a great deal more work on this subject is still required.

Incidence of the Syndrome in the Population

Since the syndrome was first described in 1964, about 80 cases have been reported [16], although as many as 150 may have been detected [8]. The number of patients affected in relation to a known population size was recently determined as a result of a meeting held in Montreal which was attended by representatives from different provinces in Canada.

Two sibling boys born in Ontario, who were investigated and reported by Partington and Hennen in 1967 [54], were the first cases of the Lesch-Nyhan syndrome identified in Canada. Both children subsequently died, and the findings at autopsy have been reported [12]. Two siblings in Manitoba were then diagnosed as having the syndrome, and, very recently, two others were identified in Northwest Ontario. One other boy with

the syndrome has been investigated in Toronto, and in Montreal a boy has been followed from the age of 6 months to 2.5 years. The last patient has the anticipated biochemical findings, and presents with spasticity and dystonia but no evidence of choreoathetosis. Within the last month this child has started to mutilate his fingers.

Some comparative calculations can be made on the basis of this incidence to give an indication of how many other patients may exist in the population. At the present time apparently 6 patients are alive in a population of 21 million, which gives an uncorrected prevalence of 1 in 3.5 million. The incidence of the disease *per annum* in the population can be calculated if we assume that the syndrome often does not present until a child is 2 years of age, that it has been described for 7 years, and that none of the patients in this series is older than 9 years of age. Thus it can be approximated that, in a population which has an annual live birth rate of 380,000 [10], one child *per annum* will be born with the Lesch-Nyhan syndrome. The difficulties inherent in calculating the incidence of a rare disease in the population are apparent. The above figures can only be regarded as minimal since it is not known how many patients with the syndrome have escaped diagnosis or remain unknown to the reviewers. The authors would appreciate being informed of all patients with the Lesch-Nyhan syndrome who are diagnosed in Canada.

Detection of Affected Children and Carriers

Knowledge of the families with the risk of having a child with the Lesch-Nyhan syndrome and the detection of heterozygous carriers has importance for genetic counseling, prenatal diagnosis, and the institution of early therapy if this should be possible. If the family at risk has been identified by the birth of an affected child, then the identification of the metabolic defect in a male fetus can be determined by prenatal diagnosis based on the incorporation of ^3H -hypoxanthine into nucleic acids in cultured cells obtained by amniocentesis [8, 15] and by enzyme assays on the cultured amniotic cells [7]. After birth, male infants at risk for the disease could be detected on the basis of their elevated urinary uric acid:creatinine ratios [29]; the mean value was 1.5 for normal infants in the 1st week of life, and the upper limit of normal (defined as the mean + 2 sd) was 2.8. Screening programs based on this principle have now been initiated in the Province of Quebec [45]. Two screening tests based upon

erythrocyte enzyme assay are also available. One is based on incorporation of ^3H -hypoxanthine into erythrocytes [7], and the other is dependent on precipitation of the nucleotide product of HGPRT activity with lanthanum chloride [3].

Heterozygotes cannot be detected on the basis of their erythrocyte HPRT activity because this is generally in the normal range. Possible explanations that have been proposed for this finding are that in the bone matrix either the inactivation of the X chromosome in heterozygous females is not random, or that following random inactivation there is selection against the cell with HGPRT deficiency [53]. HPRT activity has been measured in cultured skin fibroblasts but no limiting range for heterozygotes can be defined. Wood and Pinsky [71] have found that if the HPRT/APRT ratio in cultured fibroblasts is determined, then the heterozygote group can be more readily defined because the factors influencing enzyme concentration in cell extract appear to be similar for the two enzymes. This method may be of limited value if the proportions of HPRT +ve and HPRT -ve cells are not approximately equal. Alternative techniques require cloning of cells from heterozygotes [48, 60] or growth in selective media [20, 47, 70]. A technique of enzyme assay of isolated hair cell follicles, in which some natural cloning of cells in heterozygous carriers appears to take place, has been recently described [21, 23].

Treatment

Several forms of therapy have been proposed and employed, although no consistently successful results have yet been reported and criteria for efficacy are difficult to assess. Each of the different aspects of the clinical presentation may represent a different feature of the biochemical abnormality and could possibly respond to a different therapeutic approach. The only feature which is readily amenable to treatment is hyperuricemia with associated gouty arthritis [62] and hyperuricemic nephropathy [52]. Both of these are potentially serious clinical conditions in this syndrome and can be prevented by use of allopurinol [28]. As a result of the use of this xanthine oxidase inhibitor, the concentration in serum and the excretion in urine of uric acid are greatly reduced and oxypurines appear in the urine (hypoxanthine:xanthine = approximately 2.5:1) [67]. Xanthine itself has a very limited solubility in urine, and xanthine calculus formation in the kidney after allopurinol administration has been reported [4,

72]. Control of the level of uric acid in serum with allopurinol does not prevent development of the characteristic neurologic disorder [46], the most debilitating part of which is the choreoathetosis which may be so severe that it interferes with the patient's nutrition even if he is being fed by some other person. The patient then becomes malnourished and succumbs to infection.

The role of self-mutilation in this syndrome requires special consideration in view of the possibility that it may not be directly related to the spasticity and choreoathetosis, and might respond in a different way to therapy. It has been suggested [16] that these children have a very low threshold for the activation of a mechanism that controls repetitive, compulsive, pain-causing behavior. A pattern of aggression and self-mutilation is set up early in life, and therapeutic attempts may have to be aimed at controlling behavioral changes as well as changes in central nervous control. It is this feature of the disorder that seems to be most variable, depending on the environment and tranquility of the child, and patterns of self-mutilation vary considerably.

The degree of mental retardation has been difficult to assess because of the children's other disabilities, but some degree of mental retardation is usually present and, if this is to be prevented, treatment should be started preferably before symptoms of the disorder are evident. Indeed some evidence has recently been presented that the metabolic disorder which subsequently gives rise to the neurologic defect may have been taking place *in utero* [14]. There is still some doubt at the present time as to whether the neurologic symptoms should be regarded as the outcome of a deficiency or an overproduction disease, and treatment has been attempted with both possibilities in mind.

If the principal symptomatology arises from the failure of feedback inhibition of the first step in purine biosynthesis, the condensation of glutamine with 5-phosphoribosylpyrophosphate to give 5-phosphoribosylamine, then it is possible that this feedback inhibition could be re-instituted and the availability of 5-phosphoribosylpyrophosphate could be decreased by feeding adenine to the patients, providing that allopurinol is also administered to prevent formation of 2,8-deoxyadenine, which has nephrotoxic properties [55]. However, administration of adenine, diaminopurine, and inosine had no discernible effect on the central nervous system dysfunction [6, 63]. Van der Zee *et al.* [68] administered adenine to two patients who had the Lesch-Nyhan syndrome with megaloblastic anemia.

The rate of incorporation of ^{14}C -glycine into urinary uric acid was decreased and the vitamin-refractory megaloblastic anemia was corrected. No improvement in the neurologic abnormality was observed with or without the addition of allopurinol. At the symposium held in Montreal in 1971, Winter [69] also reported that therapy with adenine as well as folic acid reduced the daily turnover of uric acid (but not to normal) and increased levels of glutamine in cerebrospinal fluid without any objective neurologic improvement and without any reduction in the concentration of uric acid in serum. A deficiency in serum folic acid was observed in these patients as had been reported [34], although in another study of five patients no folate deficiency was observed [51]. Cultured skin fibroblasts from patients with this disorder have an increased requirement for adenine which can be obviated by the addition of folic acid [17].

Overproduction of uric acid can also be inhibited by nicotinamide [41]. This substance utilizes phosphoribosylpyrophosphate in its conversion to nicotinic acid mononucleotide and hence depletes the available PRPP which could be utilized for purine synthesis. This therapeutic approach has been used by Mongeau [50] in the treatment of a child with predominant spasticity and dystonia with hyperuricemia and a deficiency of HGPRT in erythrocytes and cultured skin fibroblasts. Clinical assessment of the outcome of this therapy will be difficult because the child does not show all the characteristic features of the syndrome. Treatment with nicotinamide (500 mg twice daily) for 5 months without allopurinol did not reduce the patient's serum uric acid level of 10 mg/100 ml, and his clinical symptomatology remained unchanged.

If the therapeutic approach of slowing down purine metabolism by depleting the cells of available phosphoribosylpyrophosphate should fail, a possible explanation could lie in the observations by Greene and Seegmiller [25] and by Fox and Kelley [18] that the concentration of phosphoribosylpyrophosphate in erythrocytes of patients with this syndrome may be 10 times higher than in those of normal subjects and hence reduction of the intracellular PRPP concentration may not be sufficient to affect a maximal overproduction of purine intermediates unless a striking decrease is achieved.

An alternative approach to therapy would be to assume that despite the overall increase of purine synthesis, important nucleotide intermediates were deficient because of a failure to recycle hypoxanthine back to IMP. This possibility was investigated by Ghadimi

et al. [22] who found in one patient that the level of glutamine in serum was reduced as compared with that in normal control children and that this could be corrected by addition of monosodium glutamate (10 g/24 hr) to the diet. According to these authors, the patient's protein intake then improved as did his general well-being, and the severity of his neurologic symptoms decreased. During part of this period he was also treated with allopurinol, but at other times this was replaced by a placebo capsule. Variations in his clinical symptoms were not related to the presence or absence of allopurinol, but continuation of allopurinol was advised to reduce the probable complications of protracted hyperuricemia. Another child, 8 years of age, with the typical Lesch-Nyhan syndrome and an erythrocyte HPRT defect was investigated at the Hospital for Sick Children in Toronto. He was not malnourished at the time of the investigation. Sodium glutamate was administered (2 g/24 hr) at a time when he was taking allopurinol. No significant change occurred in his total excretion of purine in urine or in his clinical status; however, further studies would be required at a higher dosage level to confirm the observation of Ghadimi *et al.* Raivio and Seegmiller [56] recently reported that cultured HGPRT-deficient cells can convert adenine to GMP and that this conversion is dependent on high concentrations of glutamine in the growth media.

Further information is required which would link the now well described enzyme defect with development of the clinical syndrome so that a rational form of therapy could be initiated at an early age. Essentially all the analytical procedures are now available for either antenatal or neonatal diagnosis based on a suitable screening program, so there is a high probability that the devastating neurologic consequences of the disease could be averted if metabolic correlates between the enzyme defect and the clinical syndrome could be defined.

Summary

The relation between the enzyme defect and the clinical aspects of the Lesch-Nyhan syndrome are discussed. An estimate is made of the incidence of the disease in the population and the presence of incomplete defects and enzyme variants. The methods for antenatal detection of affected males and carrier females are reviewed. The significance of control of purine metabolism in the central nervous system is discussed and the rationale and results of various forms of therapy are considered.

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