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Caring for Children
with

LESCH NYHAN DISEASE

PUMPA

A Guide for Parents and Professionals

Introduction

The objective of this book is to provide parents and professionals with the basic facts about Lesch Nyhan Disease (LND) in a simple and acceptable fashion - its clinical presentation, biochemistry, and progression, and particularly where to look when they want more help. To this end we have drawn on the experience of those involved at every level in the United Kingdom and Ireland and also in the USA.

The first edition of this book was in 1997 following the first Seminar held by the Purine Metabolic Patients Association (PUMPA) which was on Lesch Nyhan Syndrome. It forms part of a series, which will cover other Metabolic Diseases under the PUMPA umbrella and will undoubtedly fill a much-needed gap. This volume follows the second PUMPA Seminar on Lesch Nyhan Syndrome in November 2001. It contains updated material and the *Endpiece* gives details of future plans to form a European Network.

The publishers wish to acknowledge with grateful thanks the valuable contributions to this booklet from:

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Notes

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Foreword

A Parent's Perspective

Ian Potter, Parent, Purine Metabolic Patients Association.

Parents faced with the devastating diagnosis of Lesch Nyhan disease for the first time simply do not know which way to turn. After the first shock, as proud parents of a seemingly bonny baby, whom they took to the doctor because of their worry over the failure to pass normal milestones or because of these persistent orange crystals on the nappy, they want to know three things.

Why Them? Why has fate chosen their baby?

The answer is genetic change, which goes on constantly in every one of us. Our cells contain chromosomes which are made up of genes which carry the blue print for all our characteristics like hair colour, height, sex and so on. Usually this continual change alters genes that are not important for health and growth. Unfortunately in the LND a sudden change (mutation) has taken place in a gene on a particular part of the female chromosome which just happens to carry the blueprint for an enzyme which is vital to our normal growth and development. It is no comfort to parents to know that their son will be one of only about 4 boys each year in the United Kingdom whose genetic material has undergone a similar change. It is only later when they contact one another that such families learn that they can receive and give considerable comfort and support to each other from their own individual experience.

What Does This Mean?

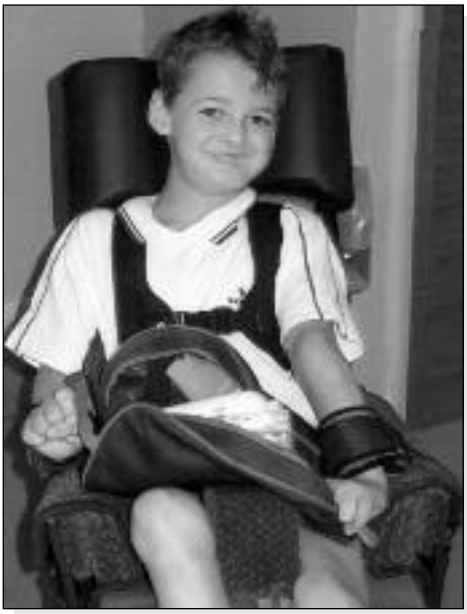
This is the second question. When the Doctors first give the parents the diagnosis that this vital enzyme essential for children to walk and talk as well as to grow normally, is missing (or not working), it is impossible to grasp. They are simply shattered. They could never have visualised this and it is only after they have returned home and the initial shock has worn off that they suddenly want to know more about this dreadful condition. LND is so rare that possibly not even the Paediatrician at their general hospital will have seen such a patient before and the doctor may only be able to give the bare facts, or refer to a chapter in a textbook.

At the local library, to which the parents then resort, they generally find only medical texts which contain details of the very first and naturally very seriously affected cases,

which can be very frightening. They are not to know that in the nearly forty years since the syndrome was first recognised, the picture, although still serious, is not quite as horrendous as in those first cases.

How Can Their Child Be Treated?

This last question is perhaps the most difficult to answer. Knowledge about the management of boys with LND has been gathered, but this information has until now not been widely published. Isolated Doctors, Therapists and Carers who have worked with this Disease have advanced the day-to-day management of the boys through their particular concern and the involvement of other equally innovative individuals. Their work is described in this book. Consequently, it is now possible to improve the quality of life considerably for a boy with LND. The sad and inescapable fact is that at present there is no treatment that will effect a permanent cure for the crippling symptoms of LND, much more research is needed.



Ian Potters son, Paul.

Section A

LESCH NYHAN DISEASE - WHAT IS IT?

H Anne Simmonds, Purine Research Unit, Guy's Hospital, London

Lesch Nyhan Disease, abbreviated hereafter as LND (referred to in the earlier proceedings as Lesch Nyhan syndrome, or LNS) is one of 28 genetic metabolic disorders under the PUMPA umbrella and one of more than 1300 inherited disorders of metabolism now recognised. It derives its name from the two astute clinicians in the USA who in 1964 recognised a recurring pattern of neurological abnormalities in two young boys from the same family, which suggested an inherited disorder. LND is just one of the inherited disorders that may be the underlying cause in a child who is not passing the normal milestones and thus presents a diagnostic problem to parents and paediatricians.

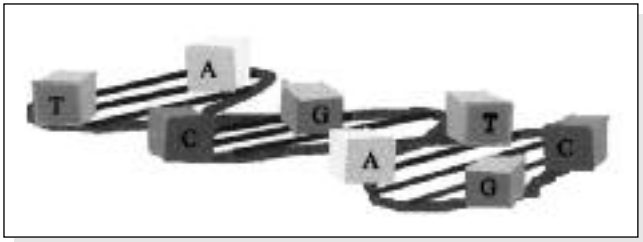
The genetic defect in LND lies in an enzyme of purine metabolism, which is a dreadful mouthful, even for those in the business - Hypoxanthine - Guanine Phosphoribosyl Transferase - abbreviated as HPRT. (Older textbooks call it HGPRT, but international convention now uses four code letters for defective enzymes).

Why does a defect in a single enzyme of purine metabolism cause such problems?

Purine metabolism is a network involving linked steps rather like the London underground, each step being carried out by a single enzyme. Like the underground, when a block (mutation) occurs in a step between two stations (i.e. in a gene coding for this enzyme) the train may not arrive with vital food in time, sometimes not at all. Alternatively, a failure of the network to remove a particular chemical may cause the problem. Thus the clinical manifestations can be caused either by a build up of toxic chemicals on one side of the block, or a deficiency of vital chemicals on the other.

The next question is: what is a purine?

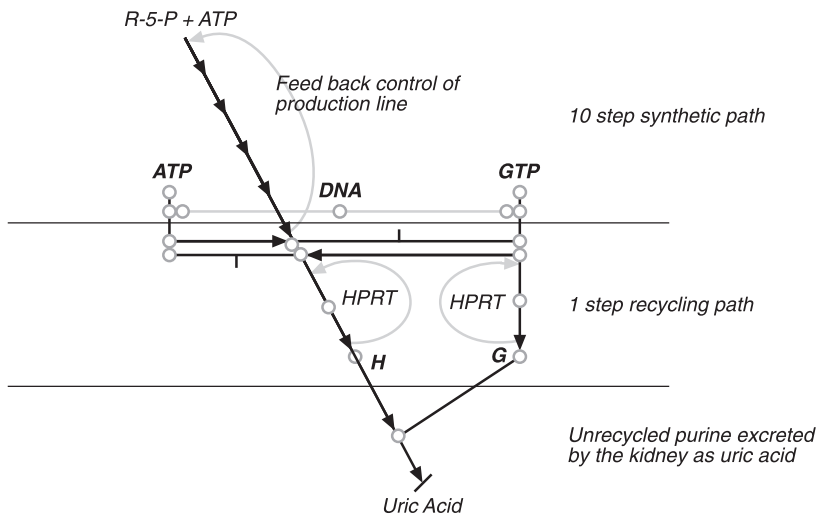
Purine is simply the name given to the structure of a group of essential chemicals, which must be built up in our body - they are not derived from our diet. The name comes from the Latin purum uricum (pure uric acid) which was given to this end product of purine turnover in humans when first identified as the main constituent of a kidney stone in 1776.



Everyone will have heard of **DNA** from the many TV programmes related to the human genome project, but few are aware that its building blocks (the letters A, G, C, T) are purines (A, G), together with companion chemicals called pyrimidines (C, T).

These A's and G's are built up from simple precursors (sugar and phosphate etc) at great expense by a 10 step 'Do It Yourself' de novo synthesis route, which not only supplies these important building blocks for our DNA 'alphabet', but also our energy in the form ATP (the largest amount of purine in the body).

Figure 3: Importance of HPRT in human cells



LND results from a defect in a single but vital step in this network - **the enzyme HPRT,** which normally recycles the purine bases HYPOXANTHINE (H) or GUANINE (G) to which ATP and DNA are degraded in our cells during metabolic work. An example is our red blood cells, which consist mainly of ATP, but have a short life and must be replaced. HPRT does this recycling by picking up an anchor - a phosphate sugar (ribose - PR) inside the cell and transfers it (T) back onto H or G - hence the name HPRT. In this way HPRT prevents H or G from being lost from the

cell. In the absence of HPRT they are transferred to the liver where they are picked up by two other WASTE REMOVAL enzymes waiting to convert them to uric acid, which is excreted by the kidney. URIC ACID is the insoluble chemical, which causes kidney stones that may block or damage the kidney (and also cause GOUT when the levels in the blood rise too high).

HPRT plays another critical role in that the chemical it forms (called a nucleotide) sends a stop message to the computer controlling the synthetic path. As a result normally only a small amount of purine is lost daily in the form of uric acid and has to be replaced by the expensive synthetic path. HPRT is present in virtually all tissues, but its highest activity is in brain and testes. It appears that a deficiency of the recycling of H and/or G in the brain is the main problem resulting from the lack of HPRT. This is understandable because the brain has essentially little *de novo synthetic* ability. The importance of this will be discussed in Section B page xx

The vital role of HPRT in the normal interplay between purine synthesis and recycling is evident from the biochemical and clinical consequences of HPRT deficiency. Without HPRT the synthetic route fails to get the usual 'stop' signal and goes on manufacturing uric acid uncontrollably. This explains why LND may present in the first weeks of life with orange crystals on the nappy or in the urine, often noted by an astute mother so it is important in any such diagnosis to listen to her. Sometimes acute kidney failure and gout occurs secondary to this.

A recurring problem in correct diagnosis of LND is the fact that some boys do not have an elevated plasma uric acid because children normally excrete their uric acid much better than adults do. Consequently when plasma uric acid alone is measured and found to be normal in boys with the classic LND symptoms they are wrongly categorised as having 'cerebral palsy of unknown cause.' Only later when they present with gout or kidney stones - often not till adolescence- is the genetic defect underlying the nervous system problems first identified. The vital message is that any boy with classic LND symptoms must have his enzymes measured in the blood and uric acid measured in both blood and urine - a blood uric acid alone can be very misleading See section C.

Not all boys with HPRT deficiency have LND.

Only the most extreme form of HPRT deficiency presents as the severely incapacitating LND. As in other metabolic disorders there is considerable genetic variation in the neurological problems depending on the amount of enzyme protein the defective gene can make. Consequently, HPRT deficiency can present with any

one of five degrees of severity, the classic LND, three intermediate forms called LND variants, all of which have varying but milder neurological symptoms. The fifth is called PARTIAL HPRT deficiency or Kelley-Seegmiller syndrome (KSS) where no neurological symptoms are found. However, uric acid overproduction occurs in all five categories. The fact that the uric acid overproduction is always present, can often be an early clue to observant parents, as we shall learn in Section B.

It is equally important for parents to know that many perfectly **normal healthy newborn babies excrete excess uric acid in the first few days,** which may show up on the nappies as orange crystals. This is of particular relevance in families with a history of LND and it is essential that the parents be advised of this to put their minds at rest.

How is LND inherited?

LND is a disorder, usually affecting BOYS but carried by females. It is thus an 'X linked recessive disorder'. We know females have 2 X chromosomes, males one X and one Y. This means that in LND the mother will carry the defective (or 'wonky') gene on one of her X chromosomes, but the other X chromosome will be **normal.** Boys inherit one X chromosome from their mother and one Y chromosome from their father (Figure 4). Girls have two X-chromosomes, receiving one X from each parent. Sometimes the mother has two normal X-chromosomes and the mutation takes place at the time of egg production (i.e. a 'new' mutation). However, if the mother is a carrier of the affected gene, each of her daughters will also have a 50% chance of being a carrier, and each of her sons will have a 50% chance of being affected with LND.

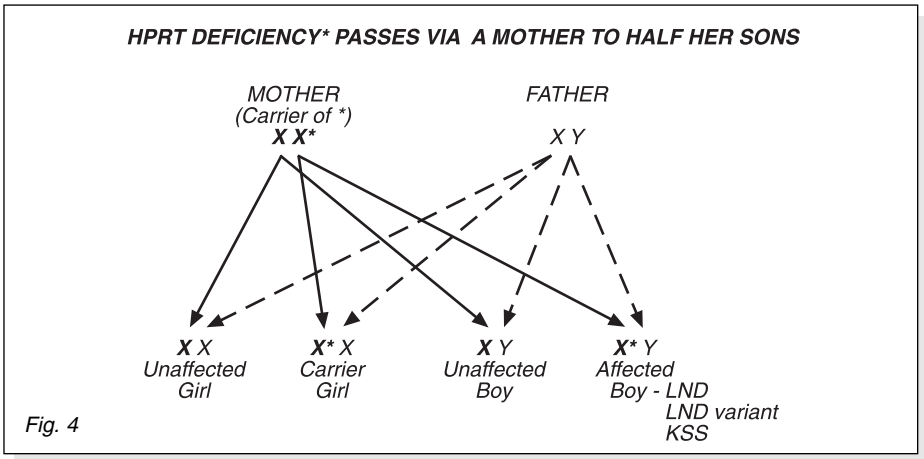


Fig. 4

A

Although rare, the incidence of LND is higher than for other purine disorders and up to four boys will be born annually in any country the size of the UK. A third of these cases may be new mutations. Rarely LND has been reported in girls, due to unusual genetic events, so this possibility should not be ruled out entirely just because a child with classic LND symptoms is a female. The appropriate diagnostic tests must be done.

Section B

MEDICAL DIAGNOSIS & TREATMENT & THERAPY MANAGEMENT OF LESCH NYHAN DISEASE

Dr Gillian T McCarthy,
Chailey Heritage Clinical Services, East Sussex

Clinical Diagnosis

It is important that diagnosis is not delayed so that appropriate management starts from an early age. This benefits the baby and parents and may prevent the birth of another affected child by promoting genetic counselling for family members.

Early signs of LND are - low muscle tone, poor feeding and excessive crying and failure to thrive. Because one of the side effects of the enzyme deficiency is overproduction of uric acid, crystals may form in the urine and appear like sand in the nappy. These crystals can cause small stones in the kidneys, causing pain and damage, which may be the first sign of the disease.

A few babies present in acute renal failure because of the gross excess of uric acid excreted in the urine. Infections can cause dehydration and add to the uric acid burden to the kidney. However, more commonly there is a history of feeding problems, an unhappy crying baby and developmental delay. Dystonia and athetosis (unwanted movements) usually appear in the second year and self-injury from the second year of life.

LND should be considered in any boy with unexplained athetoid cerebral palsy particularly if there is a family history of cerebral palsy, or self-injury. The importance of correct metabolic diagnosis cannot be over-emphasised.

Team Approach to Management

It is helpful to develop a team approach to the management of LND. Our experience at Chailey Heritage has shown the benefit of involving the skills of rehabilitation engineers, occupational and physiotherapists, speech and language therapists, teachers and carers as well as psychologists, nurses, doctors and social workers. This may seem a huge number of people but understanding the natural history of the condition and putting our heads together with the child and family to problem-solve can be immensely rewarding. The team members learn from each other and

contribute more successfully in this way. The aim is always to facilitate the development and health of the child to enable him to reach his potential.

B

Motor Disorder

In the first few months of life the baby may be very floppy, unable to hold up his head or reach for and grasp toys. He may be very irritable and difficult to feed with a poor suck and swallow. In spite of his problems he will be visually alert and sociable, smiling and responding. Dystonia is a disorder of muscle tone producing typical contractile spasms and fixed postures of the limbs or trunk. Athetosis describes large amplitude, writhing, involuntary movements made worse by emotion or intention.

Fig. 5. A standing aid with high back support to prevent neck extension. Note the tray with bowl cut in.

Fig. 6. Supporting CAPS seat with tray and high back rest, note arm splints allow some elbow flexion, also arm straps.

The degree of motor disorder is variable, some boys develop good motor control but in the majority the extreme torsion spasm and self-injury make weight bearing or independent walking impossible.

However, it is important to give plenty of motor stimulation and encouragement and to use appropriate walking aids and equipment for standing to encourage independence. Early seating support will enable hand control to develop and the use of a tray with guard will prevent toys from falling too easily. FIGURE 6.

A programme of posture management is recommended to prevent fixed deformities developing around the hips and spine. This includes night-time positioning if the posture is distorted.

Speech and Communication

The baby with LND needs to be seen by a Speech and Language Therapist skilled in management of young children with cerebral palsy. The first task is to help with eating and drinking. This moves on naturally to the development of early communication skills and play.

Feeding difficulties may be associated with the development of a hiatus hernia. This is a condition where the upper part of the stomach slides up into the chest causing some of the acid stomach contents to regurgitate upwards. There may be vomiting, chest pain, bleeding and sometimes inhalation into the lungs. Acid reflux can also occur without a hernia. Vomiting can be used by some boys as an aggressive act, also spitting. Severe complications can occur in this condition so it is important to investigate and treat actively.

Sometimes surgical treatment is required. Medical treatment includes medication to reduce acid production in the stomach and to increase stomach emptying.

The speech muscles are affected by dystonic spasm causing slurring of speech sounds, particularly under stress. Stress management by parents and carers is essential in the early years and later it is helpful to teach relaxation techniques to the boys, see page 34.

An alternative communication system for speech may be necessary to reduce stress. For example using pictures or symbols initially and later moving on to the written word, which can be linked to computers for schoolwork.

Intellectual development

Intelligence seems to be impaired to some extent though this is variable. As assessment is extremely difficult because of impaired fine motor control, language tests are most useful. Using these tests there seems to be slowing of acquisition of new information in boys assessed throughout childhood.

Reports in the literature and observational reports suggest that intellectual levels range from moderate learning disability to low average intelligence. The evidence also points to a plateau in development in the second decade of life.

Management of Self Injury and Spasm

Self-injurious behaviour concerns parents and carers most as it is distressing for the child who has normal pain perception and asks to be protected from further injury. It occurs in at least 85% of boys with LND.

Lip biting is often the first self-injurious behaviour. A children's dentist who has experience of this condition can be a great help, see page 23.

Management of SIB is dealt with in Section F.

The dystonic spasms may be a source of injury especially the extreme head extension and arching of the back which can result in damage to the spinal cord in the neck or cause pressure on the blood vessels at the base of the brain. For this reason the head should be protected from over-extension when sitting by using a headrest and positioning in bed should be attended to. Parents have developed various individual solutions to keep boys safe in bed.

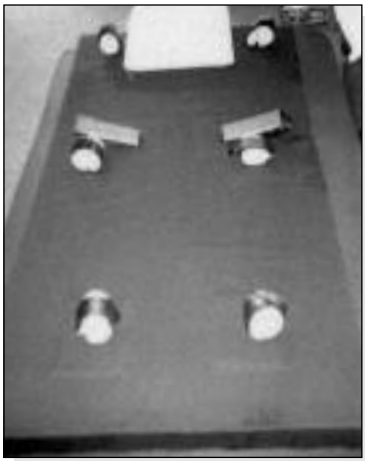


Fig. 7. Simple dressing board allows one person to manage dressing.

Boys usually ask for arms to be restrained and become very distressed if restraints are removed. However, some degree of movement can be allowed if arm splints are made with hinges allowing a degree of elbow flexion as in Figure 6.

It is also helpful to provide straps that can be used to prevent arms and legs flying out and hitting objects or people.

Dressing can be difficult for one person to achieve, so the use of a simple dressing board, which holds the child securely, can be a great help.

Provision of a suitable toilet seat allowing privacy and safety on the toilet also allows toilet training and most boys can be toilet trained. A bath seat is also helpful.

Fig. 8. Moulded toilet seat.

Sleep problems

Parents report a high level of sleep problems including difficulty getting off to sleep, noisy breathing and stopping breathing during sleep, 'sleep apnoea'. Posture during sleep may cause injury, especially extreme neck extension and various solutions have been found to improve sleeping positions. Nocturnal video observation is useful.

Day time apnoea can also occur triggered by acid

reflux from the stomach with inhalation, epilepsy and neck extension causing the blood supply to the back of the brain to be reduced.

Fig. 9. Padded bath support with high back support.

Medical treatment

- Allopurinol lowers the uric acid level in the blood, thus preventing kidney stones and gout. The dose needs to be carefully monitored as Xanthine levels may rise and cause stones instead. Mist Potassium Citrate makes the urine alkaline and increases solubility of uric acid. A high fluid intake is also recommended. It should be noted that some drugs called 'uricosuric agents' interact with Allopurinol and increase the delivery of uric acid to the kidneys and risk acute crystal deposition causing discomfort or pain. These include Ampicillin and Amoxicillin. It is important to check for this interaction when new medicines are prescribed.
- Adequate pain control when injury occurs prevents a vicious circle of pain, injury, pain.
- It is sometimes helpful to use DIAZEPAM to reduce anxiety and spasm but dependency may develop. BACLOFEN, which reduces muscle spasm, may be helpful. The dose can be adjusted to give maximum effect avoiding side effects.
- There is no one drug that we know will be helpful to treat the movement disorder in all cases. A Paediatric Neurologist will give advice if there is a particularly difficult symptom or if epilepsy develops.
- Drug treatment of SIB is also difficult DIAZEPAM, CARBAMAZEPINE, VALPROATE AND GABAPENTIN have all been used with variable success. Behavioural management is usually most successful although medication may be required for short periods.

Growth and Puberty

In the first year of life growth may be affected by feeding difficulties and stomach problems. It is helpful to take advice from a paediatric dietician, as calorie

supplements may be required. Although most of the uric acid excreted arises from the metabolic defect, the use of a low purine, low caffeine diet is recommended. This reduces the total uric acid load to the kidney and avoids peaks that may cause pain and irritability. See diet sheet page 36.

B

Many boys with LND fail to go into puberty because the testes may be damaged by the metabolic disorder. Normally the testes have a high level of HPRT, as there is high metabolic activity associated with production of sperm. The growth spurt of puberty may not occur and the boys remain quite short.

In the present state of our knowledge LND is a progressive condition. Anecdotally life expectancy appears to have improved in the past 20 years, possibly because of improved general management. Breathing problems and chest infections are often the cause of death.

The Neurological Problem

HPRT is present throughout the body and is responsible for salvaging and recycling processes. It is particularly important in the brain and normally at high levels in the basal ganglia. Recent brain imaging research has shown that the size of the basal ganglia is reduced in boys with LND and the total size of the brain is also reduced.

The basal ganglia [putamen, caudate nucleus and thalamus] are situated deep in the brain and connect to the motor cortex, the frontal cortex the brain stem and the cerebellum, acting as a complex junction responsible for motor control, co-ordination, balance and movement - and linked to emotional control. It is likely that the motor problems of dystonia and athetosis and the emotional problems of self-injurious behaviour and aggression arise at cellular level in these brain areas.

Research points to the interruption of neurotransmission [the chemical link which passes messages between cells] in the dopamine and serotonin pathways caused by the HPRT deficiency. This results in failure of dendritic arborisation of the dopamine fibres [these are the networks of connections between individual brain cells. If there is less dopamine there is less neurotransmission ergo less arborisation].

PET imaging studies make it possible to view basal ganglia function in vivo and point to a deficit of dopamine transporter binding in LND, which correlates with the dystonia and athetosis but is not sufficient explanation for the self-injurious behaviour. In vitro cellular research using nerve cells derived from neuroblastoma also points to defects in dendritic development. (Connelly G).

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Section C

METABOLIC DIAGNOSIS OF LND

John A Duley & Lynette D Fairbanks, Purine Research Unit, Guy's Hospital, London

Methods of Laboratory Diagnosis for LND

There are a number of methods used in the diagnosis of LND, or partial HPRT deficiency. Usually a battery of tests is essential.

- **From the HPRT deficiency in the cells.** This requires referral to a specialist centre aware of the many pitfalls in trying to measure HPRT activity. HPRT must be evaluated in both disrupted and intact blood cells and sometimes from fibroblasts cultured from a skin biopsy. LND patients have virtually no detectable HPRT activity in any cell types, intact or disrupted. Patients with a partial HPRT deficiency frequently have no detectable activity in disrupted cells because of unstable enzyme but may have measurable activity in intact red cells.
- **Uric acid in blood and urine.** This method of diagnosis depends on measuring raised levels of uric acid in blood plasma and urine compared with healthy boys of a similar age. However, uric acid overproduction is also found in other conditions. Consequently HPRT activity must be measured in blood cells as well. It is vital to know that because the kidneys of all children clear their uric acid better than adults, the plasma uric acid in LND boys may be normal, but the urine uric acid will be grossly elevated. *Thus both must be measured together with enzyme activity when making a diagnosis* (see below)
- **Kidney ultrasound.** In some cases this technology has provided the first clue to the diagnosis of kidney failure in baby boys with HPRT deficiency. Uric acid crystals blocking the kidney or causing tissue damage may result in kidney failure. Acute kidney failure is frequently precipitated by infection, which increases the body's burden of uric acid and causes severe dehydration. Vomiting and diarrhoea have the same effect.

Problems that can mask the diagnosis

Plasma uric acid is always lower in children than adults because of higher kidney clearance. Thus although all boys with either partial or complete HPRT deficiency produce too much uric acid, **plasma uric acid may not appear raised until**

puberty because of the high clearance of uric acid. This fact is not widely known and LND has been missed because only **blood** uric acid levels have been measured initially and found to be normal. **Uric acid must always be measured in urine as well as plasma.** Uric acid present in the urine can be compared with creatinine, which is produced in similar amounts daily in the body. The ratio of uric acid to creatinine is within fixed limits in healthy people, depending on age and is a useful yardstick for comparison. In children and adults with HPRT deficiency this ratio is increased 2 to 4 fold compared with controls of similar age.

Uric acid overproduction can be masked in kidney failure. In acute kidney failure the uric acid/creatinine ratio in urine can be normal. However, the important clue is that the plasma uric acid will be grossly raised in this case. **This further underlines why both plasma and urinary uric acid must always be measured.**

Laboratory Follow-up of Treatment with Allopurinol

Uric acid is very insoluble and can cause both gout and kidney stones. Treatment of the overproduction of uric acid is thus essential. This can be achieved by treatment with Allopurinol, which inhibits the enzyme XANTHINE OXIDASE, which is responsible for forming uric acid. However, Allopurinol treatment causes increased production of XANTHINE, which is even more insoluble than uric acid. Uric acid solubility can be improved 12 fold by the use of potassium citrate but this does not improve xanthine solubility. The correct dose of Allopurinol can be determined by frequent checks of the xanthine and uric acid concentrations in blood and urine in the laboratory. A high fluid intake is important especially if the child has an infection.

Carrier Detection

Previous methods of measuring HPRT deficiency in female carriers were based on enzyme activity measurement of hair roots or cultured cells. These methods were very unreliable. Genetic tests using DNA have improved the situation so that 85 to 90 per cent of carriers can be identified. Genetic testing depends upon first having blood or cell samples from the affected boy in the family. This is used to test for the DNA mutation. As nearly every family have a different mutation the test can be difficult and expensive. If it is successful the boy's mother and other female members of the family can be tested for carrier status, If the mother is not a carrier it is not necessary to test the family further, see section D.

Pre-natal Diagnosis.

Pre-natal detection of HPRT deficiency is possible at about 12 weeks gestation, using

a small sample of tissue from the placenta obtained by needle biopsy under ultra sound guidance (chorionic villus sampling, CVS). Such tests should only be done in specialist laboratories. Sexing of cells from the sample can be done speedily, but it is important for the parents to know that there is a 50% chance of a male baby being completely normal thus HPRT activity should always be measured as well.

Cultured amniotic fluid cells and foetal blood may also be used to measure HPRT between 12 and 24 weeks. Foetal blood can be particularly useful for confirmation of a CVS test done in the first 12 weeks if reassurance is required.

Section D

MOLECULAR DIAGNOSIS OF LESCH NYHAN DISEASE

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Structure of the HPRT gene.

The genetic code (made up of 4 bases with the letters A, G, C, T, see page xx) providing the information to make HPRT, is carried on the X-chromosome and is contained in a sentence about 42,000 letters long. Only 654 letters of information are needed to make the HPRT enzyme and this information is organised into 9 separate words (or exons). A spelling mistake in one of these words is known as a mutation and will lead to HPRT deficiency. These mistakes are extremely rare and occur with a frequency of about **1 in 380,000 births.**

Why are nearly all Lesch Nyhan patients male?

Females have 2 X-chromosomes, one inherited from the mother one from the father. If one is abnormal the other will give protection and females mostly do not have the disorder. Only one X-chromosome is active in a cell, so in females, one of the two X-chromosomes is always switched off. Inactivation of one X is usually random. When 50% of cells have the normal chromosome active and 50% of cells the abnormal chromosome active, the normal 50% with the HPRT gene protect against HPRT deficiency. On rare occasions the normal X-chromosomes may be switched off (non-random X inactivation). These females will have Lesch Nyhan Disease. At least 4 cases have been reported in the literature.

Males have one X and one Y chromosome. They inherit the X-chromosomes from the mother and the Y-chromosome from the father. If the mother's X-chromosome is abnormal, there is no normal X-chromosome to provide protection and they have the Lesch Nyhan disease, see Figure 4, page 9.

Why is carrier detection important?

Not all cases of LND are inherited. One third are called new mutations and the mother is not a carrier. This has important implications for genetic counselling. If the

mother of an affected child is not a carrier and wants more children, the chances of having another affected child are very small, perhaps 1 in 380,000. Sometimes, the mother of an affected child may not be a carrier of the mutation, but may still have HPRT deficient cells in her ovaries and thus there is a possibility that she may have another affected child. On the other hand, if she is a carrier, there is a 50% chance that a male child will be affected. There is also a chance that other female relatives will be carriers of the disorder and have the same risk of having an affected son.

Carrier detection using biochemical testing is very difficult. In most inherited disorders, carriers have 50% of control enzyme activity. However, for reasons not entirely clear, nearly all red blood cells in female carriers are normal and blood enzyme activity will not detect a carrier. Similarly, uric acid excretion in carriers is also within the control range. The only reliable method of detecting carriers is by genetic testing. The best way for this is to find the mistake responsible for HPRT deficiency in the affected child and test the mother for the same mistake.

Genetic testing represents a challenge for the diagnostic laboratory. Genetic mistakes causing HPRT deficiency may occur anywhere in the 654 letters in the 9 exons making up the HPRT gene. Such mistakes may also occur anywhere in the 42,000 bases of the gene. Sometimes, the mutations may be very complex, we can see the end result, but trying to find out how this occurred can be difficult, requiring months of work. Rarely we never find the mutation, although it is there somewhere. Unfortunately, we do not have the resources to sequence each of the 42,000 letters of the HPRT gene.

What options are available to carrier families wanting more children but not wishing to have another child with Lesch Nyhan Disease?

1. Pre-natal diagnosis is 100% reliable in experienced hands
2. Pre-implantation sexing is available in most genetic centres. The procedure involves harvesting the mother's eggs, in vitro fertilisation, sexing of the embryos and the implantation of only female embryos.

The future: Pre-implantation diagnosis is the ideal, and is already available for some genetic disorders. This technique may be become available for LND in the next 5 to 10 years.

Section E

THE PROBLEMS RELATED TO SELF-BITING

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The need to consider the use of restraints in the form of mouth guards or splints in LND may arise with the eruption of the teeth if the lips tongue or fingers become traumatised. The relentless capacity of children with LND to continue to self mutilate once the soft tissues are injured is a terrifying prospect for parents who are frightened not only by the bleeding but by the longer term prospect of scarring.

The nature of persistent self-injurious behaviour is ill understood. In the mouth once the lips or cheeks or tongue have been bitten the tissues inevitably swell and become even more susceptible to further injury. Pre-planned extraction of the teeth as they erupt is a decision commonly made by parents and professionals to avoid the risk of self-mutilation. Inevitably the experience of general dental practitioners in this field is very limited and consultants in paediatric dentistry whose training is very much focused on the needs of the medically compromised child and the management of behavioural problems may be better able to advise and help parents who are faced with such a situation.

Clearly if there is a risk that without pre-planned removal of the teeth the loss of lips or fingers has to be contemplated, the uncomfortable decision to sacrifice healthy teeth has to be faced. The argument to save healthy teeth is powerful, however. The cosmetic value of teeth is undisputed and their presence aids mastication and may contribute to the enjoyment of eating. Not all children bite, and our experience has shown that biting, when it occurs, is not necessarily relentless. The need for protective splints may be short term and therefore there is always a case for considering the use of mouth guards as a constraint in an effort to save both teeth and vulnerable soft tissue in the first instance.

Soft mouth guards made from PVC are not unlike the mouth guards used by footballers or rugby players. They can be vacuum pressed to fit a model made from dental impressions taken by the dentist. The material is sufficiently manipulable to allow for variation in design and shape. However to meet the needs of any particular child, fit by trial and error is part of finding a solution. This can be a distressing time for parents who are fearful that in the meantime the lips may be damaged irreversibly.

Also, some children successfully displace soft mouth guards and there is always a fear that children may choke.

This risk may be avoided by hard mouth guards or splints in the form of pre-cast occlusal inlays, which can be cemented on to the surfaces of the teeth to open the bite. However, obtaining impressions and fitting the splints may entail giving a general anaesthetic.

This approach is acceptable and may offer an opportunity to examine the mouth carefully to rule out a painful dental or oral underlying cause for the biting habit. The initial biting could be interpreted as a means of alerting parents to a problem about which the child cannot communicate.

Possible causes of pain

Teething

The distress that some children suffer when teeth are about to erupt is widely recognised and despite the use of teething gels containing a local anaesthetic, relief is difficult to achieve. The biting habit seen in LND tends to occur in early childhood, but according to published work, after the teething period and therefore it is unlikely that teething poses a great risk in early infancy. At this stage however finger biting can occur and arm restraints may be advisable. Without them nails and fingertips can be at great risk and the children in whom this becomes a habit should not be left alone without their arm splints

Dental Decay

Dental decay may cause toothache that can cause pain during eating and loss of sleep. Teeth may become abscessed and the development of an acute abscess may be painful.

Previously Traumatised Teeth

Dental pain from a tooth previously damaged in a fall may cause sensitivity on eating if the tooth was fractured and some of these teeth, whether fractured or not, die and become abscessed.

Other more unusual causes of pain and discomfort

Dental infection occasionally complicates the eruption of teeth and is painful and the shedding of baby teeth between the ages of 6-12 may be troublesome. Ulceration of the lining of the mouth and tongue may occur in some viral infections (e.g. herpes) and some children suffer from localised ulcers where there is not necessarily a cause.

Careful examination to rule out a focus of pain is very important in children with LND and prevention of pain an important goal for parents and carers. Regular checks should be made from the moment teeth appear, ideally with a paediatric dental specialist who can advise on infant feeding practice and dietary habits that pose a risk to teeth.

Tooth cleaning should be demonstrated and the values and use of fluoride discussed in an effort to prevent dental decay, the most common cause of dental pain. It is also possible however that pain being experienced elsewhere may promote biting. Sore throats and ear infection are common in childhood and in children with LND renal pain is common.

Lip biting and attention seeking

Lip biting may also be used as a behavioural device to seek attention, to distract or manipulate, and parents are frequently able to interpret such activity. It is important for parents to understand that their attentive response to the biting habit is normal, however, their excessive attention may perversely reinforce the habit. Thus, while responding to the emergency is essential, once healing has been achieved efforts to fade out the use of the mouth guard while encouraging the formation of more beneficial habits is an important part of behaviour modification. If removable splints have been used then withdrawal of the splints can be attempted, but if fixed splints have been used differential reinforcement of good behaviour can become more difficult.

Conclusion

Experience has shown that not all children with LND bite, of those that do some cope with mouth guards and some with splints that are cemented in. Experience also shows that the need for splints may be only short term and there is a view that in the first instance biting may be accidental or in response to pain or discomfort that is not immediately obvious to parents. Teething, dental decay, oral ulceration or infections may be the underlying cause of distress that children with LND cannot communicate and the biting that ensues may complicate and distort the clinical picture. It is clear that once the soft tissues are damaged the habit tends to take over and the lips or lining of the mouth become swollen and ulcerated and unless they are protected until they have healed the situation worsens and loss of tissue and scarring may result. Success may depend on the vigilance of parents and carers at all times when restraints are not in use. Unfortunately some children succeed in biting despite all efforts and then the difficult decision to extract the teeth has to be made.

Section F

SELF-INJURIOUS BEHAVIOUR IN LESCH NYHAN DISEASE

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In Lesch Nyhan disease, self-injury is very common. It occurs in all or almost all boys with LND and it can start as early as one year old (though it usually begins later, around 3 years old on average). The self-injury is frequently very hard to deal with at first, but boys (and their families) often learn ways of handling it as they get older, so that it gradually becomes less of a problem. It is very rare for self-injury to stop altogether in LND, and many professionals believe it is biologically driven (though it is not known how).

This chapter, reviews what is known about self-injury in LND in the context of what is known about self-injury in children and adults with severe/profound intellectual disabilities because the behaviour is quite common for them too (see below). Most of the research on self-injury has been done with people with severe/profound intellectual disabilities. There are of course some differences between boys with LND and people with severe/profound intellectual disabilities, which are commented on under each section (NB. It is important to remember that boys with LND may have only mild or no intellectual disabilities).

1. What exactly is self-injury?

Self-injurious behaviour has been defined as:

> *'Any behaviour, initiated by the individual, which directly results in physical harm to that individual. Physical harm (includes) bruising, lacerations, bleeding, bone fractures and breakages, and other tissue damage.'*

This definition focuses on the tissue damage, which is implicit in the term 'self-injury.' However, there have been some debates about the limitations of this definition. For example, whether behaviours like self-induced vomiting (which can be life-threatening) and trichillotomania (pulling out your own hair), should be included under 'self-injury' since both may involve tissue loss, if not direct tissue damage. It has also been argued that behaviours of the same topography (form) as a self-injurious

behaviour (such as light head tapping, that is not currently producing tissue damage) should be included as self-injury. Behaviours like these, that are not producing injuries, are normally referred to as stereotypies (repetitive apparently purposeless movements). There is a close connection between these two types of behaviour in people with intellectual disabilities (see also below).

In LND, self-injury tends to be very intense when it does occur, so that there is usually no doubt when it is happening. In people with severe/profound intellectual disabilities it can be very intense but it is not always so.

2. How common is self-injury?

Early studies of self-injury, from the 1960s to the 1980s and later, looked at people with severe/profound intellectual disabilities living in hospitals or the community. From all these studies, it seemed that:

- Around 8-15% of people living in hospitals and about 3% of adults with severe/profound intellectual disabilities living in the community showed self-injury
- About 3-12% of children with intellectual disabilities, living in the community, showed self-injury, the highest rates being for teenagers.

Some individual characteristics seemed to be associated with an increased risk of having self-injurious behaviour in these surveys:

- Specific syndromes, such as LND, Smith-Magenis syndrome, Prader-Willi syndrome, Tourette's syndrome, De Lange syndrome
- Sensory deficits, poor expressive language, autism, severe or profound disabilities, poor mobility.

Lots of children with intellectual disabilities had some of these characteristics but not all showed self-injury. The only factor in the list that was sufficient on its own to produce self-injury was Lesch Nyhan disease. The rarity of LND meant that professionals were more likely to meet individuals with serious self-injury who had the general risk factors (like autism, poor expressive language and so on) than individuals with LND (for example there were only 4 boys with LND out of the 596 adults and children showing self-injury in a survey of South East Thames Health Region in the UK in 1987).

3. How does self-injury start?

Very little is known about this. A research project in London and the South East of

England followed about 20 young children with early stage self-injury for 2 years to try to find out more about how and why self-injury started.

Three of the 20 were boys under 3 years with LND. Their self-injury seemed to begin with sudden intense biting (usually of the lips and cheeks) that could produce bleeding very quickly. Quite often the first incidents of self-injury occurred at night and it was common for the first obvious signs of it to be blood on the boys' pillows in the morning. In the other 17, who had severe/profound intellectual disabilities and/or autism but did not have LND, self-injury seemed to begin very insidiously, as a stereotypy, causing no tissue damage at all. Self-injury in some of these children got worse over the years; in others it disappeared. It seemed that one of the important factors in whether the self-injury increased or decreased was how teachers and parents reacted to the behaviour (i.e. whether they 'shaped it up', without meaning to). A further follow-up of these children is now under way.

4. How chronic is self-injury?

For boys with LND, self-injury seems to be very chronic. In one of the biggest studies of boys and men with LND in the USA, postal questionnaires were sent to people with LND and their families. Of the 40 replies: 28 were from families with boys aged between 2 and 18 years and 12 were from families and men aged between 19 - 32 years. The most common form of self injury reported was biting, throwing an arm or leg out going through a doorway, putting feet under the wheelchair, poking fingers between the spokes of the wheelchair, head banging and throwing the head backwards. Altogether there were 26 different forms of self injury reported by the 40 families; most of the boys and young men (25 of the 40) showed between 4 and 8 kinds at various times.

Although the men and boys with LND would sometimes injure whichever part of their body was most exposed, the self-injury varied and went through good and bad periods. Most boys and men found their self-injury was worse when they were physically ill or were anxious or stressed. Many boys and men went on to wear protective devices of one kind or another, to prevent them self injuring and one of the times that self injury was most difficult to manage was when all these were removed, for example at bath time. As boys got older, they could often predict when they were going to self injure (see also under *treatment*).

For people with severe/profound intellectual disabilities but not LND, it is difficult to be sure how chronic self-injury is. It seems that for some people with severe/profound intellectual disabilities, their self injury is not severe or chronic,

rather it comes and goes; however, for others, it is very extreme and chronic. Even so, people with severe/profound intellectual disabilities and severe self-injury tend to show fewer different *kinds* of self-injury than boys and men with LND.

5. What kinds of treatment and management help with self-injury?

Most of the research into treatment and management of self-injury has been undertaken with people with severe/profound intellectual disabilities and self-injury. There are very few reports of research into treatment for boys and men with LND. This section will therefore explain what is known about successful treatment for people with severe/profound intellectual disabilities and then comment on how this may be different in LND.

Most reports of successful treatment for people with severe/profound intellectual disabilities and severe self-injury include **behavioural treatment. Medication,** in contrast, appears not to work very well, with one exception. There are also methods of prevention and management, such as **protective devices,** which may help.

What is behavioural treatment? Behavioural treatment, which is usually provided by psychologists or behavioural specialists, works well for learnt behaviours. The rationale is that:

- Children (or adults) with severe learning disabilities and self-injury have often learnt to 'use' their self-injury to communicate with others.
- They are not necessarily doing this deliberately.
- They may just have discovered by accident that if, for example, they hit their head, then their mother or carer will come over and give them a drink or a cuddle.
- The 'messages' that self-injury often seems to convey include 'come here', 'go away', 'I want a drink' (or food or a toy), 'I'm bored' or 'I need help'.
- Behavioural treatment involves working out what 'message' the person is trying to convey and then teaching them a better way to 'say' it.

This is harder to do than it sounds because it is difficult to work out what people are trying to communicate through their self-injury. Sometimes people use their self-injury to mean different things at different times. It is also quite hard to teach better ways to 'say' things, when someone has very few language skills. Psychologists and behaviour specialists have tried teaching people to use new words or phrases (if they

can speak) or new signs (like Makaton) or picture cards to replace the self-injury and show their teachers or carers what it is they want. This process of teaching better ways to communicate is called functional communication training or FCT (because it involves teaching communication skills that match the function of the self-injury). This kind of language training has to be combined with new ways of responding to the self-injury as well: essentially the self-injury must no longer be reacted to as though it were a 'message'.

Increasingly, FCT is the treatment of choice for self-injurious behaviour. The acquisition of communicative skills, through FCT, should allow an individual to make a variety of requests, so that the person acquires more control over his/her social environment. One of the most difficult issues, however, has been how to provide such communicative skills for the most disabled individuals and this has required some ingenuity, such as the use of audiotape machines with pre-recorded messages.

For boys with LND, many families also report that their boys *sometimes* seem to 'use' their self-injury to convey 'messages' (such as, 'I want you to talk to me' or 'I don't want to do this'). It is very important for families and teachers / carers to try to avoid the self-injury serving as a 'message- system'. This means that developing the boy's communication skills, using whatever methods are possible, is of the utmost importance. It is likely that better communication skills means less self-injury, even though for boys with LND it may be impossible to eliminate the self-injury altogether. It may also be very important to teach boys with LND relaxation skills, as anxiety seems to worsen the self-injury considerably, see page 34.

What kind of medication helps? Medication was used a lot in the past to control self-injury in people with intellectual disabilities. However, it often was not at all helpful. There is only one type of medication that has been *consistently* found to help in reducing self-injury in people with intellectual disabilities: naloxone or naltrexone (but see below for LND). It is a difficult kind of medication to use and has to be employed under very careful medical and psychological supervision.

This medication works in an unusual way. It was always a puzzle that self-injurious behaviour, especially in people with intellectual disabilities who had shown SIB for years, did not seem to cause pain, at least in some individuals. This led to the suggestion that, in some cases, repeated self-injury produced an increase in endogenous opiates or endorphins (internal morphine-like substances). It was suggested that this either had the effect of deadening the pain from SIB or of producing an addictive 'high' following self-injurious responses. In either case, it was

suggested that the blocking of endogenous opiates by medication like naloxone or naltrexone would have the effect of reducing self-injury, at least while the medication was being taken. This did seem to be the case, for some people with chronic self-injury and intellectual disabilities.

Unfortunately, there are no published reports of the successful use of naloxone or naltrexone for self-injury in LND. It may be that, in LND, the pain mechanisms in relation to self-injury work differently.

In the survey of 40 boys and men with LND in the USA, 26 of the 40 people had tried medications specifically for the self injury. Most common among the medications found useful were the benzodiazepines which 13 people found helpful, the neuroleptics which 4 people found helpful and anticonvulsants which 5 people found helpful. 4 people had tried endorphin blockers but these were found either to be unhelpful (1), or to help briefly (2), or to help only a little (1).

Do behavioural treatments and medication ever get combined? It is perfectly possible, of course, that an individual with severe/profound intellectual disabilities who has been self-injuring for many years may have developed high endorphin levels as well as clear functions (or 'messages') for his/her self-injury. It might be predicted that for these people a combination of functional communication training and naltrexone might be the most effective treatment and a recent study has suggested that this is indeed a good idea for some people.

There are no published reports of such combination treatments for boys and men with LND.

What about protective devices? When SIB is very severe, protective devices are often used to try to prevent continuing injury. The kinds of protective devices used include padding (of bed sides or wheelchairs), helmets, gloves, arm splints and gum shields.

For people with severe/profound intellectual disabilities, such devices are best used as short term measures: they are usually unhelpful in the long term, as people often get very dependent on them and sometimes the devices restrict their movement and their lives generally.

For boys and men with LND, protective devices are often necessary in the longer term because it is so difficult to stop their self-injury. Indeed not using them when asked by the boys can cause great distress and aggravate the problem. It is true that the devices may sometimes restrict movement and people with LND may get very

dependent on them. However, this may be unavoidable at the present state of knowledge. The best plan is probably to keep the devices to a minimum, in terms of their number and type and the duration for which they are used. It is also wise to try to encourage the boys and men to predict when they feel 'safe', so as to take their devices off for a while, and to teach them to self-restrain (for example, by sitting on their hands or tucking them into their belts) whenever possible.

6. What about early intervention?

Early intervention programmes, in the pre-school years, have usually focused on helping children to gain skills, rather than reducing challenging behaviours, like self-injury.

However, one of the few early intervention programmes that did focus on reducing challenging behaviours maintained that very early, very intensive behavioural training for children with autism could return the children to near-normality. Not everyone has accepted these claims and there remains some doubt about whether all children with autism would respond as well as this.

It is difficult to know how successful early interventions of this kind might be for boys with LND. Most professionals think that early intervention with behavioural methods would make some difference to the boys' self-injury but would not eliminate it altogether because it seems to be partly biologically driven.

F

7. What can you do?

For parents and teachers, there are probably four really important tasks when someone with LND is developing self-injury:

- Teach communication skills, even if this involves unusual methods of communication (e.g. pictures or signs or electronic methods).
- Ensure the person is safe, using protective devices if necessary, but as far as possible do not react to the self-injury as though it were a 'message'.
- Seek specialist advice from the local clinical psychologist or behavioural specialist as soon as possible.
- Make sure the specialist knows that self-injury in LND is not exactly the same as in children with intellectual disabilities (i.e. that it may be more intense and persistent and harder to reduce).

Despite the difficulties described here, it is still possible for boys and young men to

live generally happy lives. In a survey in the USA, 14 out of the 40 families said that self-injury had only been a minor problem, or had not been such a problem that it had dominated family life. Certainly one young man in his twenties, who we interviewed, had left home to live in a supported house elsewhere but returned home for regular visits and enjoyed a trip to the local pub with his family and ourselves when we visited. When we asked him how he felt most of the time he said "Happy".

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A full reference list will be supplied on request.

Section G

PARENTAL STRESS MANAGEMENT FOR CHILDREN WITH LND

Garry and Joan Martin

One additional aspect well worth mentioning and one that will be unique to each affected child is the attempt to "manage" the very obvious stress, pain, discomfort, agony and frustration that these children suffer in varying degrees at different times.

These are a few ideas:

- Through the use of all possible/available equipment and some homebred ingenuity offer your child the opportunity to experience as much as would a child without difficulties e.g. creative play, cooking, painting and computers (games).
- Recognise that whilst restricted physically, their frustration and energy can be channelled and guided in other directions by a high level of stimulation. Seek out suitable educational establishments.
- **Avoid anything that will cause pain** - use protective headgear, ensure that medication is administered correctly and ensure the condition is monitored regularly and effectively. (Blood and urine analysis together with kidney ultra sound - six monthly intervals) N.B. The urine sample really ought to be collected over a 24hr period. Watch for early signs of any infection that might cause pain e.g. common cold leading to ear ache. These children will seek to perpetuate any pain once experienced, that is why it is vital to minimise it at the initial stage. It could be considered that sore mouths due to teething might influence mouth biting. Consider using Bonjela.
- Diet and a high fluid intake are essential to his well being. Ensure that others understand this when he is in their charge.
- Introduce new routines, locations, people, circumstances in a gentle, thoughtful, structured way. Children would seem not to manage change well if sprung upon them.
- Watch your child; be observant and aware of his bodily posture. You may see marked changes from relaxed periods to stressed periods and whilst not actually

communicating their feelings verbally, their "body language" can speak volumes.

- Take advantage, yourself, of any well thought out respite care facility. In the early days this may not seem like a good idea at all, but if you and your family are to manage your child's stress successfully, you need to have the opportunity to have a break from the situation yourselves - to recharge YOUR batteries.
- Remember you are not alone, other parents have had similar experiences. Get in touch with them. It really will help you all to talk to someone who has an understanding of what you are going through.
- Whilst not experimenting with your child's welfare without due consultation with your medical team, be totally proactive to him in his environment, considering a holistic approach to his life. Consider all the opportunities you might have thought he would never have.
- Consider:- a tricycle/quad bike; walking frame; power chair; computer; swimming; going on a train, bus, boat or plane; picking flowers, riding a horse, cricket, football, swing, sand pit - stop at nothing!
- Don't let any obstacles get in your way. Your own mental approach must be objective, open and positive. Build on the things that make him happy. His life should be full of fun, laughter, happiness and love.

Fig. 10. Floor corner seat allows play, note arm splints and padded helmet.

Fig. 11. Comfy seat for relaxation.

Section H

INSTRUCTIONS FOR A LOW PURINE/CAFFEINE FREE DIET

The instructions below apply to the collection of samples for purine investigations, but it may be helpful to parents to know which foods are rich in purines and thus should be avoided when preparing meals.

For purine studies it is advisable to try to eat a diet identical with your normal diet in terms of butter, fats, bread potatoes and other vegetables etc, but avoid the meat, fish and other food and drink outlined below with a high purine content in Section 1, and substitute a low purine equivalent from section 2 and 3.

1. Food and beverages not allowed

1.1 OFFAL - sweetbreads, heart, liver, kidney, and pate.

1.2 SEAFOOD - Sardines, sprats, herring, bloaters, fish roe, trout or salmon. Lobster, crab, prawns, oysters, cockles, mussels etc.

1.3. VEGETABLES - Asparagus, avocado pears, peas, spinach, mushrooms, broad beans, cauliflower.

1.4 Soya products, pulses and legumes.

1.5 Alcoholic beverages (beer) and yeast extracts. Meat or vegetable extracts (Marmite, Vegemite, Bovril etc).

1.6 Tea, coffee (other than decaffeinated); cocoa products such as Ovaltine, chocolate or chocolate biscuits, chocolate puddings; and Coca-Cola, Pepsi-Cola, or Lucozade.

(NB 1.6 only refers to diet when samples are being collected for the laboratory. These foods and beverages all contain methylated xanthines, which make analysis difficult in the laboratory)

2. Foods and beverages allowed

2.1 Milk, cheese, eggs, butter, margarine, cream, ice cream

2.2 Bread, flour, cakes, scones, biscuits, cereals.

2.3 Sugar, jam, marmalade, honey and sweets.

2.4 Lettuce and tomato (e.g.: salads).

2.5 Fresh, cooked or tinned fruits, nuts.

2.6 Puddings (milk etc), except those containing chocolate/cocoa.

2.7 Decaffeinated coffee or tea.

2.8 Fruit juices, soft drinks EXCEPT Coca-Cola etc.

3. Foods allowed in moderation (one meal per day)

3.1 Beef, lamb or mutton, port, bacon, ham, poultry, sausages, tongue, and meat soups.

3.2 Small helpings of vegetables (except those in 1) carrots, potatoes, leeks, cabbage, brussel sprouts, runner and French beans, marrow, courgettes.

3.3 Fish (except those in 1)

Section I

REFERENCES FOR FURTHER READING

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An impossible life by Paola Mazzuchi Cargiolli. Published in both English and Italian in the same volume by the Associazione Malattie Rare Mauro Bischirotto, Italy.

Gout at your fingertips. (2002) Published by Class Publishing. Authors Professor Rodney Grahame CBE, Dr H Anne Simmonds and Dr Elizabeth A Carrey. A simple question and answer book with cartoons only in responding to frequently asked questions. Mainly deals with gout in middle-aged males but one of the 7 chapters deals specifically with gout in young people i.e. the 3 genetic metabolic disorders under the PUMPA umbrella which can present as gout, LND being one of them.

A full list of references may be obtained on request, please send a stamped addressed envelope to PUMPA.

Contact addresses for further help

Families are welcome to contact any of the contributors to this volume at the following addresses:

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Dr Gillian T McCarthy, Honorary Consultant Neuropaediatrician, Chailey Heritage Clinical Services, Beggars Wood Road, North Chailey, East Sussex BN8 4JN (01825 722112). Chailey Heritage Clinical Services provide specialist multidisciplinary care for children and young people with complex disabilities. There are outpatient and short stay assessment facilities available as part of the NHS. It also provides clinical services to Chailey Heritage School (an independent non-maintained special school on site).

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End Piece

The presidents of both the French and Italian Lesch Nyhan Societies attended the 2001 PUMPA Seminar and made valuable contributions based on their own experiences as mothers of boys with LND. They are pictured below with, from left to right, Joan Martin, the GB LND parent and patient contact; the secretary and the President of the LNA Association Francaise Mme Aguilera Conception; Anne Simmonds, the co-ordinator of the recent EC Grant to improve research and diagnosis of LND and other disorders under the PUMPA umbrella; Paola Cargiolli, President of the Italian LN Society; and far right Vanna Micheli, EC project collaborator for Italy.

Fig. 12. The visitors from Italy and France at the 2001 PUMPA Seminar.

The two presidents jointly highlighted the funding problems of all engaged in researching these rare disorders and suggested a Europe-wide telethon to raise funds and create awareness of these "orphan diseases". The plan now is to establish a Virtual Nucleotide Centre, called The Princess Margaret Centre co-ordinated in GB. The aim is to sustain this important EC initiative, embracing experts in a wide variety of disciplines - a necessary prerequisite to advance research into devastating disorders such as LND. The PUMPA umbrella is now being extended Europe-wide.

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