A Guide to Understanding
Hurler, Hurler-Scheie and Scheie syndromes
(mucopolysaccharidosis type I; MPS I)

Introduction
This information sheet has been developed by the Mucopolysaccharide & Related Diseases Society of Australia (the MPS Society) to provide information about mucopolysaccharidosis type I (MPS I), its clinical presentation and medical management.

The content of the information sheet draws on the experiences of parents and doctors with reference to the medical literature. It is not intended to replace medical advice or care.

For reference purposes, it may be useful to provide a copy of this information sheet to your GP and others who are involved in providing medical or supportive care.

What is MPS I?
MPS I is an inherited disorder that encompasses a wide spectrum of severity. In some people the brain may be affected in combination with physical symptoms; others may develop physical symptoms with no brain involvement. Physical symptoms may include eye and hearing problems, bone and joint malformation, and heart and breathing difficulties. The rate of disease progression and age of onset vary considerably, even in affected siblings: in some it may be rapid, with diagnosis in the first few years of life; in others it may be relatively slow and diagnosis may not occur until the third or fourth decade. Generally, if clinical symptoms are apparent early in life, it is more likely that disease progress will be rapid and the brain is more likely to be affected.

Clinically, MPS I is divided into three categories: Hurler syndrome, Hurler-Scheie [pronounced shoay] syndrome, and Scheie syndrome, so named after the doctors who originally described the condition. Hurler syndrome is generally regarded as the most severe and the brain is affected; Scheie syndrome is the most ‘mild’ [or attenuated]. Many people fall between the two and are referred to as Hurler-Scheie.

What causes MPS I?
In common with the other MPS disorders, the characteristic of MPS I is the build up (or ‘storage’) of long chains of sugar molecules called mucopolysaccharides in the body’s cells. ‘Muco’ refers to the thick jelly-like consistency of the molecules, ‘poly’ means many, and ‘saccharide’ is a general term for the sugar part of the molecule. Mucopolysaccharides are also referred to as glycosaminoglycans (or GAGs for short) but for the purpose of this information sheet, the term mucopolysaccharide will be used.

Mucopolysaccharides are used by the cells to build connective tissues in the body, such as skin, muscle, cartilage and bone. They also help with many other cellular functions, including growth control, organ development and signalling between cells.

The human body is made up of billions of cells. Each cell contains various structures that carry out many functions important to life. One such structure is known as the lysosome [pronounced lie-so-soam]. Mucopolysaccharides carry out their tasks outside the cell. Once their job is complete they are transported to the lysosomes to be broken down (or degraded) into their basic building blocks. Degradation requires the action of enzymes that are found inside the lysosomes. Once the mucopolysaccharides have been broken down by these enzymes, they are transported out of the lysosomes to be reassembled and re-used to build tissue, etc. Mucopolysaccharides are therefore in a continuous process of being recycled.
In people with an MPS disorder one of the lysosomal enzymes that is needed to degrade mucopolysaccharides is either missing or is present at levels that do not allow the recycling process to work properly. This means that the mucopolysaccharides cannot be completely degraded and removed from the lysosomes in the usual way. As a result, partially broken down mucopolysaccharides remain ‘stored’ in the lysosomes: with time, lysosomes increase in size as the amount of storage increases. This interferes with normal cell functioning and causes progressive clinical problems in affected people.

![These pictures show a normal cell (left) and a cell that is filled with stored mucopolysaccharides in the lysosomes (right).]

People with MPS I are deficient in a lysosomal enzyme called alpha-L-iduronidase (or IDUA for short), which is essential in breaking down two mucopolysaccharides called dermatan sulphate and heparan sulphate. The amount of heparan sulphate that is stored influences whether or not the brain will be affected; the amount of dermatan sulphate storage influences the extent of physical symptoms.

**How common is MPS I?**

It has been estimated that about 1 in 80,000 births are affected by MPS I. Hurler syndrome represents about 1 in 88,000 births; Scheie syndrome about 1 in 500,000 births; and Hurler-Scheie syndrome is about 1 in 115,000 births.

The incidence of all MPS disorders combined [of which 11 are currently recognised] is estimated to be 1 in 25,000 births.

The MPS group of disorders are part of a larger family of about 50 inherited disorders called lysosomal storage disorders, so named because storage of materials that are unable to be properly degraded (mucopolysaccharides in the case of the MPS disorders) occurs in the lysosome. It is estimated that lysosomal storage disorders occur in about 1 in every 5,000 to 7,000 births.

**How is MPS I inherited?**

MPS I is inherited in what is known as an autosomal recessive manner. In this form of inheritance both parents must carry a copy of the same defective gene and each pass that defective gene to their child. In the case of MPS I, the defect relates specifically to the faulty production of alpha-L-iduronidase enzyme.

In autosomal recessive inheritance, in each pregnancy of a carrier couple there is a:

- 25% (1 in 4) chance of having an affected child;
- 50% (1 in 2) chance of a child receiving only one copy of the defective gene and therefore being a carrier. A carrier will not be affected but can pass the defective gene to his/her offspring; and a
- 25% (1 in 4) chance that a child will be neither affected nor a carrier.

The child of an affected person will not have MPS VI but they will be a healthy carrier of the defective gene. Only in the rare case that the affected person’s partner is also a carrier is there a chance (50%; 1 in 2) that the child will be affected.
The MPS Society has produced a specialist booklet (*The Pattern of Inheritance*) that is available.

**Genetic Counselling**

Because MPS I is inherited it is important to seek genetic counselling as there may be implications for other children in the family, future pregnancies and extended family members. Geneticists and/or genetic counsellors will explain the inheritance pattern and help determine who should be tested.

**Diagnosis**

At present, there is no routine newborn screening procedure to diagnose a baby with MPS I. If there is a family history of the disorder, however, prenatal testing can be arranged during the early stages of pregnancy (see below) or soon after birth. MPS I is not well known in the community. As the initial symptoms are variable it is often not easily recognised by doctors, hence (in the absence of a family history) diagnosis is often made after obvious problems have developed.

To diagnose MPS I, mucopolysaccharides are usually first measured in urine, followed by measurement of enzyme activity in blood. Increased dermatan sulphate and heparan sulphate in urine, and decreased alpha-L-iduronidase enzyme in blood is usually consistent with a diagnosis of MPS I. To confirm the urine and blood results it is useful to measure enzyme activity in a small piece of skin.

Diagnosis by mutation testing may also be possible. Mutations are mistakes in the genetic information (DNA) that is inherited by an affected person from their parents. In MPS I, the mutations are present in the gene that codes for alpha-L-iduronidase, and lead to a defect in its production. If the disease-causing mutations are found (which is not always possible to achieve) testing future pregnancies or other family members may be simplified. Mutation testing can be done using either blood or skin.

It is generally agreed that a comprehensive medical and supportive care plan should be started as early as possible after diagnosis to promote the best quality of life.

**Can You Test for MPS I in Pregnancy?**

Testing a fetus for an inherited condition whilst it is still in the womb is called prenatal testing and can be performed if there is a family history of the condition.

Prenatal testing is usually done within the first three months of pregnancy. If the parents of an affected child wish to consider prenatal testing, it is important to discuss it with your doctor, a geneticist or genetic counsellor prior to or during the very early stages of pregnancy.

Prenatal testing for carriers of MPS I in the family is not done routinely unless their partner is known to be a carrier. If a partner’s carrier status is not known, it is highly recommended that the advice of a geneticist or genetic counsellor is sought prior to pregnancy.

**Disease Progression**

In common with other MPS disorders, MPS I is progressive, meaning that the symptoms worsen with time.

The biological processes that determine the age at which symptoms appear and the rate at which they progress are complex and not all are clearly understood. Storage of mucopolysaccharides begins as a result of mistakes (mutations) in the genetic information (DNA) that code for the production of a specific enzyme that is responsible for breaking down specific mucopolysaccharides. These mutations determine how much active enzyme can be made, which will affect how much mucopolysaccharide can be broken down in the lysosome. As a general rule, if a mutation allows more active enzyme to be made, the mucopolysaccharide can be broken down more efficiently so disease progress is likely to be slower, with less storage occurring; if a mutation allows little or no active enzyme to be made, mucopolysaccharide break down will be much less efficient and more will remain stored, so disease progress is likely to be more rapid.
Whilst mucopolysaccharide storage is a significant cause of symptoms it is important to understand that it is one part of a complex ‘cascade’ of changes that occurs as a result of the reduction in enzyme activity: the mucopolysaccharides cannot be properly broken down in the lysosomes at the correct time and recycled; in turn, this causes abnormal changes to their function as well as to other functions of the cell. The flow-on effects of these changes significantly contribute to clinical outcome and disease progression in addition to the storage itself. Research is continuing to understand this ‘cascade’ of changes to improve diagnosis, predicting the rate of disease progression (prognosis) and treatment options.

Life Expectancy
It is difficult to be precise about life expectancy because of variation in severity and age of onset. Some individuals with Hurler syndrome have lived into adulthood but this is usually accompanied by a decline in their quality of life as brain function deteriorates.

If the brain is not affected, a more normal life span can be expected but significant physical problems can develop that, without treatment, may reduce life expectancy.

Fertility
MPS I does not affect fertility. Teenagers will go through puberty, although it may be delayed.

Clinical Presentation
This information sheet addresses a wide range of possible symptoms and presentations of MPS I. However, an affected person may not experience them all or to the degree described here. Treatment may improve some of these features (see Treatment, below).

Physical and mental development in children with Hurler syndrome may be normal at first. The rate at which mental decline will occur may be difficult to predict early on. Declining brain function and associated problems with communication may make medical examinations difficult. It is important that simple and treatable problems such as ear infections and toothaches are not overlooked as a cause of pain or distress. These children may have an increased tolerance of pain or may find it difficult to communicate that they are in pain. Do not hesitate to consult a doctor if you think your child might be in pain.

Growth
Babies with MPS I may be larger than average and may grow relatively fast during the first year of life. In those with Hurler syndrome growth then slows significantly, often stopping at around 3 years of age: final height may be no more than about three-feet (91 cm). In general, the short stature is not in proportion and the trunk is usually shorter than the legs. Those with Scheie syndrome may grow to a relatively normal height.

Facial Appearance
Children with Hurler syndrome tend to bear a close resemblance to each other: their faces are often chubby with rosy cheeks; their neck is often short and the nose broad with a flattened bridge; their lips are often thickened and the tongue may become enlarged; their eye sockets are usually shallow and the eyes may protrude slightly; their eyebrows tend to be bushy, and their hair thick and coarse.

The appearance of people with Hurler-Scheie and Scheie syndromes is variable: some may look no different from their unaffected peers but their neck may be short, their lips thickened and their jaw square.

Intellectual Ability
In Hurler syndrome there is a slowing-down of intellectual development, usually by 1 to 3 years of age, followed by a gradual loss of skills. However, the pattern is varied: some may only learn to say a few words
while others may learn to talk and read a little. Emphasis should be on helping infants and children learn as much as they can before the disorder progresses.

Mild learning difficulties may be experienced by some people with Hurler-Scheie syndrome, while in others intellectual ability may not be affected.

Intellectual capacity is not affected in people with Scheie syndrome.

However, in all individuals with MPS I the ability to learn may be affected by other complications of the disorder that are not directly related to the brain. For example, deafness may make it more difficult to learn spoken language; limitations of hand movements may slow the development of fine motor skills such as writing. This emphasises the importance of being aware of the various problems associated with the disorder to maximise quality of life.

**Eyes**
The outer layer at the front of the eye (the cornea) may become cloudy due to mucopolysaccharide storage and affect vision, especially in dim light. Bright light may be a problem for some people: wearing caps with broad visors and sunglasses may help. If clouding becomes so marked that vision is severely restricted, a corneal graft may be considered.

Occasionally, vision may be affected by changes to the retina, or glaucoma (increased fluid pressure inside the eye). Mucopolysaccharide storage in the retina can result in the loss of peripheral vision and night blindness. Night blindness may make a person not want to walk in a dark area, or wake up at night and be afraid; the use of a night light or lamp may help. If vision is a concern, examination by an eye doctor (ophthalmologist) is recommended.

**Head**
The head may be large with a prominent forehead but this does not usually cause any problems.

A condition known as hydrocephalus may develop. This is caused by a build-up of the fluid that surrounds the brain (the cerebrospinal fluid, or CSF). Thickening of tissues around the brain may obstruct the circulation and absorption of this fluid and cause pressure on the brain. This may lead to symptoms such as headache, vomiting or drowsiness; the head may also increase in size. Hydrocephalus needs to be monitored closely and can be treated surgically, if necessary, usually by the insertion of a shunt (a tube placed inside the skull that helps drain the excess fluid, usually into the abdomen).

**Nose**
The bridge of the nose may be flattened, and the passage behind the nose may be smaller than usual due to poor growth of the bones in the mid-face and thickened soft tissue in the nose and throat, and lead to narrowing of the airway. Chronic drainage of clear mucus from the nose (rhinorrhea) may occur, which is due to the abnormal drainage of normal secretions and chronic ear and sinus infections.

**Throat**
The tonsils and adenoids often become enlarged and may narrow the airway. This, combined with a short neck, contributes to breathing problems. The windpipe (trachea) can become narrowed by thickened tissue and may be floppy or softer than usual due to abnormal cartilage rings in the trachea.

**Chest**
The shape of the chest is usually abnormal and the junction between the ribs and the breastbone (sternum) may not be very flexible. The chest can therefore become rigid and unable to move freely to allow the lungs to take in a large volume of air. The muscle at the base of the chest (diaphragm) may also be pushed upward by the enlarged liver and spleen, further reducing the space for the lungs. When the lungs are not
fully cleared, there is an increased risk of infection (pneumonia). These changes also affect breathing, and can cause breathlessness and reduced endurance. Lung function and walk tests can help monitor these problems and assist with management.

**Breathing Problems**

Noisy breathing is common, even when there is no infection, and restlessness and snoring may be a problem at night. If there is narrowing of the large airways and increased secretions there is increased risk for asthma-like episodes: treatment with asthma medication during chesty illnesses may help decrease cough and ease breathing. A lung specialist can assess whether asthma-like episodes are occurring.

Sleep apnoea (not breathing for short periods whilst asleep) is common and may be a sign that the oxygen level is low during sleep, which can damage the heart over time. (Note: pauses of up to 10 to 15 seconds may be normal.) The noisy breathing, which may stop and start, can be very frightening for parents. If significant choking or episodes of interrupted breathing whilst asleep are being experienced, evaluation by a sleep specialist is recommended. It is important to know that many individuals may breathe like this for years.

**Management of airways and breathing problems**

Sleep studies measure the blood oxygen level, breathing effort, brain waves during sleep and other monitors of the body’s function. A sleep study is likely to require an overnight stay in hospital.

If sleep apnoea is a problem, treatment with continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) may be needed during sleep. This involves placing a mask on the face each night and having air pumped into the airway to keep it open. This may seem extreme but is usually well tolerated because it can improve sleep quality as well as help prevent or reduce the risk of heart failure caused by low oxygen.

In severe cases of sleep apnoea or breathing difficulties, a hole may need to be opened in the airway at the front of the neck and a breathing tube inserted (this is known as a tracheotomy). This is a significant and invasive procedure that needs to be discussed with your doctor.

Chest postural drainage can be helpful in clearing secretions from the lungs to improve breathing. A physiotherapist will be able to teach parents, teachers and caregivers how to do this.

**Respiratory Infections**

Frequent coughs and colds are common.

Medication can affect individuals differently, so it is advisable to consult your doctor before using over-the-counter medicines. Drugs to control mucus production may not help: antihistamines, for example, may dry out the mucus, making it thicker and harder to dislodge. Decongestants may contain stimulants that can raise blood pressure and narrow blood vessels, both undesirable in MPS I. Cough suppressants or drugs that are too sedating may cause problems with sleep apnoea by depressing muscle tone and respiration.

Secondary bacterial infections of the sinuses or middle ear may occur and require treatment, usually with antibiotics. Poor drainage of the sinuses and middle ear can make overcoming infections difficult: infections may improve whilst taking medication but promptly recur after it is stopped. Chronic antibiotic therapy may help with recurrent ear infections. Ventilation tubes can be used to improve drainage from the ear and help resolve infections: an ear, nose and throat (ENT) specialist will advise on which tube is best.

Infections that do not respond to antibiotic treatment may develop. Other medications can be prescribed to help manage this problem if it occurs. While over-using antibiotics is not advised, most individuals will require some type of treatment for most infections.
Ears
Deafness is common: it may be *conductive* or *nerve deafness* or both (*mixed deafness*) and may be made worse by frequent ear infections. It is important that hearing is monitored regularly so problems can be treated early to maximise the ability to learn and communicate.

**Conductive deafness** is due to impaired transmission of sound waves through the ear canal, the ear drum and the middle ear. Correct functioning of the middle ear depends on the pressure behind the ear drum being the same as that in the outer ear canal and the atmosphere. This pressure is equalised by a tube in the ear called the Eustachian tube, which runs from the middle ear to the back of the nose. If the tube is blocked, the pressure behind the ear drum will drop and the drum will be drawn in. The transmission of sound waves will then be impaired. If this negative pressure persists, fluid from the lining of the middle ear will build up and in time become thick, like glue, hence the condition being known as ‘glue ear’.

Under general anaesthetic a small incision can be made in the ear drum (myringotomy) and the fluid sucked out. A small ventilation tube called a ‘grommet’ may then be inserted to keep the hole open and allow air to enter from the outer ear canal until the Eustachian tube starts to work properly again. Grommets will eventually fall out. If the conductive deafness recurs, T-tubes (a type of grommet which stays in place longer) may be used. Due to the anaesthetic risks in MPS I (see *Anaesthetic*, below) the surgeon may decide to use T-tubes on the first occasion.

**Sensorineural (nerve) deafness**: in most cases nerve deafness is caused by damage to the tiny hair cells in the inner ear. It may accompany conductive deafness in which case it is referred to as ‘mixed deafness’. Nerve deafness is managed by the fitting of hearing aids. Some individuals may keep pulling out their hearing aids at first but it is important to persevere at wearing them to maintain communication.

Mouth and Teeth
The lips are generally thick and the tongue may become enlarged; gum ridges can be broad, and the teeth widely spaced and poorly formed with fragile enamel. It is important to look after the teeth, as tooth decay can be a cause of pain. Teeth should be cleaned regularly, and if the water in your area is not treated with fluoride it is advisable to give fluoride tablets or drops daily. Cleaning inside the mouth with a small sponge on a stick soaked in mouthwash will help keep the mouth fresh. Even with the best dental care, an abscess around a tooth can develop due to abnormal formation of the tooth. Irritability, crying and restlessness can sometimes be the only sign of an infected tooth.

If an individual has a heart problem, it may be advisable to give antibiotics before and after any dental treatment. This is because certain bacteria in the mouth may get into the bloodstream and cause an infection in the abnormal heart valve, potentially damaging it further.

If teeth need to be removed while under an anaesthetic, it should be done in the hospital under the care of both an experienced anaesthetist and dentist – never in the dentist’s office.

Heart
Heart disease is common. High blood pressure may also be a problem.

Heart murmurs (sounds caused by turbulence in blood flow in the heart) may develop if the valves become damaged as the disorder progresses. Heart valves close tightly as blood passes from one chamber of the heart to another to stop blood flowing back in the wrong direction. If a valve is weakened, it may not shut firmly enough and a small amount of blood may shoot backward, leading to turbulence and a murmur. The opening of the valves may also become narrowed and make it more difficult for the heart to pump the blood properly.
Slowly progressive valvular heart disease may be present for years without any apparent clinical effects. If the condition worsens, however, medications can be used to lessen the effect on the heart. Sometimes, an operation may be required to replace the damaged valves.

The more serious, life-threatening problem of thickening and weakening of the heart muscles can be present at birth.

Occasionally, the coronary arteries may become narrowed and cause episodes of chest pain (angina). If the person is distressed and is also pale and sweating while keeping still, medical advice should be sought.

Your doctor may recommend a test known as an echocardiogram as often as necessary to monitor the heart. The test is painless and similar to ultrasound screening of babies in the womb.

**Liver and Spleen**
The liver and spleen may become enlarged (hepatosplenomegaly). This does not usually lead to liver failure but it may interfere with eating and breathing and the proper fitting of clothes.

**Abdomen and Hernias**
The abdomen may bulge out due to posture and weakness of the muscles, as well as the enlarged liver and spleen. Part of the abdominal contents may push out from behind a weak spot in the wall of the abdomen: this is called a hernia. Hernias can come from behind the navel (umbilical hernia) or in the groin (inguinal hernia). Inguinal hernias can be surgically repaired but will sometimes recur. Umbilical hernias are not usually treated unless they are causing problems: it is common for an umbilical hernia to recur after a repair has been made.

**Bowel Problems**
Loose stools and diarrhoea are common. The cause of this is not fully understood. Occasionally, it results from severe constipation and leakage of loose stools from behind the solid mass of faeces. More often, however, parents describe it as “coming straight through”. A medical examination may establish the cause. It may disappear with time but it can be made worse by antibiotics prescribed for other problems.

The episodic diarrhoea may be affected by diet; elimination of some foods may help. If antibiotics are the cause, eating plain live-culture yoghurt can provide a source of ‘good bacteria’ to help prevent the growth of harmful bacteria within the bowel: a diet low in roughage may also help.

If constipation is a problem, an increase in roughage in the diet may assist. If this does not help or is not possible, laxatives or a disposable enema may be needed.

**Skin**
The skin may become thickened and lack elasticity, which can cause irritation and soreness, particularly in areas where the skin folds, e.g. at the back of the neck. The skin may also develop a characteristic pebble-like texture. Excess hair on the face and back may also occur: this is called hirsuitism.

**Bones and joints**
The formation and growth of bones and joints is impaired in MPS I. Some people may develop stiff hips because the supporting socket is not formed properly. Joint pain may develop. Pain may be relieved by warmth and the prescribing of analgesics (pain relievers). Surgery on the hips may be possible if pain becomes a real problem. Limited movement in the shoulders and arms may make dressing, toileting and self-care (e.g. brushing hair) difficult. Anti-inflammatory drugs, such as ibuprofen, can help with joint pain but they should be taken with or after food and monitored closely to prevent stomach irritation and ulcers.

Dislocation of the hips may be present in the neonatal period in some cases, and should be treated early as it may be difficult to treat and manage later in life.
Recent research has shown that high-dose vitamin D therapy can improve mineral bone density. Sensible exposure to sunlight will help maintain vitamin D levels.

**Spine and Cervical Spine**

The bones that support and surround the spinal cord down the back are known as *vertebrae*. The *cervical spine* refers to the bones that support the neck. The *spinal column* is the ‘backbone’, which is made up of the individual vertebrae that sit on top of each other, from the base of the spine (the coccyx) to the base of the skull.

In MPS I, the vertebrae in the middle of the back are sometimes small and mis-shaped, and one or two may be set back in line. This can produce a kink in the spine (known as *gibbus*). This is unlikely to need treatment but if it is causing problems surgery may be needed to straighten the spine. Abnormal curvature of the spine (*scoliosis*) can also occur and, if severe, may require surgery.

The spinal cord passes down the spinal column through a passage known as the *spinal canal*. The space in this canal may be gradually reduced by thickening of the tissues in and around it, and lead to compression of the spinal cord, weakness in the limbs or even paralysis. This is particularly a problem in the neck (*cervical spine*) where the spinal cord comes out through the space in the base of the skull bone. More rarely, compression may result from structural defects in the upper vertebrae leading to instability. Both problems can be treated surgically if necessary.

Your doctor may recommend regular imaging scans of the cervical and lower spine using magnetic resonance imaging (MRI) and plain X-rays as needed.

In general, care should be taken with the spine. It is recommended that high risk activities such as contact sports and gymnastics, including trampolines, are avoided.

**Legs and feet**

Many individuals with MPS I stand and walk with their knees and hips flexed. This, combined with a tight Achilles tendon, may cause them to walk on their toes. Knock-knees can sometimes be a problem; this is unlikely to need treatment but surgery may be required if severe. The feet are often broad and may be stiff with the toes curled under, rather like the hands.

**Hands**

The hands are usually short and broad with stubby fingers that gradually become curved over or ‘clawed’ as the disorder progresses.

**Carpal Tunnel Syndrome**

Carpal tunnel syndrome is common. One of the (two) nerves to each hand pass through a narrow space in the wrist known as the *carpal tunnel*. This space may become narrowed due to thickening of tissues and result in compression of this nerve. Although pain in the hands may not be a problem, carpal tunnel syndrome may already be present. This can be tested by a nerve conduction study. This test would also be done if there is weakness or numbness in the hand or decreased muscle mass at the base of the thumb. This problem may be treated by surgery on the wrist, where the nerve is compressed. A similar problem can affect the feet, in which case it is known as *tarsal tunnel syndrome*.
General Management

Diet
A balanced diet is important for health and well-being. There is no scientific evidence that a particular diet has any helpful effect in MPS I and problems such as diarrhoea tend to come and go naturally. A change in diet may ease problems such as production of excessive mucus or diarrhoea. Reducing intake of milk, dairy products and sugar, as well as avoiding foods with too many additives and colouring have sometimes helped. It is advisable to consult your doctor or a dietician if major dietary changes are planned to ensure that essential nutrients are not left out. If the problems are eased, foods can be reintroduced one at a time to test whether any particular item seems to increase symptoms.

It is important to note that no diet can prevent the storage of mucopolysaccharides because they are made by the body. Reducing sugar intake or other dietary components does not reduce this storage.

Anaesthetic
The airway may be narrower than usual and the tongue is often enlarged, making it difficult to open the mouth widely.

Because of the narrow airway insertion of a very small breathing tube may be required for surgery. Placing the tube (intubation) may prove difficult. In addition, the neck may be somewhat lax and repositioning it during anaesthesia or intubation could injure the spinal cord. In some cases, it may be difficult to remove the breathing tube after surgery due to swelling that may have occurred and it may need to be left in place.

In view of the anaesthetic risks, it is recommended that all surgery (including elective surgery) is performed at a specialist medical centre rather than a local hospital, with anaesthetists who are experienced in managing difficult airways.

It is highly recommended that teachers and caregivers are informed of the anaesthetic risks in case of emergency.

There is a more detailed explanation of this subject in the specialist anaesthetic booklet published by the MPS Society.

Physical therapy
Individuals should be as active as possible to improve their general health and a physiotherapist may be able to suggest ways of achieving this. Limitation of motion and joint stiffness can cause significant loss of function. Range of motion exercises (passive stretching and bending of the limbs) may help preserve joint function and should be started early. Physiotherapy and hydrotherapy can be useful to help individuals achieve specific and realistic goals in daily life or to drain mucus from the chest. Exercises that cause pain should be avoided. Once significant limitation has occurred, increased range of motion may not be achieved, although further limitation may be minimised. For children, the best forms of physiotherapy are exercises that are introduced through play and which do not involve stretching or rotation of the joints.
Living with Hurler syndrome (brain involvement)

Hurler children are usually affectionate, pleasant and rather placid children but sometimes may become frustrated due to difficulty communicating or not being able to do what they used to do, for example. They may be unaware of danger or become confused and occasionally may have aggressive episodes.

Without treatment, brain function in Hurler children will deteriorate. Initially, they will be able to learn although it will be more difficult for them than children without similar problems. Their rate of learning will slow by about 18 months or so, although sometimes significantly later – the pattern is varied. Their ability to talk and communicate will also gradually be lost (talking may initially be delayed due to deafness), and their ability to concentrate and understand will be less than that expected for their age. Toilet training skills will be lost and eventually also the ability to swallow. They will become more unsteady on their feet, and tend to fall frequently as they walk or run; eventually the ability to walk will be lost.

This gradual decline is very upsetting to family and friends but it is important to know that even when the child starts to lose skills they have learned there may be some surprising abilities left. Children will continue to find enjoyment in life even if they lose the ability to speak.

Behavioural problems

Difficult behaviour is generally not a major issue in Hurler syndrome but may occur. If it is a problem, therapy may offer some help but the usefulness of a particular behaviour modification technique may be short-lived because behaviour is likely to change as the disorder progresses. Medications can sometimes help but will usually require regular medical review to help maintain effectiveness.

It may be helpful for the child to join a play group or attend a school or after school program where a variety of activities can occupy them. Ideally there should be space to run around in and keep fit for as long as possible. Many children are calmed by the movement of a car and will travel well.

Seizures

Seizures are not especially common. If they do occur, however, they should be managed in the same way as any other person having a seizure, but with some extra care because of the physical problems that may be present. For example, more care should be taken when moving their head and neck as they are placed on their side to prevent the inhalation of vomit. They should be left in that position until the seizure is over. The airway should be checked to make sure it is clear; nothing should be put in their mouth. Seizures can usually be managed with conventional anti-seizure medications.

Feeding and Swallowing

In the early stages of the disorder, feeding usually causes few problems. As it progresses, however, the ability to chew food and swallow is gradually lost. Foods may need to be mashed or pureed to an appropriate consistency; it is advisable to avoid mixing ‘lumpy’ foods with food of a smooth texture; meat may be tolerated more easily if it is made by slow cooking rather than just chopped into small pieces. Many become quite picky and may reject foods for no clear reason.

As the rhythm of swallowing is lost, spluttering and coughing whilst eating may become a problem. Moving your hand gently backward under their chin and slowly down the throat can help move the tongue and encourage swallowing. As the ability to swallow worsens, food or liquids may enter the lungs, which can result in recurrent pneumonia. During this time they may lose weight and take more time to be fed.

It is often difficult for a family to consider alternate means of feeding, such as through a naso-gastric (N/G) tube or a gastrostomy (G) tube. Talking with your doctor can help with your decision making.
Choking
When a person cannot chew and has difficulty swallowing, there is a risk of choking. Choking is frightening and reassurance can be provided by rubbing their back and holding their hands. If choking occurs, they should quickly be turned upside down or placed head-down over your knee, followed by three or four sharp pounds between the shoulders. If necessary, you may need to put your finger down their throat to try to dislodge the food item. Pounding on the back while they are sitting upright can make things worse because they might breathe in the food rather than coughing it out.

Choking can also occur with liquids, including secretions made by the body such as saliva. As swallowing becomes more difficult, drooling may become a problem and may require suctioning. Medication may sometimes be used to reduce the production of saliva and should be discussed with your doctor. If fever develops within a day or so of a choking episode, consult your doctor. It is possible that some food particles have entered the lungs and pneumonia may have developed.

Vomiting
Vomiting can occur quite often, even in the absence of infection. An upset stomach may be caused by swallowing too much mucus, overeating or by swallowing air when feeding. The pressure of the enlarged liver and spleen may also make the stomach uncomfortable.

Sleeping difficulties
Sleep is usually not a significant issue except for problems associated with breathing (see Breathing Problems, above). As the disorder progresses, getting to sleep or maintaining sleep may become a problem. If this is the case, talk with your doctor to decide on the best management.

Cold hands and feet
As the disorder progresses, the part of the brain that regulates temperature may become damaged and result in cold hands and feet. It may not cause discomfort but if it does the obvious remedies of heavy socks and warm gloves may be useful. In the later stages, sweating may become a problem at night, as well as cold hands and feet by day. Body temperature may sometimes drop (hypothermia): if this happens, they should be kept warm and medical advice sought on the best ways to manage the problem.

Adapting the House
Mobility is likely to progressively worsen and dependence on parents and carers to meet everyday needs will likely increase in areas of incontinence, personal hygiene and nutrition. It is important to give early thought to how this can be managed when weight bearing, walking or climbing the stairs is no longer possible.

Parents have found it helpful to designate a room or part of a room for their affected child. If possible, the area should be within hearing and visual distance and be made safe for the child to play without constant supervision, so the parent can interact with other children or deal with household tasks.

Education
Some children may benefit from attending a mainstream school in their primary school years and enjoying the social interaction with peers; some will equally benefit from a Special Educational Needs placement with small class sizes and a range of communication systems in place. Many will need the help of a classroom assistant.

Taking a break
Caring for someone with progressive disability is physically and emotionally tiring. Parents will need regular breaks so they can continue providing care without becoming exhausted; brothers and sisters also need to have their share of attention and to be taken on outings that may not be feasible with an affected child.
Palliative care
Palliative care is any form of medical care or treatment that concentrates on reducing the severity of disease symptoms. The goal is to prevent and relieve suffering and to improve quality of life for people facing serious, complex illness and that of their family. This may include respite care, symptom management and bereavement support and may extend over a period of time. It is important to talk with your medical team to ensure you are aware of and have access to the various services and support networks that are available.

Enjoying your child
A child with Hurler syndrome will have a life that is different from the majority of others, but they have delightful personalities and are extremely lovable. They will give you love that is totally unconditional; they will make you laugh when you think you may never laugh again. Their love is infectious to everyone around them. They communicate with you even when they lose their verbal skills. Their eyes will beguile you, their smiles will entice you and their spirit will raise yours when you think nothing else can.

Living with Hurler-Scheie or Scheie syndromes (no brain involvement)

Psychosocial Issues
At the present time no research has been carried out that explores the psychosocial development of individuals affected by Hurler-Scheie or Scheie syndromes.

However, it is important to consider how the additional challenges in life may be experienced. People with Hurler-Scheie or Scheie syndromes can adapt socially and emotionally in different ways to new challenges or problems. The adolescent and teenage years may be more difficult because of all the physical and psychological changes that occur, whilst also having to cope with the problems caused by the disorder itself. Mental health is an important issue and it is therefore vital that steps are taken for an appropriate psychology referral as part of a comprehensive, on-going package of support.

Siblings also need to be considered. No formal studies have been carried out to assess the psychosocial effects of MPS I in siblings. It is not uncommon for unaffected siblings to feel somewhat neglected or less important in the family unit as the greater share of attention is placed on the needs of the affected person. Parents may need to monitor the broader impact of the disorder on siblings and seek medical or psychological help if necessary.

Education
The majority of people with Hurler-Scheie and Scheie syndromes will attend mainstream school and achieve academically. To reach their full academic potential it is important that the education authority and school are aware of resources that may be required: this may include appropriate classroom furniture, access to an individual computer, hearing or visual aids, and extra time to complete tasks that may not seem difficult but which may require more effort to complete due to the physical problems associated with the disorder.

Independence
Independence should be encouraged as much as possible. It may help to meet or be put in touch with other teenagers and adults with the same or similar conditions.

Developing the necessary skills to lead an independent adult life can be very difficult and some may experience difficulty in establishing independence from their family - an important step in achieving social maturity. Adults have the potential to live independently and claim appropriate financial support to purchase the services needed, including, for example, that of a personal assistant.
Employment
The disabilities caused by the disorder should not prevent access to meaningful employment. There is considerable responsibility on the part of employers under the Disability Discrimination Act to meet the needs of employees with a disability.

Adapting the House
 Appropriately adapted living space will greatly enhance the development of independent living skills. Where mobility is restricted, a wheelchair may be required. In addition, pain and joint stiffness, when associated with short stature, may impact on the person's ability to undertake personal care and daily living tasks. Should this be the case, a carer may be required. If a wheelchair is needed, plans to adapt the home should allow adequate space to accommodate it, and it may also be important to think about for the future even if a wheelchair is not needed at the time. It is, therefore, prudent to plan ahead whenever possible.

Treatment

Overview
The goals of managing MPS I are to improve quality of life, slow down its progression, and to prevent permanent tissue and organ damage. Early intervention may help prevent irreversible damage.

The involvement of the brain in some people with MPS I presents a special challenge in devising effective therapy. This is primarily because the brain is protected from the rest of the body by a barrier (the blood-brain barrier) that controls what can and cannot enter the brain. This creates problems for treatments that are given via the bloodstream, such as enzyme replacement, for example (see below): the enzyme circulates throughout the body to treat the physical symptoms of the disorder but it does not readily enter the brain to stop the progressive decline in brain function. Researchers are therefore devising different methods by which to deliver enzyme to the brain, and progress is being made.

Several forms of treatment for MPS I are in use. These include:

Haematopoietic Stem Cell Transplant (HSCT)
Bone marrow transplant (BMT) and umbilical cord blood transplants are both forms of HSCT.

BMT involves the reduction or removal of an affected person's bone marrow and replacing it with bone marrow cells from a tissue-matched donor who is not affected by the same condition. This donor may be a family member or an unrelated donor from a bone marrow donor panel. It can take a considerable amount of time to find a suitable donor match.

Umbilical cord blood transplant is based on the same principle as BMT but involves taking stem cells that are found in umbilical cord blood. Cord blood is collected from the afterbirths (placenta) of newborn babies (with parental consent). The baby donors are not normally related to the patient although the cord blood needs to be a suitable match for it to be considered. In all other aspects the two procedures are the same.

The principle of HSCT is that the donor cells (cord blood or bone marrow) will reproduce (or replicate) within the affected person to produce normal amounts of enzyme (alpha-L-iduronidase in the case of MPS I) to treat the disorder: the IDUA enzyme is not only produced within the transplanted cells but is also released by those cells into the circulation where it can be taken up by other cells of the body. If the procedure is done early enough in the disease course, some of the donor cells will establish themselves in the brain (by-passing the blood-brain barrier) and produce enzyme that may prevent its deterioration.
In contrast to people with cancers (where HSCT is regularly used) in the case of MPS I it is not necessary to completely remove the individual’s own bone marrow; the level of marrow reduction must be sufficient enough to allow room for the new bone marrow cells to establish and grow. A treatment necessary to reduce a person’s own marrow (known as ‘conditioning’) is used to minimise the risk of the transplant procedure. It is important to understand, however, that HSCT in all its forms is an extensive procedure that may require quite a long stay in hospital. There are still significant risks involved with HSCT, including infection, graft vs. host disease and other complications which may be life-threatening.

HSCT has been shown to have a positive outcome in altering the progression of MPS I and improving life expectancy. Many of the physical features (such as harshness of facial features, hearing, enlarged liver and spleen and heart function) may also improve following transplant. However, HSCT has less effect on the skeleton, and problems such as curvature of the spine (scoliosis), severe joint stiffness and pain, carpal tunnel syndrome and compression of the spinal cord can still occur. Considerable long-term physical, medical, surgical and psychological supportive care is necessary after successful HSCT.

In view of the risks, HSCT is not usually recommended as the first choice treatment for Hurler-Scheie or Scheie syndromes. However, it may be considered in these individuals where other forms of treatment are not available or considered inappropriate on medical grounds, or where the risks of the treatment are higher than the transplant procedure.

Currently, HSCT is the treatment of choice for Hurler syndrome. It is generally considered that if the procedure is performed within the first two years of life, brain deterioration may be stabilised or even prevented; however, once brain deterioration is significant, HSCT will not prevent further decline.

**Enzyme replacement therapy (ERT)**

Following extensive clinical trials ERT is now the treatment of choice for most individuals with Hurler-Scheie or Scheie syndromes. ERT is based on the same principle as HSCT except that the missing enzyme (alpha-L-iduronidase) is replaced with a pharmaceutical-grade enzyme prepared commercially and given by infusion into the bloodstream rather than being produced inside the body by transplanted cells. The advantages of ERT over HSCT are that (i) the problems and long-term risks associated with transplantation are avoided; (ii) there is no need to find a suitable donor; and (iii) there is no need for ‘conditioning’. However, many of the same advantages and limitations apply: for example, the earlier ERT is commenced the better the outcome but skeletal and related problems can still develop.

The commercial name of the enzyme preparation for MPS I is called Aldurazyme. People who have received ERT over the long-term (up to 10 years) have shown it is safely tolerated. With the reduction in mucopolysaccharide storage resulting from ERT, sustained improvements have been demonstrated in endurance, walking and stair-climbing ability, joint mobility, lung function, growth and puberty. Marked improvements have also been noted in certain characteristics such as softening of the hair and facial features, and sometimes improved growth. Individuals have also noticed that their tummies are far less prominent due to the reduced liver and spleen size. However, whilst these improvements have contributed to better quality of life, patients usually continue to require physical, medical and surgical supportive therapy alongside ERT in the longer term.

ERT is not a cure and for it to be effective it needs to be given regularly during the person’s life. Currently, this is usually on a weekly basis. Infusions are usually given slowly over several hours to minimise the risk of reactions to the introduced enzyme. In Australia, infusions are usually done in a hospital setting.

In Australia, ERT is currently funded under the Commonwealth Government Lifesaving Drugs Program (LSDP) for people whose brain is not affected by MPS I. In young children where HSCT is recommended (generally those with Hurler syndrome and under two-years of age), ERT may be considered for a short period before and after HSCT: studies have suggested that it may improve the outcome of transplantation and reduce some of the risks associated with the procedure. At present, use of ERT in this way is not funded by the LSDP although this is under review. If there is uncertainty about whether an individual’s
brain is affected, treatment may be approved until this becomes clear. Further information is available through the LSDP website (www.health.gov.au/lsdp) and should be discussed with your medical team.

Other combinations of ERT and HSCT are also being considered, and improved methods of HSCT are being developed. This may reduce the risks of these procedures and alter medical recommendations with regard to each treatment. The choice of treatment should always be made in discussion with your doctor and in careful consideration of all the available information.

Other Treatments
Other forms of treatment that are being researched include:

*Gene therapy*, which aims to replace the defective gene with a functional one. The principle is that the functional gene will code for the normal production of the enzyme, reproduce within the cells of the body (and brain) and produce sufficient amounts of enzyme to remove stored mucopolysaccharide and prevent further storage. Unlike ERT, which requires repeated administration, it is hoped that gene therapy will be a once-off treatment.

*Substrate deprivation/reduction therapy*: this form of treatment aims to reduce the amount of mucopolysaccharide that is being made by the body, leading to a reduction in the amount being stored.

*Chaperone therapy* uses chemicals to protect and activate any enzyme that may be present in the lysosome, so as to increase its activity and ability to break down mucopolysaccharides and thereby reduce the amount being stored.

As a general rule, both substrate deprivation/reduction therapy and chaperone therapy will only work in those individuals whose mutations allow some active enzyme to be made by the body. Chaperone therapy is usually specific to the individual mutations.

For current information about clinical trials that are recruiting or underway, visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

The Future
In common with all of the MPS disorders, treatment and management for MPS I continue to evolve so the information presented here will change with time. It is important to keep up a regular dialogue with your medical team. Regular monitoring is an important way of managing problems before they become potentially serious, and to maximise quality of life. Living with a progressive disorder such as MPS I can be difficult and challenging and this monitoring is also a way to share some of that difficulty. As knowledge is built up and shared new treatments can be developed and quality of life improved for all.