



# THE ALSTRÖM SYNDROME HANDBOOK

*~ A Guide to Understanding, Managing, and  
Treating Alström Syndrome*



## DEDICATION

~To the children and adults who have Alström Syndrome - in the past, in the present, and in the future. We acknowledge with awe their courage, humor, and indomitable spirit.

~To the families in 'Alström Land' everywhere who live ordinary lives yet meet extraordinary difficulties with courage and conviction day in and day out.

~To the physicians and researchers who give of themselves tirelessly and with determination to fight and cure Alström Syndrome.

## *Special Acknowledgements*

*"A word grows to a thought; a thought to an idea; an idea to an act. All the pieces are put together, and the whole is yours."*

~ Beryl Markham: "West with the Night" (1942)

Beryl Markham was the first pilot to fly the North Atlantic from east to west. Jan Marshall first wrote the first words of this manuscript a very long time ago. But, it was Mary Smart and the Smart Family Foundation, with their personal and financial support of ongoing research and endless editing, spanning more than a decade of growth and change, that gave wings to this project and brought it safely home – at last! Alström Land is a better place indeed for having Mary Smart and her co-pilot, Irving Fletcher, in it.

Robin Marshall, Executive Director of ASI and “Jan’s Husband,” tirelessly promoted the need for patients, families, and physicians to have this book, literally, at hand. Without his committed support and encouragement, his skill as an organizer, and his persistence, The Handbook would still be a dream, not the reality you are holding and reading.

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**SMART FAMILY FOUNDATION**



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## TABLE OF CONTENTS

<b>Carl-Henry Alström Biography</b>	<b>1</b>
<b>INTRODUCTION</b>	<b>2</b>
<b><u>SECTION ONE: INFORMATION FOR FAMILIES</u></b>	
<b>CHAPTER ONE:</b>	<b>3</b>
<b>CHAPTER TWO: INFORMATION</b>	<b>17</b>
<b>CHAPTER THREE: DEVELOPMENT</b>	<b>24</b>
<b>CHAPTER FOUR: EDUCATION AND LEARNING</b>	<b>30</b>
<b><u>SECTION TWO: THE MEDICAL JOURNEY</u></b>	
<b>CHAPTER FIVE: PHYSICAL FEATURES</b>	<b>38</b>
<b>CHAPTER SIX: ENDOCRINE SYSTEM AND GROWTH</b>	<b>42</b>
• <b>THYROID</b>	<b>43</b>
• <b>GROWTH</b>	<b>45</b>
• <b>SEXUAL DEVELOPMENT</b>	<b>48</b>
<b>CHAPTER SEVEN: OBESITY</b>	<b>54</b>
<b>CHAPTER EIGHT: DIABETES</b>	<b>61</b>
<b>CHAPTER NINE: VISION</b>	<b>68</b>
<b>CHAPTER TEN: HEARING</b>	<b>76</b>
<b>CHAPTER ELEVEN: CARDIO/PULMONARY</b>	<b>82</b>
• <b>THE HEART AND CARDIOMYOPATHY</b>	<b>82</b>
• <b>PULMONARY/RESPIRATORY</b>	<b>87</b>
<b>CHAPTER TWELVE: HYPERTENSION</b>	<b>96</b>
<b>CHAPTER THIRTEEN: HYPERLIPIDEMIA /ATHEROSCLEROSIS</b>	<b>101</b>
<b>CHAPTER FOURTEEN: GASTROENTEROLOGY AND THE LIVER</b>	<b>104</b>
• <b>GASTROENTEROLOGY</b>	<b>104</b>
• <b>HEPATIC SYSTEM (LIVER)</b>	<b>106</b>
<b>CHAPTER FIFTEEN: NEPHROLOGY (KIDNEYS)</b>	<b>114</b>
<b>CHAPTER SIXTEEN: UROLOGY</b>	<b>120</b>
<b>CHAPTER SEVENTEEN: NERVOUS SYSTEM</b>	<b>124</b>
<b><u>SECTION THREE: THE FUTURE</u></b>	
<b>CHAPTER EIGHTEEN: GENETIC RESEARCH</b>	<b>129</b>
<b>AFTERWORD, A NEW BEGINNING</b>	<b>138</b>
<b>Appendix I – Scientific Advisory Board contact information</b>	<b>139</b>
<b>Appendix II – Quick Reference Profile</b>	<b>141</b>
<b>Appendix III – References</b>	<b>143</b>
<b>Appendix IV - Glossary</b>	<b>156</b>

## Carl-Henry Alström

**1907-1993**



Carl-Henry Alström was born in Västerås, Sweden on May 3, 1907. He received his doctorate in 1935 from the Karolinska Institute of Medicine in Stockholm, Sweden. In 1938, he began a long and successful career as a research scientist, pursuing varied subjects of interest to him in the fields of clinical medicine, psychiatry and genetics.

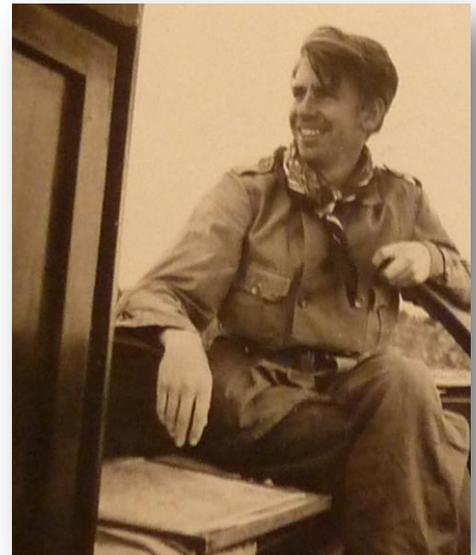
Relatives have shared that Carl-Henry and his family loved sailing, canoeing, and biking in and around the Stockholm archipelago – an area which he loved with a passion.

In 1946, he saw a 14-year-old boy and two of his cousins from a region in central Sweden. These children appeared to have features in common with Laurence-Moon-Bardet-Biedl Syndrome, yet they differed in several important ways. He published a report about this family in 1959 in

a prominent Scandinavian medical journal. The new syndrome was known for a short time as the Alström-Hallgren Syndrome but was eventually shortened to Alström Syndrome.

Although they searched throughout Sweden, Alström and his colleagues found no additional cases of the new syndrome other than the three members of this family.

Today there are a number of patients with Alström Syndrome living in Sweden, but scientists have not been able to determine if any are related to the first family described by Carl-Henry Alström. Since he discovered the first three Alström Syndrome patients, more than 800 individuals with Alström Syndrome have been identified throughout the world.



*Photos courtesy of Cilla Alström-Rapaport*

## **INTRODUCTION**

Too often, parents and families of children with Alström Syndrome are unable to find resources to help them understand what is happening to their child. There is a similar lack of resources for physicians to guide them in treating a child with Alström Syndrome. Without information, it is difficult to monitor a patient's condition or to provide appropriate therapeutic interventions. By far, the most common frustration expressed by families and physicians alike is *the lack of information*.

With this manual we attempt to address the many problems and concerns faced by parents and families, as well as to provide a resource for the physicians who must understand and treat the disorder. Our main goal is to arm parents with knowledge and resources so they can then inform the physician. Therefore, many aspects of the Handbook will define the issues of Alström Syndrome in a rather technical manner. For this reason, we have included short definitions of **bolded** medical terms at the end of each chapter, as well as a comprehensive list of definitions in the Appendix.

***This book is NOT a substitute for medical treatment or medical care.  
Please consult your medical doctor if you have any questions or  
concerns.***

Every physician and professional treating your child will need to be aware that Alström Syndrome affects many organ systems in very complex and complicated ways, and this central reality needs to be taken into account when any treatment interventions are considered. You should encourage your physicians and specialists to consult and collaborate with each other in the treatment of Alström Syndrome *as a whole*.

While many common features exist in everyone affected with Alström Syndrome, it should be noted that Alström Syndrome develops in each person in different ways and *not every child will experience exactly the same patterns*. There are conditions and complications described here that *may not* develop in every person with Alström Syndrome. Therefore, generalizations have been made using the latest clinical and research data, all in an effort to help parents and clinicians monitor the current health of their child as well as to anticipate any possible future needs.

Mastery of the medical facts about Alström Syndrome can be the first step towards living with the disorder. **KNOWLEDGE IS POWER!!**

## ***CHAPTER ONE ~ FAMILY ISSUES***

### ***Welcome to Alström Land***

Most, if not all, Alström parents are completely unprepared for the diagnosis. Initial shock and grief can be overwhelming. Diagnosis is frequently followed by a frenzy to understand the disease, often resulting in minimal, inconsistent and confusing information. There may be shock and disbelief among family and friends. It is difficult to understand and accept the invisible abnormalities lurking inside our infants and children, since they look so healthy and normal. As the diagnosis and circumstances slowly sink in, there will be a roller-coaster ride of emotions: denial, sadness, confusion, anger, and fear of the unknown future. Recognize these are natural responses to grief and anxiety, and that men often grieve differently than women. To help ease the fear and isolation, alleviate powerlessness and hopelessness by educating yourself. ***Education is your key to coping.*** An informed parent is a prepared parent. Find out everything you can about Alström Syndrome.

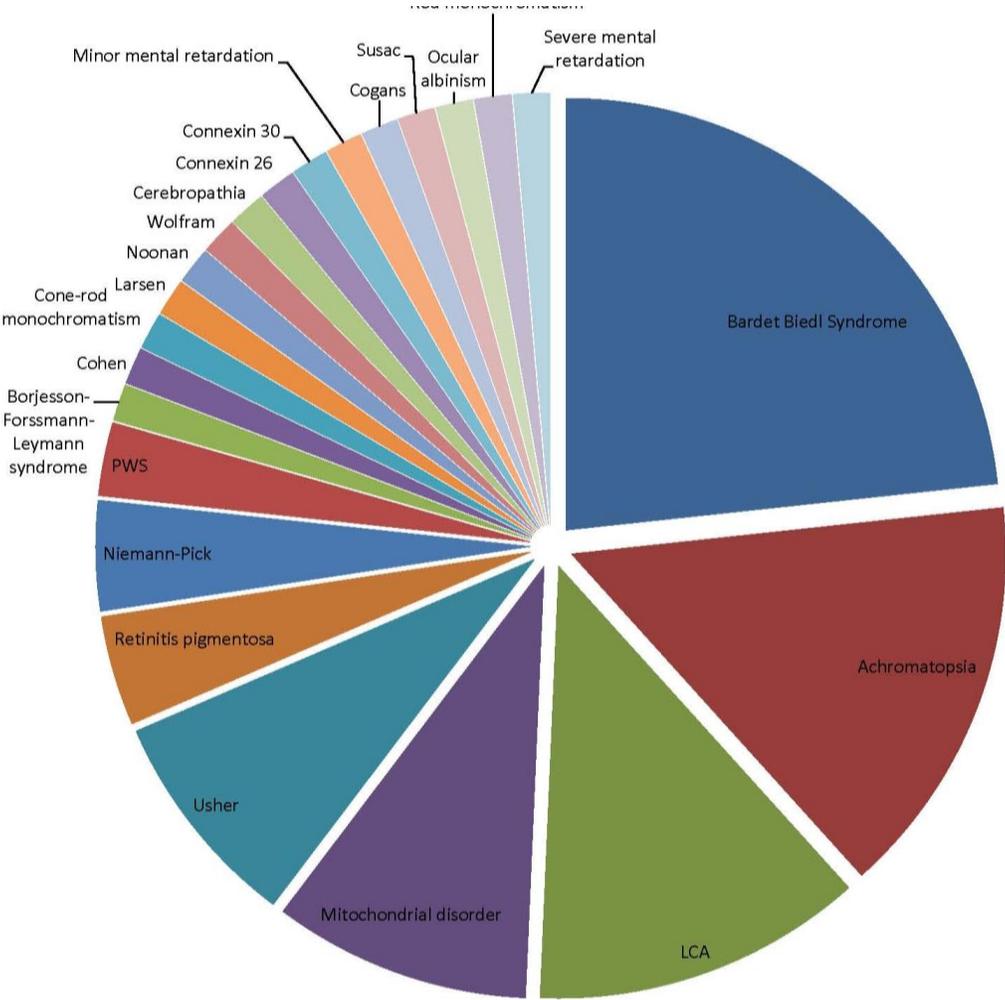
***Prepare Yourself Daily.  
Prepare Yourself for Setbacks.  
Alström Syndrome is a Roller Coaster Ride.***

### ***Getting the Diagnosis***

It may seem obvious, but the very fact that Alström Syndrome is rare makes it very difficult to be recognized. You may see many doctors before you finally find one who knows something about Alström Syndrome, or has ever even heard of it. Doctors are trained to look at more common causes of symptoms first, so they may not be thinking along the lines of a rare disease like Alström when they examine your child. There are other obstacles to a quick diagnosis. Because specific diagnostic genetic tests are not readily available or practical for Alström Syndrome, diagnosis is initially based upon clinical findings alone. Unfortunately, diagnosis may be delayed or incorrect due to the progressive appearance of many of the cardinal features and incomplete information available to the diagnosing physician. Your child may have Alström, but his/her symptoms do not fit the “classic” or typical picture. Your child may have symptoms that don’t usually go along with Alström, or he may not have all the symptoms that are expected. Doctors may hesitate to diagnose your child with Alström because of this.

Misdiagnosis is common. Because so many of the features of Alström Syndrome develop as children get older, more than seventy percent of the known Alström Syndrome patients have received previous misdiagnoses, and almost half of these have received multiple misdiagnoses.

Spectrum of Common Misdiagnoses.



It is important to note that the subsequent clinical course of the vision deterioration in each of these commonly diagnosed syndromes is very different from that seen in patients with Alström Syndrome. Therefore, careful monitoring of the visual symptoms in conjunction with other systemic manifestations, should direct your physician to the correct diagnosis.

### ***What Do I Do Now?***

When a child is first diagnosed with Alström Syndrome, it is a terrible shock. You have just learned that your child has a very complicated and frightening condition – Alström Syndrome. A whole range of complex feelings can engulf a parent when the diagnosis of Alström Syndrome is suggested. Once you find out that your child has, or may have Alström, you may experience all or some of these feelings. This is true even if the family has had years to search for a correct diagnosis, all the while knowing that something is wrong. Although not all family members will go through the same pattern of feelings or will feel them to the same degree, knowledge and understanding of these and other emotions may help the family work towards finding peace with these difficult issues.

- *You don't believe it can be true.*  
You are in shock. Part of you may be saying, "I don't believe it! It can't be! No way! There must be a mistake!" It seems an impossible concept for your very precious child to have Alström Syndrome. You may feel that if everyone just stops talking about this, you will wake up tomorrow and everything will be fine. A mother or father often believes that even if their child has the diagnosis, they won't have it as bad as other kids with Alström. Maybe he or she has a "milder" form. Denial is a normal occurrence. It's what our brains do to protect ourselves from shock.
- *You feel guilty.*  
Because all parents seem to have a basic belief that a "good parent" should protect a child from illness and suffering, many parents blame themselves when their child gets sick. It is hard work to unlearn and ignore this kind of myth.
- *You are heartbroken.*  
It can be a devastating blow that your child isn't, or may not be, the perfect being you imagined and hoped for ... even if you sort of expected that something wasn't right. You may not be able to imagine ever being able to get through this or accept this.
- *You feel devastated with loss and grief.*  
Grief is not simply feelings of sadness and pain, but also shock, confusion, numbness, anger, fear, anxiety, and guilt. The grief can often be hidden and parents tend to put their feelings "on hold". Because few people, including family, friends, and professionals, take the time to inquire about those feelings, you might begin to believe that your emotions are abnormal and that no one feels as you do. It is very common for intense feelings of grief to be triggered, not only at the time of diagnosis, but also at times of medical crises, at times of missed opportunities for their child, and even at simple occurrences such as seeing another child who is healthy. You feel isolated and you are mourning.

- *You are angry.*

You may feel angry at the unfairness of having your life rudely disrupted with the stark new reality of something being wrong with your child. You did not ask for this situation. Prospects for your child's future (and your own) may seem bleak. "How can this happen to me?" "How will I ever manage?" Raising your child, which you once looked forward to, may seem like an impossible obstacle in light of the disabilities your child will probably face. Anger can be turned on family members unless you make extra efforts at communication. Family strife and even divorces have occurred as the result of the stress. On the other hand, many wonderful families have taken responsibility to protect their stability by accepting the emotions they are experiencing, and choosing to face this challenge, united.

- *You have anxiety and fear of the future.*

You are worried for your child. What will he/she be able to accomplish in life? Will others accept him? Will he die? You wonder if your son or daughter will eventually become independent - or if you will be in a caretaking role for the rest of your life. You panic for you, wondering if you can handle this in your life. How do you deal with all this complicated information? Where can you find the kind of support that will help you be strong?



- *You are completely overwhelmed.*

In addition to your regular hectic life, you now have all these "special" things to take care of like endless medical appointments and meetings with school specialists. Making space for yourself to unwind by doing nothing can help you to recharge and gather the strength you need to keep on going. Remember that you have friends and support through Alström Syndrome International.

***Inspired after reading another mom's perspective on 7 things you may not know about a Special Needs Mom. Here is my story....***

*There are approximately 6000 rare diseases known at the National Center for Rare Diseases. Alstrom syndrome has only a little over 700 cases identified worldwide. Even though there are many disabilities in this world such as cognitive, behavioral, medical, chronic or life-threatening, very few children even with the same diagnosis have the same issues. My son Sam is complicated and original.*

*Here are the 7 things I think most people don't know about me, Diane, a special needs mom.*

*#1. I am often tired. Parenting can be an exhausting job with just a typical child but parenting a special needs child takes things to another level. Tending to the constant needs of medical, educational and safety concerns for Sam never ends, it never sleeps. I have a video "baby" monitor on him when he is sleeping just so I can see and hear him at all times. His breathing mask has become disconnected and oxygen alarms have gone off. Even if I get a good nights sleep it never seems enough for what the day can bring. Doctors appointments are not just a few times a year, they are a few times a week. Music therapy, physical therapy, counseling and home bound schooling are just a few of the things that are done in our home now. Sam has had over 90 appointments in the last 10 months. Whether it was blood work, CT scans, doctor appointments or surgeries it has added up. I wondered why I found it hard to go back to work. There is no routine to my day. Some days are good, some days there is physical and mental exhaustion. The amount of time I spend on the phone with hospitals, office staff, teachers, therapists and insurance companies parallels the amount of time I spend on paperwork, emails, organizing, advocating and recording all Sam's medical records. There are no words to tell you all how much the smallest of kind acts you have bestowed upon us helps. My neighbor routinely cleans my driveway with his snow blower. Friends call to say they are at the grocery store and ask if they can pick something up for me. Small gifts and kind words are monumental to me.*

*#2 I am jealous. This isn't easy to admit or discuss. I have Joe who is a "typical" kid, bright, good-looking, athletic. He is blessed with good health. Then I look at Sam as compared to his peers. His life has changed so dramatically that it's hard to watch other kids pass him by. He has not one friend his age that comes to play with him. However, Joe has some amazing friends that spend time with Sam from time to time. Over the years a few kids have come by the house but after awhile they stop returning your phone calls. What do I say to Sam who wants me to keep calling and leaving messages. I hide the truth that they are just not interested anymore. He's hurt enough, I'm not going to be the one to hurt him more. I get upset easily over people complaining about their kids. Really?? I would love for Sam to be running around getting into trouble. That would be more normal, right? I have even felt jealous of other Alstrom kids because they don't have as many problems/illnesses as Sam does. Doesn't that sound crazy? They have the same devastating disease my son has - how can I have those thoughts?? I pray constantly for God to help me find peace for where I am, where Sam is, where my family is right now. But, I'm not going to lie, it's a constant battle. Believe me, Sam has given us much to rejoice about, much to brag about and much to feel blessed about over the years. But sometimes, I'm still jealous of not having two healthy boys.*

*#3 I feel alone. I can be surrounded by people but feel so alone. It's hard to explain how you are functioning in the world doing all the same things other people are doing but feeling isolated. I don't expect people who do not walk in my shoes to understand how I feel all the time. When people ask me how I am, or how Sam is, I don't know what to say. I know they don't have time to hear the long version, but there really is only a long version. My pastor has talked to me and told me to tell everyone I'm fine. Take all my cares to God. I don't want to burden others with all that I am dealing with, it scares people. I have lost friendships over the years and I know this is one of the reasons. People don't know what to say, what to do, or how to deal with our ups and downs. I am very aware that the world keeps moving with or without me. Every time I learn about a new diagnosis or a new problem with Sam's health I start all over again with the stages of grief. **Denial**- This can't really be the diagnosis, it can't be this, not yet, not now. Then the stage of **Anger**- "why is this happening to my son". **Bargaining**- "If I call this doctor and get this medication and do this test then it will get better" **Depression**- "I'm just so sad to watch my son slowly lose his life to this awful disease we call the "Alstrom Monster".....The last stage is **Acceptance** - I only come to acceptance when I am seeking God. As long as I try to fight this Alstrom monster in the world, I lose. When I seek God all is well, there is peace even when there is not complete understanding. That is a good place to be. But I don't get to be there often because the cycle starts all over again, each and every time I get bad news about Sam's health, and as most of you know this is constant. There is something different about going through a one-time traumatic event as compared to a long term chronic event. Some say things to me like "you have had time to get used to it" or "at least he is smart."*

*I know people want to find away to lessen my blows but the best thing you can do for me is to just listen, let me cry, let me feel accepted no matter what part of the cycle I am in at the time. I know deep down the Lord never leaves me but I still feel lonely without real friendships around me.*

*#4 I am scared. Every time Sam complains of pain, has a fever, coughs, gets blood work or xrays done, every time he doesn't answer me if I call to him from the next room. Every time he has surgery (13 times now) I pray to God that when I kiss him on the cheek as they put him to sleep that it won't be the last time. What if people take advantage of him when he is away from me? What if I don't catch the next medical mistake? What if I don't ask all the right questions? What if I don't educate the people taking care of him all about Alström syndrome? I have feared that Sam may never walk again outside independently by himself because of his fractures in his spine. What happens if John and I die? Who will care for Sam? I have been to many functions with blind people and know that they can have full and rewarding lives. I have been to many Alström conferences and have witnessed other Alström individuals with amazing lives. I believe God is in control, but sometimes I slip and I worry. I'm working on that. God is working on me. God is very clear that we are to be anxious for nothing. Philippians 4:6-9 "Be anxious for nothing, but in everything by prayer and supplication with thanksgiving let your requests be made known to God. And the peace of God, which surpasses all comprehension, will guard your hearts and your minds in Christ Jesus." Matthew 6:33 "Seek first the kingdom of God and His righteousness" I know that my heart has to follow God in order for my fears to cease. I hope I can instill the words of God onto Sam's heart so that he does not fear like I have over his life. Pray for this.*

*#5 I am human. I am not some "super mom" I am not more incredible than any other mom I know. I don't like to be called super wonderful because when I fail, and I do, it just makes me feel like I fall so much further. I am happy, mad, angry, joyful, disappointed, and excited just like everyone else. My journey is a little different than the norm but we all have our crosses to bear. I make bad judgments, hurt people's feelings and can be unbearable at times. I love my family, I love my friends and there isn't anything I wouldn't do for any of you!! I love to have quiet time. I love to shop. I love to have lunch with friends. I like pedicures and having my hair done. I am not special, maybe in God's eyes, he sees us all that way. Don't hold me to a higher standard or a lower standard. I'm just me, I'm human.*

*#6 I wish people would stop taking advantage of the disabled. Don't block the handicap parking at the school because you just want to let your kid out of the car. I wish I could let my kid jump out of the car. But while you are blocking the space, I have to wait, or drive around again, I need that space to get Sam to school. A handicap placard does not mean VIP parking. There is a price Sam pays for that. He is blind and in a wheelchair. Please don't take advantage of the handicap parking by saying, "I'll only be a minute". Don't use grandma's pass for yourself. Don't stare at handicapped people. Come up to them, ask them their name, feel free to ask them "what is wrong or different about them." It is so much better than being stared at all the time. Don't be scared because you used a phrase such as "what are you blind?" when you are around Sam. We are not that sensitive. We try to find ways to have fun with the situation. We still want to laugh about things.*

*#7 I want to talk about Sam. I love him. I am blessed by him every day. I am inspired by him. He brings me just as many laughs as there are tears. I love to talk about Alström syndrome. I love to educate others. It's OK to talk about the "elephant in the room" (Alström syndrome) We live with him, why ignore him. It just makes it uncomfortable for everyone. Ask specific questions, ask general questions. Ask anything at all. I'll tell you if it's too personal but pretty much I'm an open book. I've learned that over time I have shut down and shut people out who truly did care, but I didn't know at the time they really did want to hear the long version. I could hear myself as I am talking, like I'm hovering over the situation, and see the person on the other end becoming squirmish or distracted and I immediately assumed they weren't interested so I would find a way to quickly wrap it up. If I'm talking too much, just tell me you gotta go. I know I talk too much ....lol I also love to talk about Joe, John, and our dog too!*

*The most important thing is that I know I am blessed. I have a good husband, an incredible teenage son and a miracle child in Sam. Even my dog is awesome. I love you all and I'm thankful to have you all in our lives!! Have a blessed day!*

## ***Marital Stress and Strain***

Having a child with Alström Syndrome can place enormous psychological, financial, emotional and physical burdens on parents. Sometimes the parents become closer by working together to overcome these burdens. However, often the burdens can strain the relationship. Parents may feel guilty about the fact that their child has inherited Alström Syndrome from them. In addition, medical care can be expensive and can cause the parents to miss work. Sometimes, one parent assumes the burden of the care, which can lead to feelings of resentment in the care-giving parent or feelings of isolation.

Each parent may express grief in different ways. Often this can be a source of friction, especially if, for example, one parent needs to talk, while the other needs to withdraw. It helps if each parent can recognize his or her style of dealing with tension and anxiety and can give one another the freedom to be different. Individual and family counseling can also help family members deal with the pressures of living in “Alström Land.”

Brennan and Kelly  
ASI Conference 2004



## ***The Family***

There are added stresses to families when one member has any disability, let alone one as demanding as Alström Syndrome. When parents have to cope with the time and energy drain created by the situation of caring for their Alström child, other children in the family are also affected. Time that used to be available for siblings is gone. The brothers and sisters of a young person with Alström may feel left out or feel as if they are getting less attention because of the attention directed towards the sibling with Alström, and they

may act out when they are jealous for attention. They might even wish they were sick too - to get attention or because they feel guilty for being the “healthy” one. A brother or sister of a child with special needs might resent being asked to assist with care and wonder if, eventually, the full burden of care might fall on them. Even if they are happy to help out, and even if later on they will actually provide care for their sibling, some feelings of anxiety are normal.

At the other end of the spectrum, siblings may act “too” good, attempting to lead quiet lives so that they can assure that their parents’ lives run smoothly. They are afraid of adding more hassle to an overburdened mother or father.

It is very important to allow siblings to talk about their feelings regarding their life with a brother or sister with Alström Syndrome and to allow them to express their feelings. Older siblings may have many questions which are very hard to voice. “Could I be a carrier?” “Should I marry?” “Might it happen to my children?” “Why did it happen to my brother and not to me?” Talking with a trained genetics counselor can help address these concerns.

***“None of us are powerless. All of us have assets upon which to draw that will enhance our children’s lives, and our own with them.”***

***From Donald J. Meyer,  
Uncommon Fathers***

### ***Grandparents***

As a grandparent, you hope and pray that your new grandchild will be healthy. You keep an eye on your grandchild’s development to make sure that everything is “normal.” When you hear that your grandchild has Alström Syndrome, you feel shocked. You find it hard to understand how this could have happened to your family. You ache for your grandchild—and for the child's parents. These feelings are understandably painful. You can't change what has happened to your grandchild, but you can offer your support to the child and to the rest of the family. They need you more than ever. That's because you have many special gifts to offer your family right now.

- Inform yourself about Alström Syndrome.
- Show your grandchild every day that you love him for the special person he is.
- Give equal special attention to the other, unaffected siblings in the family.
- Listen when the child's parents need to talk.
- Support the decisions they are making, even if you don't agree with all of them.
- Relieve the parents as much as possible to provide them some free time.

It is important to stay as involved as you can in the child's life. This will help you, and your family, become more comfortable and knowledgeable about living with Alström Syndrome. Become active in the ASI support group for families and talk to other grandparents. You will feel better when you can share your feelings with people who know what you're going through. Finding out that your grandchild has Alström Syndrome is difficult, and raising a child with Alström is challenging. You and your family can meet this challenge if you work together and support one another.

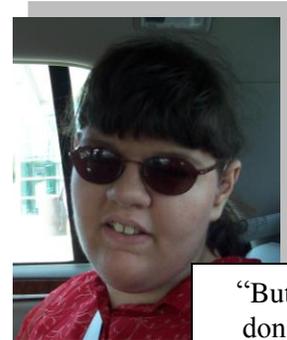
### ***Talking to Your Child About Alström Syndrome***

Discussing the diagnosis with your child is a very important issue and one for which many parents seek advice. “How much should I tell my child about Alström Syndrome?” Many



parents have a deep wish to protect the child from all of the implications of Alström Syndrome, and to delay telling the child seems the kind and easy way at the time, but most parents have found that, if a child is not told the truth from the beginning, it is much harder for anyone to tell him/ her later. No child is too young to have questions simply and honestly answered.

Confusion and anxiety can plague a child with Alström. There are questions your child may have but is afraid to ask. Your child's maturity, personality, and the specific manifestations of Alström he or she is experiencing are all factors to consider in determining when a child is ready for more information about Alström Syndrome. The child may worry even more than necessary if there is an impression that there is a family secret about it. Evasive answers often provoke fear rather than provide reassurance, and false answers may impair later trust. There is no single correct approach to this and there is no exact age or time that is "best" to tell a child about their diagnosis. Children are sensitive to atmosphere and will, however young, sense that something is wrong. Most children do not ask questions if they cannot cope with the answers. At any age, knowledge is better than the lack of it.



"But I don't want Alström"

Ultimately, every child with Alström will begin to question why he must go to so many doctors, why he has such trouble seeing and hearing, why he is different from other children. Your child may even wonder and worry about whether they are going to die. Even the child or adult who does not ask or verbally express concern about Alström may still be thinking those thoughts and not be able to express them. Specific questions are a clear indication that your child needs some information about the diagnosis. Most children just need minimal information to start and you do not need to go into great detail with a young child. More information can be added over time. If any general advice can be given here, it is to answer the child's questions honestly, giving as much information as the child seems to be able to understand. Be positive! Your positive attitude and the manner in which you convey the information is important. People with Alström who are successful have learned who they are and accept and use that information to help themselves become the best they can be.

We repeatedly find that when children and adults with Alström Syndrome have an opportunity to meet others with a diagnosis who also have the same situation, they find it is a very rewarding and life-changing experience. Such interaction can help individuals realize that there are other people that experience the world the way they do, and that they are not the only



one.

There are various possibilities for meeting other children and young adults with Alström. There is the ASI family conference and the ASI newsletter which frequently publishes letters, poems, and other contributions from individuals of all ages with Alström.

Alström Syndrome International hosts a Forum where questions and answers from families and physicians are posted and archived according

to subject: [www.Alström-families.org/forum](http://www.Alström-families.org/forum). Adults over the age of 18 with Alström have a private discussion Forum on that site. Alström Syndrome International also hosts a web blog site, where the latest news is posted. [www.Alström-families.org/blog](http://www.Alström-families.org/blog). Additionally, there is a listserv group on the internet [www.groups.google.org](http://www.groups.google.org) that consists of patients, families, physicians and researchers.

TIPS FOR PARENTS OF A YOUNG CHILD: When your child enters elementary school, consider the following:

- Talk to your child about Alström Syndrome, so he or she is able to tell others about it.
- Teach your child to monitor his own glucose levels.
- Teach your child the importance of proper nutrition and exercise.
- Encourage your child to ask his own questions of the doctor and other health care providers.



TIPS FOR PARENTS OF AN OLDER CHILD: When your child is an adolescent, consider the following:



- Reassess your teen's knowledge of Alström Syndrome and fill in any gaps in his or her understanding.
- Teach your teen to pay attention to how he feels and to be aware of danger signs; such as shortness of breath or excessive fatigue.
- Teach your teen to take their own medication and monitor their own blood glucose levels. There is adaptive equipment for the blind to help with this.
- Discuss the long-term course of Alström Syndrome with your teen, and what he or she might expect in the future.
- Encourage your teen to ask questions of the doctor and other health care providers directly.
- Encourage your teen to participate in the Alström Syndrome International teen and adult support groups.

***Parent-Physician Partnership: Telling Your Story the First 50 Times Was Easy...***

***The Doctor's Office***

Try to develop a strong family-professional team, a mutual commitment that recognizes and respects the knowledge, skills and experience that each brings to the relationship. Promote collaborative decision making with your medical team because no one knows your child better than you do! Ask questions and be recognized as your child's expert. Medical professionals have a snapshot view, but you see your child on a daily basis. Parents are a valuable source of information and can make a tremendous difference by becoming proactive; you can ensure quality care and enhance outcomes.

Doctors have tight schedules to keep, so make every minute count.

- ✓ Take the time to write down all questions, concerns, and needs *before* a doctor's appointment.
- ✓ Remember that Alström Syndrome is rare and your doctor may be learning along with you. Never be afraid to take copies of the current medical literature about Alström Syndrome. Your doctor will appreciate it.
- ✓ Save and keep track of all of your child's medical records. Ask for copies of all testing results to keep in a binder for all of your child's medical notes and test results to take with you to each and every doctor's appointment. The information a parent provides can aid the physicians in making good decisions.
- ✓ Report changes in your child's health. Even seemingly insignificant changes could be important problems developing. For instance, something that seems minor, like bad breath, could actually indicate signs of gastrointestinal issues developing. Be specific, not vague, about issues you want to discuss.
- ✓ If a test is ordered, make sure you understand why it is being ordered and what is being evaluated. Don't leave the office without having your questions answered.
- ✓ Doctors are people too, so remember you get more with honey than vinegar. Be assertive, yet nice!
- ✓ The development of trust is an integral part of a relationship with your doctor. If you do not have mutual commitment and respect, you cannot get satisfaction from the medical team, and you may need to go elsewhere for care.

"An observant parent's evidence may be disproved but should never be ignored"  
Lancet 1:688, 1951  
Anonymous

### ***Manage Your Own Medical Journey***

Adapted from *How Are You? Manage Your Own Medical Journey*, Patricia Foote, *Medical Journeys Network*, 1998.

- Understand Alström Syndrome. Prepare for doctor visits with a list of intelligent questions.
- Become a Team Leader of your medical team. Remember that *you* are paying, so hire professionals who are competent, compassionate and communicate well. Encourage specialists to communicate with each other and with others who treat patients with Alström.
- Acknowledge the emotions that come with a diagnosis of Alström Syndrome. Recognize fear, denial, anger, depression, frustration, and isolation. Seek professional help if things are really bad. Become involved with Alström Syndrome International or other national support groups.
- Be sure to schedule a break for yourself.
- Stay on top of health insurance issues. For example, what procedures require pre-approval; what is your annual deductible; what is your lifetime limit or cap; what protections do the laws of your country offer?
- Maintain a positive outlook - an "I can do" attitude. Replace negative thoughts with positive action - not "Why me"? but "What can I do?"
- Realize that sometimes blessings and insights come from living with Alström Syndrome. Perhaps you learn to value the use of time, become more empathetic, learn who your true friends are.
- Learn to accept the diagnosis and live your new life. Integrate the business of living with Alström into your life and move forward. Accept and understand that it may not be possible to "win the fight" with Alström Syndrome. The knowledge gained from the battle could be considered precious, and victory a deeper love of those who have shared the journey.

### ***The Second Opinion - Moving On...***

Sometimes, even though a parent doesn't believe they're getting the level of care they require, they feel compelled to stay with a doctor out of respect for shared history, or fear of hurting their physician's feelings. Others simply are unwilling to embark on the ordeal involved in finding a new doctor and establishing another relationship that may turn out to be no better than the one they're ending. Settling for second best isn't the answer.

Second opinions may clarify any uncertainties, and at the very least, they can provide reassurances. If you question the recommendations or plan of your physician, you have the right to ask for a second opinion from another physician. Do not be afraid to tell your doctor that you would like another specialist or qualified physician to review the case and give a recommendation. When a parent makes such a request, physicians are generally very cooperative and will send test results and other information to the physician of your choice.

The days of doctors being viewed as the "authority figures" and "doctor knows best" have changed. Passivity has been replaced with empowerment; finding quality care is up to you! If you have a bad experience with one of your child's specialists, you do have options! "Shop around" and interview potential new doctors to be sure he/ she will be right for you. Other Alström families can also provide invaluable help in locating resources. It is critical that you settle into a relationship with someone you trust and who recognizes the complexity of Alström



Syndrome and your child's situation. From there, you must do your part and physicians must do theirs; only by working together can the best outcomes be achieved.

Nobody likes to go to the doctor, but when your child has Alström Syndrome, doctor visits are a regular part of life. Doctors have different philosophies, and so do parents. To develop the strongest, most productive relationship between the two, it's necessary "to have a good fit." A good working relationship between you and your child's various doctors goes a long way toward making the experience positive for everyone involved and helps ensure that your child gets the best medical care.

To that end, there are steps both doctors and parents can take to help create an effective and successful partnership. You want your family and your child's doctor to be "in it together."

Naturally, you want a physician for your child who is exceptionally knowledgeable in his/her specialty, and also willing to learn as much about Alström Syndrome as possible. Unfortunately, most physicians will not have any prior knowledge of Alström, and the parent may have a better overall knowledge of the syndrome. You should seek a doctor who is interested in the "whole picture" and be willing to learn, study, and consult with others in order to have all of the information available to treat your child. Your doctor should be willing to "go the extra mile" because that is what Alström Syndrome demands. If your doctor is not, look for someone else!

#### Some comments from parents:

- *"I know that most doctors are not familiar with Alström Syndrome, since it is so rare. What I want is for my doctor to be open minded and willing to learn about it!"*
- *"What we as parents wish is that our doctors could first take a look from their side, which is the clinical side, and then also take a look from the parents' side and try to understand what it's like to live with the disease on a day-to-day basis,"*
- *"Technicians come in and they sit there and take notes, and they look at you like you're a person in a cage."*
- *We want a doctor who avoids making assumptions based on what they've seen in the past and who recognize that their patients are all different.*
- *"I know they're on top of it in their own specialty, but I want to be sure they're also on top of my kid."*
- *"I want my family and my child's doctors to be "in it together."*



### TIPS FOR SMOOTH DOCTOR VISITS FOR THE VERY YOUNG CHILD:

- Be honest about the upcoming appointment
- Describe why he/she needs to see the physician (again!)
- Talk about what will happen, including the taking of vital signs, lots of talking, and the actual examination. Children with Alström like to be prepared ahead of time with no surprises!
- Remember that because your child cannot see well, some procedures may startle or take him by surprise.
- Spend special time or have a treat after the visit so that ‘doctor day’ isn’t all bad!



### TOP FIVE THINGS YOUR DOCTOR SHOULD BE AWARE OF!

- Alström Syndrome affects nearly every organ system in the body – the patient should be treated in a holistic way.
- Even for routine minor surgery or infection, it is vitally important that medical and nursing staff be aware that hypoxia (dangerously low blood oxygen levels) can occur *very* rapidly in these patients.
- There is risk for recurrence of CHF in patients who have cardiomyopathy as infants who have achieved a significant recovery of heart function.
- Over time, fibrosis slowly develops in every organ.
- If you wonder if a particular symptom is part of Alström Syndrome... it probably is!!

These issues will be discussed in depth in ‘The Medical Journey’ portion of the Handbook.

## CHAPTER TWO ~ INFORMATION

### *What is Alström Syndrome?*

We all have the “Alström gene,” *ALMS1*. Alström Syndrome is recessively inherited; therefore both of the parents are obligate carriers but will not exhibit the features of Alström. We do not yet know exactly how this gene works, but we do know that when something goes wrong within this gene, the consequences are many and encompass multiple organ systems. Alström Syndrome is called a “syndrome” because it is a cluster of abnormalities seen together and associated with several organ systems, all thought to have only one underlying cause: alterations (mutations) in one gene, *ALMS1*. In syndromes, the organ systems involved may interact with each other to produce a complexity of features that create a “cascade” over time.

Alström Syndrome is traditionally defined by the following general profile: low vision caused by progressive retinal dystrophy, which begins in infancy and leads to eventual childhood blindness; hearing loss in childhood; childhood obesity; type 2 diabetes mellitus; and slowly progressive liver and kidney problems. Many serious symptoms are observed in some, but not all patients with Alström Syndrome, including heart, lung, urological, and liver dysfunction.

Because the features of Alström Syndrome can be so wide-spread and also variable, misdiagnosis is common, especially early on before some of the classic symptoms develop.

### *Profile of Typical Alström Syndrome Child*

This is a brief overview of what is “typical” for an Alström child. Each area of concern will be discussed in-depth in later chapters. Alström Syndrome involves multiple organ systems with complex interactions between these systems. Keep in mind that there is considerable



variability of the features seen in Alström, even between siblings. A typical child first presents symptoms in infancy with severe light sensitivity and wobbly eyes called nystagmus. By age 12-16 years, most children are legally blind. Early in childhood hearing appears normal, although, usually within the first decade, hearing impairment is noted, and bilateral hearing deficits evolve throughout the school age years. Intelligence is normal, although developmental milestones may be delayed in some children. A few children can demonstrate behaviors within the “autistic spectrum”.

Many children with Alström Syndrome experience problems with heart function, called cardiomyopathy, and subsequent heart failure can develop either as infants or in adolescence. In infants, cardiac symptoms may precede vision defects, and most infants appear to have a recovery by the age of three years. It should be noted that in children who have recovered from congestive heart failure in infancy, recurrent cases of

cardiomyopathy have been noted in adolescence or adulthood. Occasionally, a patient has cardiomyopathy that does not resolve, and congestive heart failure persists.

Toddlers are chubby, and serious truncal obesity evolves with Body Mass Indices (BMI's) ranging from 20 to 57. BMI is simple to calculate. The formula is weight in kilograms divided by the square of the height in meters. **BMI= weight (kg) / height (m<sup>2</sup>)** There are numerous websites that will automatically calculate BMI for you by inputting your values in kilograms and meters or pounds and inches.

Children often have very large appetites and sometimes have an obsession with food. Nearly all children are above the 95<sup>th</sup> centile for weight. However, obesity often moderates after puberty. Most children have normal height in the early years, but final height after puberty is often below the 50<sup>th</sup> centile. Children typically have short, thick, wide feet and stubby fingers, but no extra fingers or toes and no fused digits. Small genitalia are a common occurrence in boys.

Insulin resistance, high levels of insulin in the blood, and glucose intolerance eventually develop into type 2 diabetes during adolescence or early adulthood. That is much earlier than usually seen in typical adult onset diabetes. It is not known how early children with Alström Syndrome exhibit insulin resistance, but hyperinsulinemia has been reported in children as young as four years old.

The liver is often affected in early childhood. Typical liver problems usually begin with what is called “fatty liver”, often accompanied by abnormal liver function tests in the blood. In some children, the liver problems can progress to more serious conditions that prevent the proper functioning of the liver.

Kidney function is also affected by Alström Syndrome. The kidney problems develop slowly, and sometimes lead to renal failure in later years necessitating dialysis and kidney transplantation.

Not all children with Alström Syndrome develop the symptoms in exactly the same way. As in all children, there are differences. Some children have serious urological problems; others have reduced respiratory function. Some have behavioral issues, seizures, tactile defensiveness, or an acute sense of smell; some do not. If your child has Alström Syndrome, nothing is unexpected!

### ***Diagnostic Criteria***

Alström Syndrome is characterized by a very complex interaction of progressive, highly variable symptoms, many of which are often viewed as NOT related to the syndrome, but they frequently are!

The five “cardinal diagnostic features” described in the medical literature for decades have traditionally been the combination of early retinal degeneration, hearing impairment, obesity, diabetes mellitus and renal failure, with the absence of mental retardation and normal fingers and toes. As more is known about the syndrome, it becomes clear that the fundamental features should be broadened to amend and expand the previously accepted diagnostic criteria.

Delay of onset of some of the characteristic features (type 2 diabetes, cardiomyopathy, liver disease, and kidney failure, for example) makes differential diagnosis very difficult, especially in young children. Many of the manifestations do not become apparent until after the teenage years. As the child grows, the characteristic pattern of Alström Syndrome evolves and the clinical picture becomes clearer. Therefore, the most recent advice concerning diagnostic criteria takes into account the age of the child as well as the symptoms that the child exhibits.

**Management**

It is always best to have information BEFORE it is needed. Having a child with Alström Syndrome increases the need for advance information, although routine pediatric preventative care still applies, such as immunizations and regular checkups. It is recommended that the baseline blood tests such as glucose, cholesterol and triglycerides, and liver enzymes be done at the time of diagnosis and at regular intervals for all individuals with Alström Syndrome. Regular follow-up with several subspecialists should occur throughout life. At each age, people with Alström have specific health care needs. The following charts and tables detail routine care for people with Alström Syndrome needed by specific age groups, including infancy, early and late childhood, adolescence and adulthood. We hope that this will be useful both for your doctors and for you.

**Clinical Features of Alström Syndrome**

<b>OTHER FEATURES OBSERVED</b>	
<ul style="list-style-type: none"> <li>• Early cone-rod retinal dystrophy (nystagmus and photophobia beginning in infancy) leading to eventual blindness in adolescence.</li> <li>• Truncal obesity</li> <li>• Bilateral sensorineural hearing impairment</li> <li>• Infantile or adolescent/adult dilated cardiomyopathy</li> <li>• Hepatic dysfunction; elevated GGT and transaminases (ALT and AST)</li> <li>• Elevated triglycerides</li> <li>• Insulin resistance in childhood, type 2 diabetes mellitus in childhood or adolescence</li> <li>• Progressive renal insufficiency</li> <li>• Normal extremities (no polydactyly or syndactyly)</li> </ul>	<ul style="list-style-type: none"> <li>• Chronic pulmonary problems, COPD</li> <li>• Urological instability</li> <li>• Neurological disturbances (absence seizures, epilepsy, ataxia)</li> <li>• Normal mentation but sometimes a delay of early milestones</li> <li>• GERD</li> <li>• Autistic spectrum behavior</li> </ul>

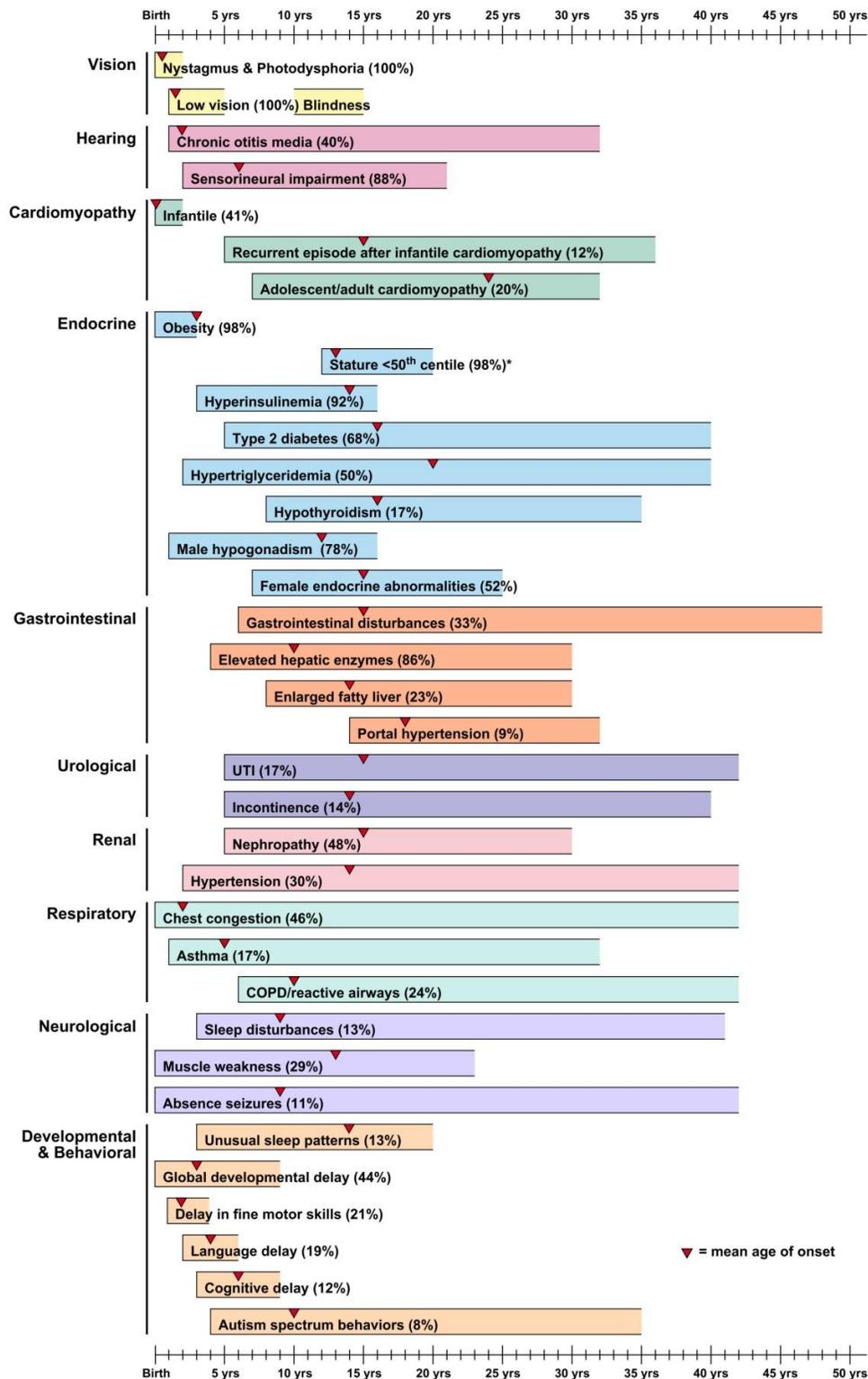
*LEGEND: A phenotype is listed as “Common” if present in over 60% of patients at the appropriate age. “Other” features are observed less frequently (10-59%.)*

## Diagnostic Criteria for Alström Syndrome

	<i>Birth - 2 years<sup>a</sup></i>	<i>3 -14 years</i>	<i>15 years - adulthood</i>
Proof <sup>b</sup>	2 ALMS1 mutations	2 ALMS1 mutations	2 ALMS1 mutations
Minimum diagnosis requires	a) 2 major criteria or b) 1 major and 2 minor criteria	a) 2 major criteria or b) 1 major and 3 minor criteria	a) 2 major and 2 minor criteria or b) 1 major and 4 minor criteria
Major criteria	<ul style="list-style-type: none"> <li>▪ ALMS1 mutation in 1 allele and/or family history of Alström Syndrome</li> <li>▪ Vision (nystagmus, photophobia)</li> </ul>	<ul style="list-style-type: none"> <li>▪ ALMS1 mutation in 1 allele and/or family history of Alström Syndrome</li> <li>▪ Vision (nystagmus, photophobia, diminished acuity, if old enough for testing: cone dystrophy by ERG)</li> </ul>	<ul style="list-style-type: none"> <li>▪ ALMS1 mutation in 1 allele and/or family history of Alström Syndrome</li> <li>▪ Vision (history of nystagmus in infancy/childhood, legal blindness, cone and rod dystrophy by ERG)</li> </ul>
Minor criteria	<ul style="list-style-type: none"> <li>• Obesity</li> <li>• DCM/CHF</li> </ul>	<ul style="list-style-type: none"> <li>• Obesity and/or Insulin resistance and/or T2DM</li> <li>• (history of) DCM/CHF</li> <li>• Hearing loss</li> <li>• Hepatic dysfunction</li> <li>• Renal failure</li> <li>• Advanced bone age</li> </ul>	<ul style="list-style-type: none"> <li>• Obesity and/or Insulin resistance and/or T2DM</li> <li>• (history of) DCM/CHF</li> <li>• Hearing loss</li> <li>• Hepatic dysfunction</li> <li>• Renal failure</li> <li>• Short stature</li> <li>• Males: Hypogonadism</li> <li>• Females: irregular menses and/or hyperandrogenism</li> </ul>
Other variable supportive evidence	<ul style="list-style-type: none"> <li>○ Recurrent pulmonary infections</li> <li>○ Normal digits</li> <li>○ Delayed developmental milestones</li> <li>○ Recurrent UTI</li> </ul>	<ul style="list-style-type: none"> <li>○ Recurrent pulmonary infections</li> <li>○ Normal digits</li> <li>○ Delayed developmental milestones</li> <li>○ Hyperlipidemia</li> <li>○ Scoliosis</li> <li>○ Flat wide feet</li> <li>○ Hypothyroidism</li> <li>○ Hypertension</li> <li>○ Recurrent UTI</li> <li>○ Growth hormone deficiency</li> </ul>	<ul style="list-style-type: none"> <li>○ Recurrent pulmonary infections</li> <li>○ Normal digits</li> <li>○ History of developmental delay</li> <li>○ Hyperlipidemia</li> <li>○ Scoliosis</li> <li>○ Flat wide feet</li> <li>○ Hypothyroidism</li> <li>○ Hypertension</li> <li>○ Recurrent UTI / urinary dysfunction</li> <li>○ Growth hormone deficiency</li> <li>○ Alopecia</li> </ul>

*Adapted from Marshall et al European Journal Human Genetics [2007]*

A list of features reported in Alström Syndrome patients according to organ systems involved and showing the typical age range when the onset feature can be expected.



Taken from Marshall et al, Archives Internal Medicine [2006]

## DIFFERENTIAL DIAGNOSIS OF ALSTRÖM SYNDROME

	<b>Alström Syndrome</b>	<b>LCA*</b>	<b>Congenital Achromatopsia <sup>Δ</sup></b>	<b>BBS <sup>◊</sup></b>	<b>Wolfram</b>
Vision impairment	Cone-rod retinal dystrophy (infancy)	Retinal dystrophy (infancy)	Loss of cone function (infancy)	Retinal dystrophy (age 10-186)	Optic atrophy
Hearing impairment	Yes (90%)	Sometimes impaired	No	Sometimes impaired	Yes
Mental development	Normal / sometimes delayed	Normal/ cognitive delay reported	Normal /sometimes delayed	Cognitive impairment (50 - 90%)	Normal
Extremities	Short stubby fingers, wide flat feet	Normal	Normal	Poly/syndactyly 66%	Normal
Diabetes	Type 2 diabetes (89% over age 15)	No	No	Type 2 diabetes (5-15%)	Type I diabetes
Obesity	Yes	No	No	Yes	No
Hypogenitalism	Yes	No	No	Yes	No
Cardiac	Yes – DCM	No	No	Rarely	No
Hepatic	Yes	No	No	Yes	No
Renal	Renal failure-adults	No	No	Structural renal abnormalities	Diabetic nephropathy
Urological	Urological dysfunction (15%)	No	No	No	Urinary atony
Neurological	Sometimes (seizures)	No	No	No	No
Short stature	Yes	No	No	Yes	No
Other abnormalities	Pulmonary Urological Dental	No	No	Dental Situs inversus	Diabetes insipidus
Inheritance pattern	Autosomal Recessive	Autosomal recessive	X-linked recessive	Autosomal recessive	Dominant

**LEGEND:** \* LCA: Leber Congenital Amaurosis ◊ BBS: Bardet Biedl Syndrome Δ Congenital Achromatopsia: also known as rod monochromatism

The combination of vision and hearing impairments and obesity can be seen in a number of disorders. There will be further discussion of these common misdiagnoses in later chapters.

## Monitoring Guidelines

<i>Organ system or clinical problem</i>	<i>Evaluation</i>	<i>Regular yearly assessments</i>	<i>Consider additionally, if indicated by symptoms</i>	<i>Interventional options</i>
Vision	ERG	Once, as soon as old enough to aid diagnosis		Medical counseling Visual aids with dark glasses while photophobia persists. Early teaching of non-visual language skills
	Visual acuity	1-3 yearly		
	Fundus examination	1-3 yearly		
Cardiac	ECG	1-3 yearly	24-h ECG monitoring	Medications, pacemaker
	Echocardiogram	2-3 yearly if symptomatic, yearly if asymptomatic	Heart catheterization	
	Blood pressure	Regularly	24-h BP monitoring	
	6-Minutes walk test, if old enough	Yearly for patients with a history of DCM/CHF		
Respiratory	Pulmonary Function (PFT)	1-3 yearly, if old enough	Chest X-ray In the case of surgery and/or severe disease, monitoring of O <sub>2</sub> -saturation, polysomnography	CPAP or BiPAP for sleep-apnea
Hearing	Audiometric assessment, OAE	Yearly, if old enough		Hearing aids cochlear implant
Renal	Renal function tests (creatinine, BUN)	Initial assessment in childhood, Yearly, if over 14 years old	Uric acid, 24-h urine albumin, Creatinine-clearance Ultrasonography if indicated by abnormal blood chemistry	Medications, Dialysis, kidney transplant <sup>a</sup>
Endocrine	Fasting glucose, HbA1c, TSH	Yearly, from 3 years age	OGTT, Insulin, FT4, GH, IGF-1, 17-beta-estradiol, Progesterone (females). Lower abdominal (females) or testicular (males) US.	Diet, exercise, weight control medications (diabetes hypothyroidism, hypogonadism, growth hormone deficiency)
	Gonadal function in males (LH, FSH, testosterone)	1-3 yearly from 12 years of age	Pituitary NMR, Hand x-ray (bone age)	
Neurologic	Vestibular function	Yearly, in childhood	Neurological evaluation EEG Brain NMR	
Gastro-intestinal	AST, ALT, GGT, bilirubin, prothrombin, total and HDL cholesterol, Triglycerides	1-3 yearly from 3 years age	Upper abdominal US If history of esophageal reflux, 24 hour pH-measure EGD	Medications for GERD, portal hypertension, surgery (TIPS)
Development	Developmental milestones Height/weight, growth BMI	Regularly in infancy and childhood 1-3 yearly	Skeletal age assessment may aid in diagnosis	
Urologic	Urine analysis	1-3 yearly	If history of urologic problems, dynamic tests for urological function	Medications, self-catheterization, surgery
Orthopedic	Check for skeletal abnormalities, flat feet, scoliosis, kyphosis	Yearly	X-ray	Orthopedic bracing, surgery

*Marshall et al., European Journal Human Genetics [2007]*

## CHAPTER THREE ~ DEVELOPMENT



### *Overview of Child Development*

Child development is how your child grows through a progression of developmental milestones. Although the pattern and sequence of growth and development is roughly similar for all children, it is necessary to remember that every child is unique and will develop at his/her own individual pace.

### **The main areas of child development are:**

**Gross motor:** Using large groups of muscles together to sit, crawl, stand, walk, run, keep balance, and change positions.

**Fine motor:** Using hands to be able to eat, draw, dress, play, write, and do many other things that require coordination and precision.

**Language and communication:** Speaking, using body language and gestures to communicate thoughts and desires, as well as understanding what others say.

**Cognitive:** Thinking skills including learning, understanding, problem-solving, reasoning, and remembering.

**Social and relationships:** Interacting with others, smiling for the first time, waving ‘bye- bye,’ having relationships with family, friends, and teachers, cooperating, and responding to the feelings of others.

The early years of a child's life are very important for his or her health and development, particularly in Alström Syndrome. Parents, health professionals, educators, and others must work together as partners to help children grow up to reach their full potential.

A parent knows his/her child best. If your child is not meeting the milestones appropriate for age, or if you think there could be a problem with your child's development, talk with your child's doctor and share your concerns. Don't wait!



### ***Autism Spectrum Disorder (ASD)***

Because many children with Alström Syndrome can show varying degrees of unusual behavior that could be termed “**autism spectrum**” behavior, it is appropriate to include this topic in the consideration of a child’s development. **Autism spectrum disorder** is a range of complex neurodevelopment disorders, which can include impairment or difficulty with social interactions, communication problems, and restricted, repetitive, and stereotyped patterns of behavior. ASD varies significantly in nature and severity. It can occur in all ethnic and socioeconomic groups and affects people of every age in the general population. Experts estimate that, in the general population, three to six children out of every 1,000 will have ASD. In Alström Syndrome, the frequency appears to be higher (3-4%). Conditions along the autism spectrum range from true autism to a milder form known as **Asperger syndrome**, and **pervasive developmental disorder** (usually referred to as PDD.)

### ***Development in Alström Syndrome***

Early developmental delay of milestones is common in young children with Alström Syndrome. In a recent study, nearly 30% of parents reported that their child had some degree of motor, language, or intellectual developmental delay. Delay varies widely in severity and symptoms and may go unrecognized, especially in mildly affected children or when it is masked by more debilitating handicaps.

It should be noted that, since so many aspects of early development depend on the ability to see and hear, early developmental delay is not surprising. Most often the delay is in gross motor skills in very young children. In particular sitting, standing, and walking may be delayed up to 12-18 months. Deficits in coordination, balance, and fine motor skills (picking up small objects) may continue into childhood.

### ***Intellectual Delays - IQ***

It is very difficult to assess the intellectual ability in a young child with Alström Syndrome because of the impact poor vision and hearing loss has on development and there are few appropriate testing methods. There is conflicting data on whether children with Alström Syndrome have learning disabilities. Although normal mentation is a diagnostic feature of Alström Syndrome, several cases have been reported using the nebulous and confusing term “mild mental retardation.” Many early studies used the controversial IQ tests which were not tailored to visual impairment, which could account for this confusion. In the current population of children and adults with Alström Syndrome, severe mental retardation is very rare.

***The learning delays in Alström syndrome are not necessarily learning disabilities.*** Although true learning disabilities have been documented, many children, particularly those with more severe sensory deficits, are simply slower in developing certain skills. Because all children show natural differences in their rate of development, especially those with Alström Syndrome, what seems to be a learning disability may simply be a delay in maturation.

### ***Receptive and Expressive Language Delays***

Some children with Alström Syndrome have trouble understanding certain aspects of speech. It is not clear how much hearing and vision deficits may be a factor ~ causing children to be unable to make sense of certain sounds, words, or sentences they hear. Because speaking and understanding speech are strongly related, many children with a receptive language deficit also will have an expressive language delay. Delay in speech may be up to 3-4 years, but most children 'catch up'.

### ***Limitations in Social Participation and Behavior***

Keeping in mind that all children everywhere are unique individuals, the following observations have been described by parents and teachers. Children and young adults with Alström Syndrome may not have a lot of patience and can be stubborn. They can be fearful, sensitive, and have exaggerated emotional reactions to relatively minor occurrences. They usually prefer familiar activities and lack flexibility when facing a change from the daily routine. The loss of vision and hearing may contribute to a strong need for regularity and clarity in their daily lives.

Social contacts with other children their own age can be difficult. They often are passive with children their own age, and prefer to socialize with younger children who appear to be more equal to them both developmentally and socially. Open aggression is uncommon, but they often can be stubborn and react angrily by screaming/crying, especially in the teenage years.

### **DEVELOPMENTAL ISSUES REPORTED IN SOME CHILDREN WITH ALSTRÖM SYNDROME:**

- Early motor developmental delays (gross and fine motor skills)
- Delay in toilet training
- Difficulty in social (difficulty mixing with other children, preferring to be alone)
- Inappropriate social behavior (lacking social cues)
- Inflexible adherence to routine
- Language perception difficulties, possibly related to diminished hearing
- Speech and expressive language delays
- Autistic-spectrum or inappropriate behaviors
- Delay in reasoning and concept construction
- Inappropriate attachment to objects
- Extreme preoccupation with subjects of interest
- Prefer routine, strongly resist change
- Tantrums, quick to show extreme distress
- Unexplainable phobias
- Over-sensitivity to smells and odors
- Selective mutism
- Tactile defensiveness

The above information was collected through questionnaires completed by families and compiled by the Alström Syndrome International Scientific Advisory Board. These observations may assist you in understanding some of the difficulties faced by the child with Alström Syndrome. It is also noteworthy that many of these issues resolve as the child grows. It is crucial that these points be taken into consideration when discussing any issues relating to education.



### ***Fears and Anxiety***

The fear of going blind while losing hearing is very genuine in most children. Dealing emotionally with the increasing loss of vision and hearing is extremely difficult. Many children also have problems with admitting that they need to use a cane. It takes time to become emotionally ready for this step.

### ***Detection and Diagnosis***

Health care providers will often use a questionnaire or other screening instrument to gather information about a child's development and behavior. Some screening instruments rely solely on parent observations, while others rely on a combination of parent and doctor observations.

A more comprehensive evaluation requires a multidisciplinary team, including a psychologist, neurologist, psychiatrist, and other experts in child development.



### ***Treatment***

Therapists use highly structured and intensive skill-oriented training sessions to help children develop social and language skills. Family counseling for the parents and siblings of children with Alström Syndrome often helps families cope with the particular challenges of living with a child with multiple disabilities. Most health care professionals agree that the earlier the intervention, the better.

## *Frequently Asked Questions*

### ***FAQ: Do behavioral symptoms associated with Alström Syndrome change over time?***

For many, symptoms improve as the child grows older. During adolescence, some children may become depressed or experience behavioral problems, and their treatment may need some modification as they transition to adulthood.

### ***FAQ: Can diet impact behavioral problems in Alström Syndrome?***

Parents should use caution before adopting any unproven treatments. Although dietary interventions have been helpful in some children, parents should be careful that their child's nutritional status is carefully followed.

### ***FAQ: What kind of hobbies do children with Alström Syndrome enjoy?***

People with Alström Syndrome are just like everybody else. Alström doesn't stop people from enjoying the things that interest them. Some of these hobbies include music (piano, horn, drums, jazz,) reading in Braille, computers, skiing, horseback riding, and making pottery.

### ***FAQ: How can I help my child cope with things that s/he is not able to do?***

Focus on the things that make him/her special. Children with Alström often find a way of doing the things that they really want to, regardless of their limitations. Encourage it!

### ***FAQ: What should I tell my friends and family when they ask me about Alström Syndrome?***

Be truthful and educate them about Alström. Your friends and family have probably never heard of it and they may wish to learn more about it. You will play an important role in educating others about this condition.

## SIDEBAR DEFINITIONS ~ DEVELOPMENT

**Asperger syndrome** - Children with Asperger syndrome have difficulty with social interaction and communication, can have a narrow range of interests, have average or above average intelligence, and develop normally in the areas of language and cognition. Children with Asperger often also have difficulty concentrating and may have poor coordination.

**Autism** - A complex neurodevelopment disorder, characterized by social impairments, communication difficulties, and restricted, repetitive, and stereotyped patterns of behavior.

**Autistic Spectrum** - Can range from classical autism, the most severe form, to other conditions along the scale, including a milder forms known as Asperger syndrome, and childhood disintegrative disorder and pervasive developmental disorder

**Autism Spectrum Disorder** - A range of complex neurodevelopment disorders which can include impairment or difficulty with social interactions, communication problems, and restricted, repetitive, and stereotyped patterns of behavior. ASD varies significantly in nature and severity.

**Expressive language delay** - Failure to develop speech, expressing thoughts and language abilities typical of other children in their age group, but often understand what is being said to them.

**Pervasive developmental disorders (PDD)** - A range of conditions that involve delays in the development of many basic skills, most notably the ability to socialize with others, to communicate, and to use imagination.

**Receptive language delay** - A problem understanding and processing words and sentences.



## ***CHAPTER FOUR ~ EDUCATION AND LEARNING***

### ***Overview***

Four steps are required for learning to take place.

- 1) Input: information is entered into the brain via the senses – visual, auditory, and tactile.
- 2) Integration: the information that is received is processed and interpreted.
- 3) Memory: the information must be used or stored and later retrieved.
- 4) Output: the information must be sent out through language or motor activities.

A learning disability is a dysfunction in any of the above steps. Any learning task involves more than one process and any learning disability can involve more than one area of dysfunction

### ***Education and Learning in Alström Syndrome***

Early education is so important for all children, but particularly for a child who will develop increasing physical obstacles. Children with Alström Syndrome are generally very capable, but, due to communication difficulties and social isolation, their overall cognitive ability is often underestimated. In fact, many children with Alström are very clever, have an impressive capacity to learn information, to retain ideas, and to do very well in academic subjects.

As your child goes through the school system, he or she should be encouraged to take part in as many activities as possible, both in the classroom and outside, and every effort should be made to help minimize the impact of their multisensory problems.



### ***What Does My Child's Teacher Need to Know About Alström Syndrome – Educating the Educators!***

Since it is unlikely that your children's teachers will have seen another child with Alström Syndrome, they will likely have questions. To assure that school personnel are fully informed about Alström Syndrome, before your child starts at any level of schooling, we recommend that parents organize a meeting with all those in the system who will interact with your child, including the school principal and vice-principal, office staff, teachers and assistants, the school nurse, the school counselor, bus driver, etc. Consistent teamwork is critical.

You will need to make sure that your child's teachers know as much as possible about Alström Syndrome. In addition, it is vitally important to be sure that the teaching staff is aware of the "whole" syndrome and not just the obvious visual and hearing impairments. For example, there is a significant negative impact involved when a child with Alström has an improper diet and lack of exercise. ***It is crucial that you stress the importance of exercise in your child's daily routine.*** Of course, playground and other school activities can be difficult because of the visual impairment. Provided that unnecessary risks are not taken, you should encourage the teacher and staff to include your child in all physical education activities in which they show an interest. Explain to them all facets of Alström Syndrome. *Give them a copy of this handbook and the educational materials ASI provides!*

### ***IEP - Individualized Education Plan***

These meetings should take place at least once, if not several times, through the year to keep up an appropriate IEP and to choose the educational tools and approaches most suitable for your child. When your child is of an appropriate age (it differs from child to child), consider including him\her in these meetings.

### **TEACHING STRATEGIES FOR CHILDREN WITH ALSTRÖM SYNDROME:**

Because Alström Syndrome is so extremely complicated, educating a child with the syndrome can also be very complex. When developing an educational program many components should be considered by the educational team and teachers need to be diligent with respect to the following:

#### **Sensory Loss:**

- Determining how far away and how well your child sees and how far out and how well your child hears, taking into account things like lighting, ambient noise, and other factors. Your child should be allowed to sit in front so that the teacher's voice can be heard.
- Understanding that your child's vision and hearing loss may possibly result in fine motor and writing difficulties, usually just delayed, as well as having difficulties with social perceptions and interactions.
- Enlarging, in the earlier years, teaching materials on a photocopier. Ordering large print textbooks from Printing Houses for the blind, available in most countries.
- Facilitating special training in Braille and adapted computers.
- Addressing hearing impairments by using FM receivers and loop amplification systems.
- Avoiding tasks that involve copying from the board or from books.
- Allowing tape recording of the class or lecture. Taped text books are available from a number of sources.
- Presenting work in an organized manner (left to right, top to bottom).
- Allowing extra time to complete work.
- Beginning Orientation and Mobility (O &M) training at an early age in anticipation of blindness.

### Physical Illness:

- Being aware that fatigue can quickly overcome a child with Alström Syndrome, particularly in view of the physical issues such as diabetes, scoliosis, cardiomyopathy, and overweight.
- Creating a flexible schedule that allows for “breaks” (a quieter room with low lighting and comfortable seating).
- Being alert to “behavior signals” and anticipating the need for a break to minimize any behavioral outbursts.

### Emotional Needs:

- Dividing tasks into smaller steps that allow the child to feel successful and avoiding activities that have too many steps or are too long.
- Giving extra time to complete activities.
- Providing enough time for response – children with Alström tend to take a little extra time.
- Having predictable schedules and routines.
- Fostering peer-to-peer interactions with classroom activities.
- Including the child in as many activities as possible and discouraging isolation.

#### **FOOD FOR THOUGHT**

- If you want specialized modifications or equipment for your child, be sure it is written in the child’s IEP. This makes schools responsible by law to comply.
- In most countries children with Alström Syndrome can qualify for assistance from the government. It is NOT based on parent’s income, but rather on the disability of the child.
- In cases of need, ASI can help families to obtain necessary equipment that may not be available in various countries.

### ***Choosing a School***

All options for the education of a child with Alström Syndrome will need to be considered. You have the right to choose the school for your child that best ensures that appropriate help is given and that your child has the best possible school situation.

### ***Pre-schools***

Some areas in various countries offer a program for three to five year-old children for pre-school readiness, and parents should inquire with their local schooling authorities for further information that may help the child prepare for more formal school settings. Pre-school Vision Teachers are available in many areas and parents should definitely request early services.

### ***Schooling Issues –To Mainstream or Not***

Many parents wish their child to attend a mainstream school where they will be fully integrated with other students. In some cases, there are

### A BIT ABOUT COMPUTERS

Computers and computing skills are a regular feature in school work and social networking, and they can help to provide your child with a whole new world at their finger tips. Using a computer may take some adjustment. For the younger children, it may be sufficient to enlarge the size of the text on the screen and many children may find it easier to read a light colored text on a dark screen, instead of the more conventional dark print on a white background.

As your child grows and vision is lost, special computer adaptations for voice read-outs and Braille are available. The past ten years have seen tremendous growth in technology adapted for people with visual impairments. Computers can be linked to Braille embossers and ordinary printers to produce a Braille copy to keep and a print copy to turn in to the teacher. There are also Braille laptop computers which have Braille keys instead of a standard keyboard available through various assistive technology suppliers.

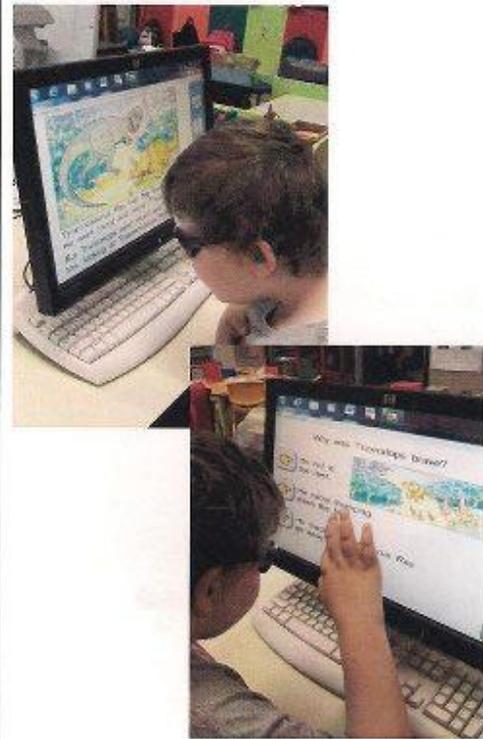
With good resource personnel (one to one time with the teacher's assistant), your child should be able to follow the regular curriculum in the school, using a good background of Braille combined with audio-and computer technology. Integration can be very important for a child, if they are to have the full experience of going to school with their peers, an important life experience at any age. Something as simple as remembering to tell a child with Alström Syndrome who else is in the room, can make all of the difference in the quality of their experience.

Alternatively, you may choose a school specializing in teaching children with vision and hearing impairment. The amount of help required at school will vary from child to child and the decision should be made on the basis of many factors, for example, distance from home and/or the maturity level of your particular child.

A recent survey has shown that the majority of children with Alström Syndrome were able to remain in mainstream education in the early years, provided that adequate classroom assistance and/or visual aids were available. However, in the older grade levels, *almost half* chose placement in special schools.

opportunities to send the child to a mainstream school with additional special units for children with vision/hearing impairments. There seems to be a benefit to keeping things as normal as possible for as long as possible to expose the child to rather more than less of life experiences right from the start and at the same time combat some of the isolation so much a part of rare disorders. Vision Teachers are available in many areas and parents should request services for their child as early as possible. Some areas have laws that require schools to hire certified Braille teachers for students with vision impairment.

Logan enjoyed using the Touch Screen computer to complete print reading tasks.

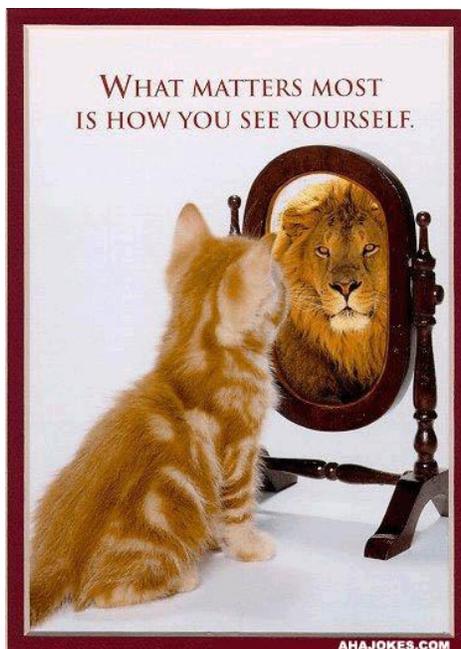


Lily Anne Ekelund



1958-2001

As a ten month old baby, Lily had what the doctors called “infectious myocarditis.” She was very ill for about 4-5 weeks but recovered, and had no residual heart trouble until later in life. Lily was the fourth daughter in a family of six girls and one boy. Early on, she knew that she and her sister Tina were different from the rest of the family, as they both were blind and had hearing loss. But in those days, we had no diagnosis of Alström Syndrome. As a child Lily was fiercely independent, and not always easy to get along with. She worked hard to keep up with “normal” requirements through school and high school. When she was 20, Lily went to California to learn life skills for the blind, and after returning home, she insisted on moving out on her own, and lived from then on independently all her life. She had a number of guide dogs and was always very fond and protective of them. She trained as a shiatsu massage therapist and took her certification for the City of Vancouver, B.C. She worked until the onset of diabetes made it too difficult for her. Lily was very intelligent and her interests knew no limits. She loved music, mostly classical and opera. The last 5 or 6 years of her life became full and enjoyable, in spite of her suffering of which she never complained. Lily was a very strong and courageous person who lived her life to the fullest according to her wishes, overcoming the obstacles of her disabilities.



*Below is a sample letter that can be requested for your child's IEP file and tailored to reflect your child's particular needs.*

TO: Teachers, Counselors, and Education Support Personnel  
FROM: Robert P. Marshall, Executive Director  
RE: Alström Syndrome and Education

Alström Syndrome is one of the most brutal of the orphan diseases, affecting every part of the human body. Although most children have normal intelligence, vision impairment/blindness, hearing impairment, diabetes, scoliosis, and the degeneration of all major organ systems are just some of the physical complications involved in the syndrome. Furthermore, the progressive, degenerative nature of the disease can cause emotional, physical and social issues that become even more detrimental to the affected individual and their family.

Just as significant, but sometimes not as apparent, are the neurological, psychological and cognitive impairments that in some youngsters can be part of this rare, genetic disease. The tolls of the physical, cognitive, psychological and social challenges on an Alström individual are immeasurable. Sadly, the toll on their education IS measurable and certainly cause for distress.

Alström Syndrome International (ASI), a worldwide entity and registered charity, which provides support, research, and education regarding Alström Syndrome, has established a *Task Force on Education for the Alström Syndrome Student*. Through numerous questionnaires and the collection of data regarding Alström individuals over many years, ASI is pleased to present the following information regarding this particular genetic condition as it relates to the educational setting.

**ALSTRÖM SYNDROME FACTS:**

\*Alström Syndrome students may present with none, any or all of the following developmental, neurological and psychological issues that may seriously and negatively impact their learning process: \*  
*Based on diagnostic criteria from DSM-IV-TR (American Psychiatric Association)*

- Developmental delays
- Motor and Fine Motor Skill delays
- Communication Disorders (speech and language delays, language perception difficulties)
- Pervasive Development Disorders (Autistic spectrum, Asperger Disorder)
- Anxiety disorders
- Depression
- Mood disorders
- Behavioral disorders
- Absence Seizures (zoning out episodes)

## RECOMMENDATIONS

In order to address the issues stated above and to insure full and fair opportunities for the Alström student, ASI urges that educational institutions and personnel seriously take into consideration the following recommendations:

- Proper assessment and testing of the student's developmental, cognitive, and communication levels are imperative and should be conducted periodically throughout the educational process.
- Based upon the results of all testing and assessments, an Individualized Education Plan (IEP) that addresses the needs of the student in a positive, goal-oriented modality while keeping in mind that the Alström student also has severe and true challenges related to being a deaf/blind and medically-challenged student.
- Accommodations in scheduling and programming need to be implemented. For example, the deaf/blind student must learn Braille, special technology, etc; and, therefore, will need to have allowances (via an individualized student plan) that do not penalize the student for being "away" from the regular curriculum and classroom while learning these vital tools that will carry them through the educational system. Allowances such as fewer questions for testing purposes, verbal testing, etc. will prove to be a very positive and stress-relieving avenue for this already much-challenged student.
- Full-time teachers' assistants are crucial to the success of the Alström student. Without this one-on-one support, the student will not be able to successfully keep up with the heavy work load demands and will succumb to stress, anxiety and depression. It has been proven beneficial to retain the same assistant through several years in order to create a positive, trusting relationship between student and the assistant.
- Teachers and teachers' assistants involved with the Alström student must become familiar with the specialized technology (i.e.: JAWS, Braille Note) as well as Braille.
- Teachers and teachers' assistants should familiarize themselves with all aspects of the syndrome, i.e.: health, psychological, and social issues related to the disease. For information on Alström Syndrome, please visit the website at [www.alstrom.org](http://www.alstrom.org).

The minimal recommendations presented above will benefit the student living with this disease. Our students are intelligent. However, they live with extra challenges that moderate their ability to function in the same manner as the "regular student" population.

All educational institutions are urged to provide the necessary financial, educational and emotional supports required by any Alström Syndrome student. ASI firmly believes that in appropriately accommodating the needs of our students, the outcome for both educator and student will be both positive and enriching.

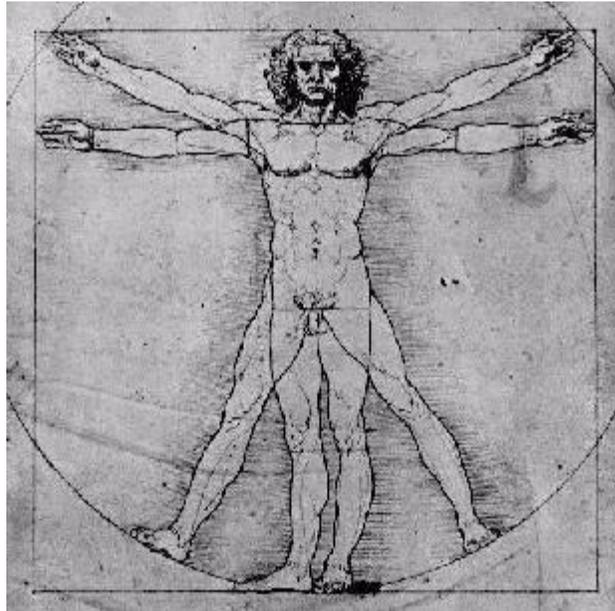
Should you have any questions regarding this information, I look forward to hearing from you. I may be reached by phone at (207) 244-7043 or by e-mail at [ASIRobin@hotmail.com](mailto:ASIRobin@hotmail.com).

Sincerely,

Robert P. Marshall  
Executive Director  
Alström Syndrome International

## **SECTION TWO**

# **THE MEDICAL JOURNEY**



## CHAPTER FIVE ~ PHYSICAL FEATURES

### Overview of Physical Features

In many syndromes, factors come together to make a recognizable pattern that can also aid the physician in making a diagnosis. Although not as obvious as in some other more common syndromes, this is also true for Alström Syndrome.

### Facial Features in Alström Syndrome



David



Doru



Marko



Patrick



Millie



Phoebe

There is no clear-cut facial characteristic described with Alström Syndrome. Nevertheless, parents from all over the world remark on the similarities of their unrelated children. Children with Alström Syndrome seem to resemble each other more than they resemble their own brothers and sisters.

Often the eyes may be deep set with a rounded face. Premature frontal balding appears common among males, and hair may be thin in females. **Hyperostosis frontalis interna**, which can be typical in people who are blind, is reported in many Alström patients. Ear lobes are often thicker than their unaffected siblings.

**Scoliosis** is rarely present at birth. It is most common in the early teenage years, when, especially at the start of the adolescent growth spurt, it can progress rapidly. It can be



disfiguring because when the spine bends to the side, the **vertebrae** become twisted and pull the ribs out of shape along with them, which sometimes form a "bulge" on the back and cause the shoulder blades to stick out. The spine can bend towards either side of the body at any place in the chest area (thoracic scoliosis), or in the lower part of the back (lumbar). If the curve is low down in the spine, the ribs may not be affected but one hip may be higher than the other.

**Kyphosis** is a term that describes the exaggerated curve of the upper spine that results in a rounded or hunched back. Additionally, many people with Alström can have increased fatty tissue above the shoulders, producing a "Buffalo hump."

### ***Treatment and Recommendations***

**Scoliosis:** Exercises to strengthen the abdomen and stretch the hamstrings may help correct postural kyphosis. Bracing is the usual first treatment for children and adolescents with a curvature of 25-40 degrees. Treatment of severe scoliosis can require corrective surgery that, as always, must be undertaken with caution in Alström Syndrome. The severity of the curvature, the general health of the child, and potential for further growth should all be considered.

### ***Hands and Feet***



Another aid in diagnosing Alström Syndrome and distinguishing it from other similar disorders such as Bardet-Biedl Syndrome is that the hands and feet are normal (i.e. no **polydactyly** or **syndactyly**.) However, most children have characteristic shapes: wide, thick feet and short stubby fingers. Flat feet are also a very common feature in Alström Syndrome, sometimes so severe as to cause discomfort or require prosthetic shoes. Other occurrences commonly reported are uneven leg length, thick toenails, uneven leg diameter, hip dysplasia and bowed legs.



### *Skin tags*

Skin tags are small 1-3 mm in diameter outgrowths of epidermal and dermal tissue that may be **pedunculated**, smooth or irregular. They are flesh colored and benign. They occur most often on the neck, eyelids, and **axillae** (underarms,) but they may be seen anywhere on the skin. Most do not require treatment unless they are bothersome. Occasionally one will twist and cause discomfort, so removal is recommended. Skin tags are more prevalent in association with hyperinsulinemia and obesity.



### *Hair*

**Alopecia** has been described in many patients with Alström Syndrome. The hair loss is usually mild and patchy with less than 50% of scalp hair lost. This is noted in both males and females, but more often in males, and usually after puberty. The hair loss is without discomfort and can occur in some children as early as adolescence.



### *Dental*

There are many reports of so-called “dental anomalies”. A large number of parents comment on a characteristic space between teeth in young children with Alström Syndrome, and in some children, there are extra or missing teeth. Anecdotally, there are a surprising number of children who do not seem to get cavities. In addition, there are reports of baby teeth slow to come out and adult teeth growing over the baby teeth still in place. Some parents note a distinct band of yellow discoloration in the front teeth.



## **SIDEBAR DEFINITIONS ~ PHYSICAL FEATURES**

**Axillae** - The underarms

**Buffalo hump** - The increased fatty tissue between the shoulder blades.

**Hyperostosis frontalis interna** - Overgrowth of the frontal bone of the skull, usually bilateral (both sides) and symmetrical, it is harmless and of no clinical significance.

**Kyphosis** - A convex, forward curvature of the upper spine producing a “hump” when viewed from the side.

**Pedunculated** - Elevated, as on a stem (peduncle) or stalk.

**Polydactyly** - More than five fingers or five toes.

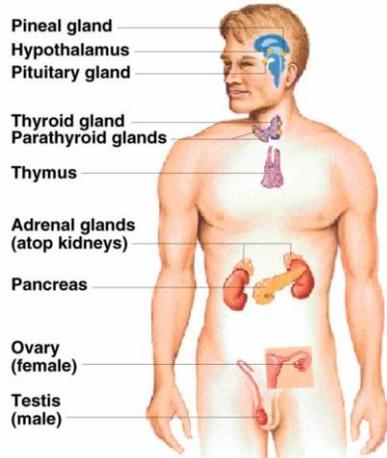
**Scoliosis** - A lateral (sideways) curvature of the spine into a C or S-shaped configurations when viewed from behind.

**Syndactyly** - Fused fingers or toes.

**Vertebrae** - Individual bones that make up the spine.

## CHAPTER SIX ~ ENDOCRINE SYSTEM AND GROWTH

### Introduction



*Used with kind permission of Dr. Jay Pittochelli, St Anselm College.*

The endocrine system is an elegant and complex system of checks and balances in the form of “feedback loops” which control metabolism, growth, maturation, reproduction, water balance, appetite and behavior.

A small part of the brain called the **hypothalamus** is the main region for controlling the operation of the **endocrine** system. It receives input from all areas of the central nervous system, and it directs the “master gland” – the **pituitary**. The endocrine glands are comprised of the pituitary, **thyroid, parathyroid, adrenal, ovaries** and **testes**, and the **islet cells** of the **pancreas**. These glands secrete chemicals called **hormones** that work along with the nervous system to regulate almost all of the body’s normal functioning.

The **hypothalamus** is located deep in the brain and controls the functioning of the pituitary gland. It does this through direct nerve stimulation as well as through the actions of nerve cells that secrete hormone-releasing and hormone-inhibiting factors into the bloodstream for transport directly to the pituitary. The pituitary in turn releases stimulating hormones, which control secretions of the thyroid, adrenal glands, ovaries and testes. In addition, the pituitary gland releases its own **growth hormone**, which directly affects metabolism, controls water balance, and indirectly causes growth and development in childhood.

If hormone deficiencies result from pituitary under-activity, they are called “secondary”, but if they result from the failure of one of the endocrine glands itself, they are referred to as “primary.”

A wide range of hormone deficiencies have been described in young people with Alström Syndrome which include:

- Primary **hypothyroidism**
- Primary **hypogonadism**
- Secondary hypogonadism
- Low levels of growth hormone
- **Hyperinsulinemia**

The effects of these disturbed endocrine functions overlap and interact, sometimes causing multiple and complex health management issues for the person with Alström Syndrome.

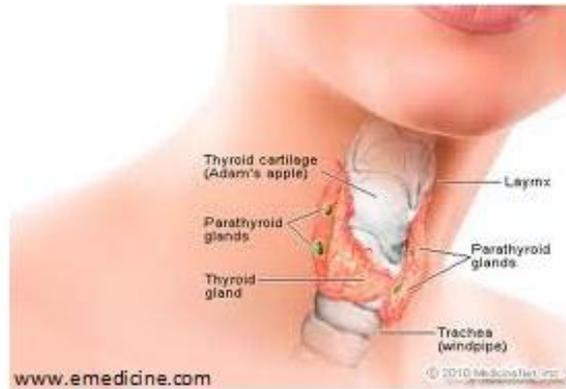
# ***THYROID***

## ***Overview***

The thyroid is a small butterfly-shaped gland located in the neck, under the Adam's apple. It releases hormones into the bloodstream that help regulate other organs. The hormones that the thyroid gland secretes are **thyroxine (T4)**, **triiodothyronine (T3)** and **calcitonin**. The pituitary gland functions as a measure for the thyroid by detecting increases and decreases in T4 and T3 hormone levels and responding with the release of the right amount of **thyroid stimulating hormone (TSH)** which in turn stimulates the thyroid to release the T4 and T3 hormones.

T4 and T3 regulate how the body uses energy and how the organs function, including: heart rate, cholesterol level, body weight, energy level, muscle strength, skin condition, menstrual regularity, mental state and many other conditions. A deficiency in thyroid hormone is called hypothyroidism.

## **Thyroid Gland**



## ***Hypothyroidism in Alström Syndrome***

A significant number of Alström Syndrome patients (20%) have this condition. Although it is not known whether hypothyroidism results specifically from the action of *ALMS1*, or the Alström Syndrome gene, the incidence of hypothyroidism is significantly higher in the Alström population than that of the general population.

## ***Signs and Symptoms***

The symptoms of hypothyroidism are relatively non-specific, and each symptom could have many other causes, so hypothyroidism can be easily overlooked. The symptoms vary widely depending upon the degree of the deficiency of thyroxine. Mild hypothyroidism may not cause any symptoms and patients may not even be aware of their condition.

With severe hypothyroidism there may be:

- Fatigue, sluggishness
- Depression, mood swings
- Hoarse voice, difficulty swallowing
- Forgetfulness
- Intolerance to cold
- Dry, coarse skin and hair
- Muscle aches and cramps
- Constipation
- Increased menstrual flow

### ***Detection and Diagnosis***

Many children remain undiagnosed and untreated for years, due to lack of awareness of the possibility of hypothyroidism in Alström Syndrome.

Fortunately, there are simple blood tests to determine thyroid function measuring TSH and thyroxine levels so that a diagnosis can easily be made. TSH is the more sensitive indicator of hypothyroidism because T4 may still be within normal range when the pituitary begins to increase the supply of TSH. If TSH levels are elevated above 6 mU/L, regardless of T4 levels, a diagnosis of hypothyroidism can still be made. A T4 in the low or low normal range, plus a high TSH, confirms the diagnosis of hypothyroidism.

These sensitive tests can diagnose **subclinical hypothyroidism** at earlier stages when the patient has no symptoms.

### ***Treatment***

Hypothyroidism in Alström Syndrome responds well to therapy. The goal for treatment is to restore normal blood levels of thyroid hormone by supplementing the body's naturally produced hormone with levothyroxine (Synthroid, Levotheroid, Levoxyl, LEVO-T). This drug is a synthetic form of T4, and it normalizes blood levels of TSH. The dose is gradually adjusted until the blood levels of TSH are in the normal range. In instances where the patient has an underlying heart condition, it is extremely important to start with a very low dose of thyroid hormone until the body gets used to the more normal thyroid hormone levels. Symptoms of hypothyroidism may take as long as three months to resolve. The medication must be taken in the morning (in a fasting condition) and you should not eat for 20-30 minutes after taking the medication.

### ***Recommendations***

Because hypothyroidism is so common in patients with Alström Syndrome and thyroid hormone tests are inexpensive, thyroid function should be routinely tested every year and sooner if symptoms develop. Regular yearly testing could prevent progression to hypothyroidism in children with subclinical hypothyroidism.

If you change doctors, remind your new physician that thyroid problems often occur in Alström Syndrome and thyroid function must be re-evaluated at regular intervals.

## ***GROWTH***

### ***Overview***

Several hormones work together in a finely tuned system to regulate normal growth in a child. Some act directly on target organs, while others act by triggering the production of other hormones that activate specific organ functions necessary for growth. **Growth hormone (GH)** is one of the most abundant hormones produced by the pituitary gland. It is secreted into the bloodstream and, unlike the other pituitary hormones, exerts its effects directly on target tissues, such as muscle, fat, and bone cells, promoting growth and metabolism in these tissues. **IGF-I** (an insulin-like growth factor- also known as (somatomedin C) is a protein similar in structure to insulin. Growth hormone stimulates the liver and other body tissues to produce IGF-I, which then acts as the link between growth hormone in the blood and the machinery inside cells that causes growth.

Other pituitary hormones that affect growth indirectly by stimulating other endocrine glands include:

- Thyroid Stimulating Hormone (TSH): Causes the thyroid gland to produce thyroid hormone, which regulates body metabolism and is essential for normal growth.
- Adrenocorticotrophic Hormone (ACTH): Causes the adrenal glands to produce cortisol (a “stress hormone”) and other hormones that enable the body to respond to stress. Too much cortisol will cause growth failure in a child.
- Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH): Cause the ovaries or testes to produce sex hormones, which are necessary for adolescent sexual development and the growth spurt that accompanies puberty.

### ***Growth in Alström Syndrome***

In Alström Syndrome the precise coordination necessary for normal growth malfunctions in several ways. Researchers strongly suspect that the part of the brain called the **hypothalamus** is a major source of the growth differences observed in Alström Syndrome. The hypothalamus is a small part of the central brain that connects the nervous system and the endocrine system. It is likely that in people with Alström, essential instructions to the hypothalamus could be disturbed.

Most children with Alström Syndrome have an atypical, but distinct pattern of growth that is surprisingly similar from child to child. Length and



weight at birth are almost always within the normal range. Young children grow rapidly and are tall for their age initially, but their bones also mature more rapidly. Most of the young children have **advanced bone age** (usually 2 or 3 years advanced). Growth in height normally slows and stops when puberty is achieved. Although puberty usually occurs within a normal age range, there is also some evidence that the growth spurt may occur earlier than normal in children with Alström. By age 12 to 16, height growth ceases, resulting in short adult stature. Adults with Alström Syndrome are almost always short, but proportionally short (e.g. length of legs is relatively consistent with the length of the trunk). Growth hormone deficiency has been documented by a sophisticated series of tests in some Alström patients. Some growth hormone is produced, but not enough to support normal growth.

### ***Detection and Diagnosis***

#### ***Growth Charts***

Growth charts are reference standards that depict normal growth for male and female children from infancy to 20 years of age. The 50<sup>th</sup> percentile represents the median height or weight for each age group, so that 50% of most children will be above this point and 50% will be below it. In addition to plotting a child's current weight and height on a growth chart, it is also very important to consider previous measurements to determine if the child's growth fits the expected pattern.

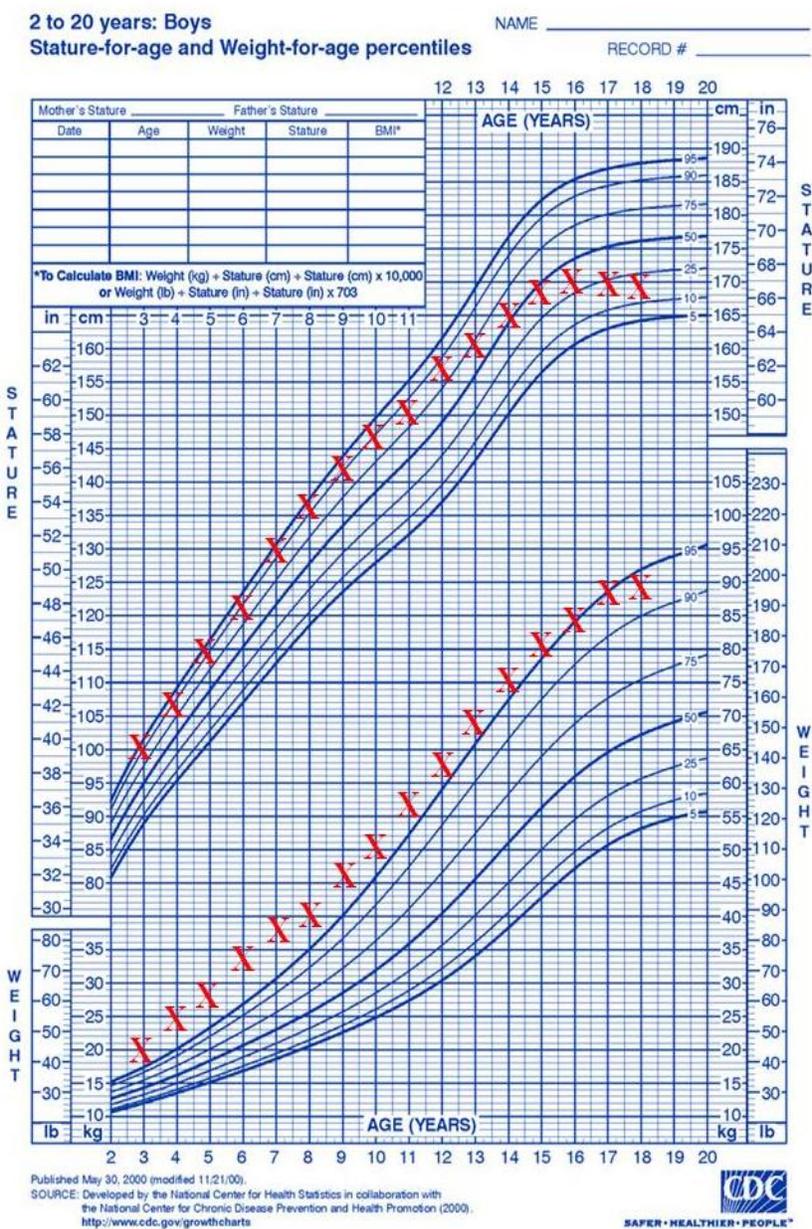
#### ***Bone Age***

Skeletal maturity, expressed as **bone age**, is often used to assess growth in childhood. The measurement is taken by x-ray of the hand and wrist and compared to an atlas of films obtained from "typical children" of various ages called the Gruelich and Pyle scales. By using skeletal age, it is possible to estimate how much growth potential remains and to predict final adult stature with some degree of reliability.

#### ***Growth Hormone Deficiency***

GH deficiency is somewhat difficult to diagnose because the pituitary gland produces growth hormone in bursts and the amount in a single random blood sample might not reflect an accurate overall level. One better way of testing for GH is called a "provocative test" where the child is given a substance (**GHRH** or GHRH-arginine, or insulin) that causes the release of a GH burst and measures the amount present in several blood samples obtained over a period of time. A great deal of research is being done to develop more accurate and reliable ways of diagnosing GH deficiency. Careful testing is necessary to establish that growth hormone deficiency is present in a child. Growth hormone measurements are usually combined with other laboratory tests, such as IGF-1 levels.

## Typical Growth Chart of a Child with Alström Syndrome



The growth chart illustrated here shows the height growth velocity of a typical boy with Alström Syndrome of the span of 20 years (Top graph). The observation that this boy's height tracks along the 90-95th centile at age 5 may initially suggest a normal growth rate.

In contrast, the same child's height at age 14 begins to level off below the 25<sup>th</sup> centile in adulthood. The bottom graph of the same "typical boy with Alström" is well above the 90-95<sup>th</sup> centile throughout most of his childhood. There is some indication that in adolescence and adulthood, weight begins to normalize.

### TYPICAL PATTERN OF HEIGHT AND WEIGHT IN ALSTRÖM SYNDROME

The growth chart consists of a grid with age plotted along the bottom horizontal line, and weight and height along the vertical line. It consists of seven curves; each curve represents a percentile (5<sup>th</sup>, 10<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>, 90<sup>th</sup>, and 95<sup>th</sup>). The range of heights and weights generally considered within normal limits for a growing child is from the 10<sup>th</sup> to 90<sup>th</sup> percentiles. The data used to create these charts was gathered from a large survey of children from different racial and ethnic backgrounds at different ages to get a more representative sample of children.

### ***Treatment***

GH supplementation in Alström Syndrome is the subject of intense controversy, and many physicians wrestle with the pros and cons. It has been shown to be effective in a few other disorders characterized by a GH deficiency by stimulating normal growth and providing beneficial effects on metabolism and other organ functions. Although there have been a few good results reported, the benefits and risks of GH supplementation in young children with Alström Syndrome have not yet been proven. A doctor's recommendation to begin a child on GH therapy must be based on consideration of many factors, including a complete evaluation of the child's growth pattern, pubertal stage, general health, and results of laboratory tests.

### ***Considerations:***

- GH therapy requires a long-term commitment by the child and family in order to achieve the best possible response. Treatment usually continues until the child has completed puberty or has stopped responding.
- It is expensive.
- GH has an anti-insulin effect, so for Alström Syndrome patients with a high probability of developing diabetes, GH therapy may not be appropriate.
- GH can influence blood sugar, thyroid function, fluid retention, hypertension, etc. so a patient receiving growth hormone therapy must be closely monitored.

### ***Recommendations***

One of the most important things a parent can do is to have their child examined and measured regularly by a pediatrician, family doctor, or other qualified health care provider. If GH supplementation is used, the child's response to GH therapy should be monitored closely by a pediatric endocrinologist.

## ***SEXUAL DEVELOPMENT AND FERTILITY***

### ***Overview***

The pituitary gland secretes **gonadotropins** called **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)** into the bloodstream. LH and FSH function together to stimulate the ovaries and the testes to produce sex hormones such as **testosterone** in males and **estrogen** and **progesterone** in females. LH and FSH also stimulate the ovaries to produce ova (eggs) and the testes to produce sperm cells. These “sex hormones” also influence other body changes called **secondary sex characteristics**, including increased muscle mass, deepening of the voice, body hair distribution, and growth of the penis and testicles in boys. In girls, it influences breast development, body hair distribution, achievement of menarche, and fertility.

The menstrual cycle in women is a complex interplay between levels of FSH, LH, estrogen, and progesterone. An adolescent girl usually starts her menstruation (**menarche**) between 12 and 14 years old.

Hypogonadism is a condition that can affect both males and females. In males, it is characterized by decreased function of the testicles, a failure to go through puberty naturally, low levels of testosterone, reduced bone and muscle strength (long term) and lack of sexual development. **Primary hypogonadism** is a failure of the sex organs themselves, and **secondary hypogonadism** is a failure of the pituitary hormones to stimulate the ovaries or testes.

### *Sexual Development in Alström Syndrome*

Although the median age is 14.5 for males and 12 years for females, the onset of puberty in both males and females is quite variable. Fertility has not been documented in either sex.

### *Males with Alström Syndrome*

In males, puberty is usually somewhat late in onset (mean=17 years). The basal level of testosterone is typically low. Adult levels remain within the adolescent range, but below normal adult range. The majority of young boys with Alström Syndrome have **hypergonadotropic** hypogonadism, which means that there is a primary gonadal failure. The testes do not produce enough testosterone to feed back to the pituitary to regulate the rate of LH and FSH, resulting in elevated LH and FSH levels in some males.

Typically, males with Alström Syndrome have small testes for their age, a small penis and delayed **pubertal stages**. There are several reports of **cryptorchidism**. **Gynecomastia** is also a common occurrence in young boys with Alström Syndrome (55%).

Biopsies of the testes show that there are few **Leydig cells**. There is evidence of atrophy of the testes and fibrosis in the tubules. However, the small amount of testosterone produced appears to be enough for normal secondary sexual characteristics and **virilization** to develop. Sexual drive is normal in most adult males with Alström Syndrome, but they have a lack of mature sperm or low sperm count and are unlikely to be fertile.

### *Signs and Symptoms*

Hypogonadism in males with Alström Syndrome is generally associated with the following physical and laboratory findings:

- Normal-to-high FSH and LH level relative to testosterone
- Low testosterone level
- Small testes and penis
- Impaired or delayed puberty
- Gynecomastia

### ***Detection and Diagnosis (males)***

**Physical Examination:** The testes are measured (length and width) to determine testicular size and consistency. The physician will note the amount and distribution of body hair, including beard growth, axillary and pubic hair, and the presence and degree of gynecomastia. Other possible tests may include semen analysis, pituitary imaging studies, or testicular biopsy.

**Laboratory tests:** Male hypogonadism is evaluated by determining testosterone, LH and FSH levels in the blood. Normal values vary according to the age of the male.

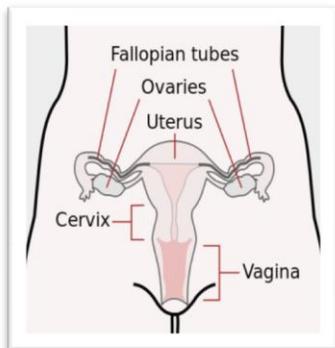
### ***Treatment***

Few studies have been done to evaluate the effects of testosterone therapy on sexual function and well-being in young men with Alström Syndrome, but there are some cases where these therapeutic options have proven effective. The therapy generally consists of testosterone replacement or augmentation using transdermal patches or injections from puberty onwards. Orally administered testosterone is quickly metabolized by the liver and cannot achieve sufficient blood levels over time to be useful.

### ***Recommendations***

Regular follow-up of males receiving testosterone therapy is recommended. Progress and results as well as any side effects should be monitored at 3 to 4 month intervals initially and then annually.

### ***Females with Alström Syndrome***



There is less information known about female gonadal function in Alström Syndrome, and there is very little information to refer to in the medical literature. In girls, sexual development seems to progress normally, and puberty is not delayed (average age 12 years). The presence of secondary sex characteristics such as normal breast and pubic hair development indicates adequate estrogen production during early development. In some female patients puberty has occurred early (age range 6 - 10). External genitalia (**labia, vagina, and clitoris**) and the **uterus and fallopian tubes** are normal.

### ***Signs and Symptoms***

Menstruation is often scant, sporadic, or irregular. In some cases, menstruation never occurs at all (primary **amenorrhea**), which could imply that ovulation and the secretion of gonadotropins, estrogens, progesterone are not sufficient. A relatively high frequency of **ovarian cysts** have also been reported (approximately 16% of females with Alström Syndrome), which may also be related to obesity. The presence of abnormal hair growth (**hirsutism**) or

masculinization (**virilization**) implies excessive **androgen** production, which is common in females with Alström.

### ***Detection and Diagnosis***

The assessment of the hormonal status of females can usually be made by obtaining a thorough history and physical examination. However, for females with Alström Syndrome, laboratory and diagnostic tests are recommended to monitor LH and FSH, and estrogen/progesterone and androgen levels. When girls approach puberty, a gynecological examination should be made. Ultrasonography may also be useful for assessment of the size of the ovaries, presence of cysts, and ovarian functioning.

### ***Recommendations and Treatment***

It is recommended that females with Alström Syndrome have a thorough work-up by an endocrinologist. Treatment of menstrual irregularities with cyclical estrogen and progesterone can be important and effective. However, women with liver disease should not start hormone replacement therapies. Hirsutism, in some cases, can be improved by the use of spironolactone.

## ***Frequently Asked Questions***

### ***FAQ: Do thyroid medications interact with other prescriptions my child might be taking?***

Although it is rare, thyroid hormones could affect the actions of other medications. Because most patients with Alström Syndrome are taking numerous medications, dosages may need to be adjusted. *Be sure to advise your physician and your pharmacist of other medications your child is taking.*

### ***FAQ: What happens if my child forgets to take his thyroid medication?***

Establishing a habit of taking the medication at the same time may help prevent missed doses. The hormone remains in the body for several days, so one missed dose should not cause a problem.

### ***FAQ: Are my son's breasts enlarged simply because he is overweight?***

Breasts may enlarge in overweight boys due to accumulation of fat. However, the increase in estrogen from the metabolism of testosterone can result in true breast tissue enlargement – known as gynecomastia. True gynecomastia will not resolve with weight loss or hormone treatment. If it causes distress, then mastectomy by a skilled breast surgeon could be considered. However, any surgery should be undertaken with caution in individuals with Alström Syndrome.

### ***FAQ: Will my child be fertile?***

There is evidence that testes in males with Alström Syndrome fail to show signs of normal sperm development and production, therefore, males are unlikely to be fertile. However, motile sperm have been noted in a few patients. In the adult females, pregnancy probably could not be carried to

completion. There are many aspects that should be considered: 1) pregnancy might cause deterioration of the kidney, heart, liver, pulmonary, and endocrine functions of the mother. 2) medications taken by the mother could pose a risk to the fetus 3) the parent may have a reduced life expectancy posing an ethical issue regarding the new-born. We do not know of any patients with confirmed Alström of either gender who have produced a child.

## **SIDEBAR DEFINITIONS ~ ENDOCRINE & GROWTH**

**Amenorrhea** - The total absence of, or prolonged cessation of, menstruation.

**Androgen** - The generic term for any steroid hormone, such as testosterone, that stimulates or controls the development and maintenance of masculine characteristics.

**Bone age** - A measure of the relative maturity of a child's skeletal system performed by x-raying several growth centers and comparing to large numbers of other children of the same chronologic age.

**Clitoris** - A small, pea-shaped organ just above the urethra.

**Cryptorchidism** - The failure of one or both testes to descend.

**Estrogen** - The hormone produced by the ovaries in response to LH and FSH which stimulates certain target tissues such as breast tissue, uterus, and fat cells, and is responsible for maintaining bone, brain, and lipid metabolism.

**Fallopian tubes** - Two tubes through which the ova travel to the uterus.

**Follicle-stimulating hormone (FSH)** - A hormone that stimulates sperm production in the male and ovarian follicle development in the female.

**Gonadotropins** - A collective name for the pituitary hormones that stimulate the genital organs to produce the sex hormones, ova and sperm cells.

**Growth Hormone (GH)** - The most abundant hormone produced by the pituitary gland, known to be critical for energy and metabolism, bone and muscle growth and strength, brain function, physical and mental health, especially during adolescence.

**Growth hormone Releasing Hormone (GHRH)** – A hormone that precedes the release of growth hormone (HGH), by stimulating its release from the pituitary gland.

**Gynecomastia** - The enlargement of the male breast due to proliferation of glandular tissue.

**Hirsutism** - The appearance of hair in females where it should not normally be, for example facial, chest or back hair in females that may arise from excess male hormones called androgens, primarily testosterone.

**Hypothalamus** - Plays a key role in growth and sexual development and also regulates appetite, metabolism, body temperature, mood, and other functions affected by Alström Syndrome.

**IGF-I** (Insulin-like Growth Factor 1 or Somatomedin C) - A protein synthesized by the liver and circulated in the blood in response to growth hormone stimulation that stimulates growth in cells and tissues.

**Labia** - The inner and outer lips of the vagina.

**Leydig cells** - Cells in the testes that release hormones called androgens.

**Luteinizing hormone (LH)** - Secreted by the pituitary gland and acts directly on the testes or ovaries to stimulate production of gonadal hormones (androgens and estrogens).

**Menarche** - The onset of menstruation.

**Ovarian cysts** - Generally harmless fluid-filled sacs which are similar to blisters, common among girls with Alström Syndrome.

**Progesterone** - Female sex hormone that induces thickening of the lining of the uterus that, when fertilization does not take place, decreases and menstruation occurs.

**Secondary Sex Characteristics** - Physical traits that distinguish males and females but are not a functioning part of the reproductive system, such as beards in males.

**Spermatogenesis** - The development of sperm cells in the testes.

**Subclinical hypothyroidism** – High TSH levels but still normal T4 levels with no apparent symptoms.

**Testosterone** - Produced by the testes and responsible for masculinization, hair growth, muscle development, and influencing sexual desire.

**Thyroid hormone (TH)** - Consists of **Thyroxine (T4)** and **triiodothyronine (T3)**, which are secreted into the bloodstream from the thyroid gland in response to stimulation from the pituitary hormone TSH.

**TSH (thyroid stimulating hormone)** - A hormone produced by the pituitary gland which acts on the thyroid gland to stimulate more thyroxine production when levels drop.

## CHAPTER SEVEN ~ OBESITY

### *Overview*

Obesity is a condition generally resulting from an energy imbalance between ingested and expended calories. There is usually an excess of fat in relation to other body components, technically defined as an excessively high fat to muscle ratio. Traditionally, one is considered obese if one is 20% or more above **ideal body weight**. The most common method to measure obesity is the Body Mass Index (BMI). A person is considered “overweight” when their BMI is over 24 and “obese” if BMI is over 30. Morbid obesity is a BMI over 40.

### *Obesity in Alström Syndrome*

Alström Syndrome is an “obesity syndrome”, which means that there are likely many factors contributing to the weight gain, including a complex combination of disruption of the feeling of satiety, alteration in the amount of calories used, and lack of exercise, perhaps due to sensory impairments. Despite the wide range of medical issues that people with Alström Syndrome may have, obesity is one of the most disturbing symptoms. Obesity is highly prevalent in Alström Syndrome and is present to some degree in nearly all patients. The obesity observed is probably a primary consequence of the alteration of the Alström gene, *ALMS1*, as it is an early and consistent feature observed in nearly all affected children. Children with Alström are not necessarily overweight because they eat too much, although this is true in some cases. Researchers are still trying to understand it.

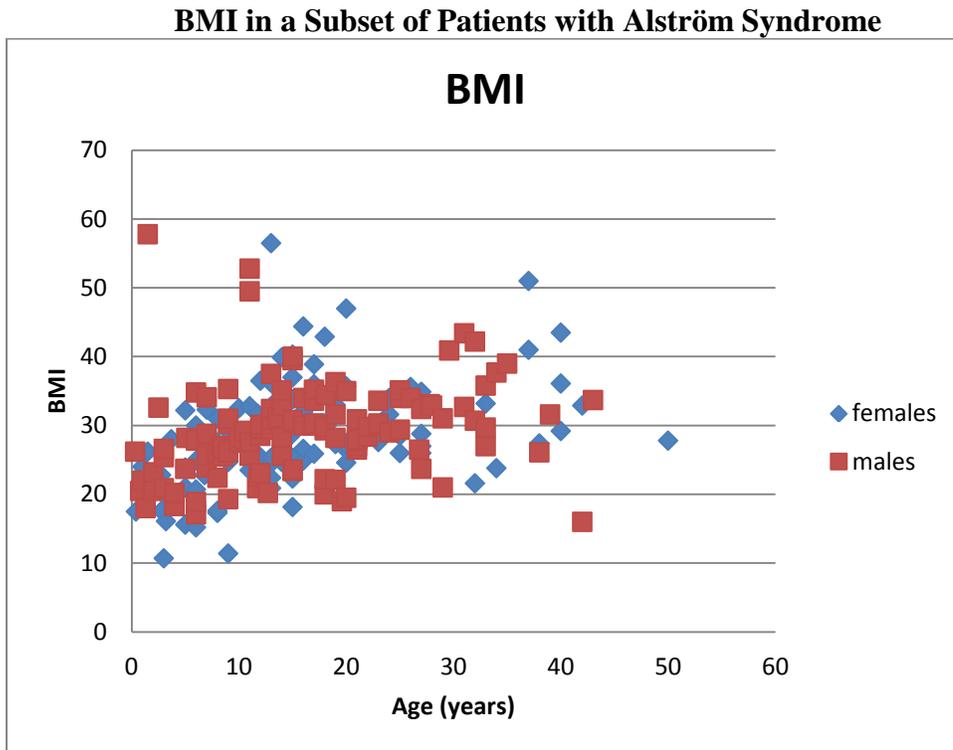
Several regions in the brain are known to be involved in appetite regulation and energy balance. Within the hypothalamus, the **arcuate nucleus** is considered to be a major site for the control of energy and regulation of physiological processes. In addition to possible hypothalamic defects, abnormalities in **adipogenesis** (the growth and differentiation of fat cells) could also contribute to the obesity in Alström Syndrome.

Also, since *ALMS1* is expressed in almost every cell type in the body, peripheral tissues such as liver and skeletal muscle may contribute to the pathogenesis of obesity. However, the contribution of these alterations remains to be determined.

The birth weight of a baby with Alström Syndrome is usually within normal limits. Nevertheless, very young children, even at 1 year of age, are described as having a “stocky” build when compared to other unaffected siblings. Toddlers usually rapidly gain weight and begin to exhibit **truncal obesity** during the first year or two of life. There is more abdominal (central and truncal) fat accumulation when compared to children who do not have Alström.

Obesity can precipitate many other serious complications in Alström Syndrome, since it is well known that children and adults with Alström Syndrome are at risk for problems with nearly all of their organs. Even in the general population, obesity confers additional risk for type

2 diabetes, heart disease, hypertension, joint and muscle problems, sleep apnea, and stroke. These are all significant issues for those with Alström Syndrome.



*Mean BMI is 28.4 (age range: 0.4-50 y) for females and 29.0 (age range 0.4 – 43 y) for males.*

### ***Hyperphagia and Food Obsession***

Hyperphagia, or obsession with food and excessive eating, is an issue that is quite variable and therefore also controversial in Alström Syndrome. Although the condition is less severe than in some other obesity syndromes, most of our young and adolescent children complain of a chronic feeling of hunger that makes them think about food all of the time. Many parents have said that their child “lives from meal to meal”, looking forward to the next meal as soon as the last one is finished. This obsessive, insatiable feeling of hunger and fixation on food can lead to excessive eating and increased obesity. The food compulsion makes constant supervision necessary. Adults with Alström Syndrome are often able to exert the self control and self-monitoring to control their consistent feeling of hunger.

**Leptin** is a hormone produced mainly by fat cells (adipocytes) that interacts with areas of the brain that control hunger and appetite regulation and signals that the body has had enough to eat. Recent findings suggest that resistance to leptin in the brain (leptin resistance) could be one of the underlying causes for increased appetite and obesity in people with Alström Syndrome.

Understanding that problems in the regulation of hormones involved in appetite regulation may be the root of the obesity associated with Alström syndrome. Many children and adults have insatiable hunger and the usual advice about controlling portion size and food intake

can be extremely difficult to implement. The recent research into hormonal regulators of appetite has led us to exploring different ways to control hunger and weight management.

It is also possible that energy needs are different in our children and even strict reduction of calories and maintaining a regimen of healthy foods could still lead to weight gain.

#### *A Mother's Story*



*Hi to all the parents, friends, relatives and students that struggle with the food/hunger/weight dilemma that Alström brings.*

*For those of you that don't know my son, Chris, he is 22 years old, very opinionated, fixed in his views and also loves a routine bordering on army life! Having said all that Chris is an accomplished Bass Guitar player, has played in 2 bands at college, and has made 2 CD's of his own music and lyrics. Chris is a confident, friendly young man who will chat to anyone and has run up huge telephone bills to prove it! Chris has always loved his food and even when suffering with the worst illnesses has managed to eat a full dinner!*

*My son, Chris, had the results back from his latest blood tests which showed a high cholesterol reading. I have been really careful with Chris's diet for over 3 years now, since he was diagnosed at 19 years old. I have always encouraged Chris to be independent and enjoy life to the fullest. So Chris has learned how to use his cash card to withdraw money from his bank at cashpoint machines safely and he has a mobile phone with a 'talks' package so that he can use his phone independently. All good empowering, independent stuff, I thought?*

*Chris eats mostly organic, home cooked, low fat food. We have discussed his favorite meals and how to make them 'healthy but tasty' and I came up with ways of producing really good wholesome food that didn't cost the earth as we live on a tight budget. So it was really puzzling that his test results showed high cholesterol! Chris had been waiting until I left for work and had ordered food from his talking mobile phone, to be delivered to the house. He had become very clever at concealing the take away wrappers by storing them in his bass guitar case, spraying the smelly wrappers with aftershave and then discarding them at his music lesson!!! Then I happened to find a receipt from the local take away and unraveled the mystery! Judging by the take away receipts, he had been ordering enough food to feed a small army! So how about that for ingenuity?*

*Chris is very aware of the health implications of over eating but it really makes no difference to him. The compulsion to eat is greater than the desire to be healthy! So it's back to the drawing board for me to try to find new ways for this to work.*

#### **Treatment**

There is no 'quick fix' for being overweight when you have Alström Syndrome, but exercise is a key factor. To lose weight, you need to burn more calories than you take in. Reduction in caloric intake is also an effective method of moderating insulin resistance. Sadly, the visual impairment in Alström Syndrome precludes many forms of vigorous exercise that could potentially moderate the over-weight. However, beneficial effects are observed with even a small amount of weight loss.

The effects of exercise are complex. Although exercise can decrease insulin resistance, it is not very effective in terms of weight loss unless it is also associated with a strict control of

calorie intake. Unfortunately (although it can certainly help,) in Alström Syndrome simple calorie reduction and moderate exercise may not be as effective as it is for children and adults who do not also have simultaneous problems with hypothalamic function.

### ***Recommendations***

Progress in defining the biological basis of the obesity in Alström Syndrome may help patients and families dispel any perception that their child's weight issues are due to a lack of discipline or personal behavior failure. However, it remains crucial to pay attention to eating habits and levels of activity. Many people have found it helpful to keep track of everything they eat by recording it in a daily food journal. The obvious challenge for Alström patients is to establish an exercise regimen adapted for the visual impairment. Group sessions with friends/partners and buddies with whom to exercise will help. Consulting with an experienced dietician or nutritionist who is also practiced in exercise advice is often helpful, but the dietician needs to understand that in Alström Syndrome the problems go beyond just overeating.

#### Some Suggestions:

- Understand that the obesity in is not necessarily your child's fault, nor is it your fault – it is a biological part of Alström Syndrome.
- Acknowledge that obesity is part of Alström Syndrome that requires attention and vigilance.
- Begin intervention early and anticipate that your child will have major "food issues".
- Choose more nutritious meals that are lower in fat and carbohydrates. Just because a product is fat free or low carbohydrate, doesn't mean it is calorie free. In fact, some of these foods can have as many, if not more, calories per serving than regular products.
- Children with Alström Syndrome have a very keen sense of smell. Recognize and control environmental cues (like inviting food smells) that increase your child's hunger.
- Become more physically active along with your child and encourage adaptive sports, dancing, involvement in chores around the house, walking, and using stairs.
- Make a long term family plan that involves life style changes so everyone may benefit from joining the "program."
- Keep records of food intake and physical activity.
- Involve outside caregivers such as grandparents,
- Let babysitters, daycare facilities know that your child has a disorder that involves hunger and food issues that affect his/her health.

## ***Frequently Asked Questions***

### ***FAQ: How do you calculate BMI?***

This calculation is shown as follows: Weight (in kilograms) / Height (in meters) Squared (Ht. x Ht). For example, a man who is 5' 10"(1.78 meters) and weighing 285 lbs. (130 kg.) would have a BMI of  $130/(1.78 \times 1.78) = 41$ . There are several websites that will calculate BMI.

### ***FAQ: Why is it recommended to limit fat intake when attempting to lose weight?***

Fat is higher in calories than carbohydrates or protein. Protein and carbohydrates have approximately 4 calories per gram vs. 9 calories per gram of fat.

### ***FAQ: What about discrimination with respect to obesity?***

For obese persons, clear and consistent stigmatization, and in some cases discrimination, can be documented in three important areas of living: employment, education, and health care. This inevitably takes a toll on the emotional well being of many people with Alström Syndrome and overweight people in general.

### ***FAQ: My child is an adolescent, and she seems to be losing fat around her hips and legs, but not in her chest and stomach – why?***

Recent research has suggested that the severe insulin resistance in Alström Syndrome can lead to a failure or reduction of adipose (fat) tissue in selected areas of the body, such as buttocks and legs.

### ***FAQ: How can my child exercise when limited by vision impairment?***

A recent survey indicated that children with Alström Syndrome report a wide variety of innovative forms of exercise, including swimming, tandem cycling, horseback riding, and starting a “Walking Club” for school age children. However, unfortunately, many report that they do not have a planned, regular exercise regimen.

### ***FAQ: Should my child exercise if s/he has dilated cardiomyopathy?***

Yes, moderate exercise is beneficial – even for patients with DCM for whom it is also recommended. If the exercise causes breathlessness or increased heart rate, stop the activity. Consult with your cardiologist for further advice.

## Exercise Tales



Jane is showing her champion swimming medal



Chelsea is demonstrating her skills in riding



Nothing slows down JJ



Adam the archer



Katelyn playing volleyball with a sighted guide



Ricole rock climbing with friends

## **SIDE BAR DEFINITIONS ~ OBESITY**

**Adipose tissue** - A type of tissue that stores fat in cells.

**Adipogenesis** - The differentiation of fat cells (adipocytes) into fat tissue.

**Body Mass Index (BMI)** - A mathematical formula to assess stature and body fat based on weight in kilograms divided by height in meters squared ( $BMI = \text{kg}/\text{m}^2$ ).

**Hyperphagia** - Abnormally increased appetite for and consumption of food, thought to be associated with the hypothalamus in the brain.

**Ideal Body Weight** - An estimate of what your healthy weight is, taking into account gender, height, and size of your frame.

**Leptin** - Leptin is a hormone produced by fat cells that is essential in the regulation of appetite and metabolism.

**Lipodystrophy** - The loss of adipose tissue in selected areas of the body, usually associated with insulin resistance, hyperglycemia, hyperlipidemia, and other metabolic disturbances.

**Truncal obesity** - Fat concentrated around the waist and upper body.

**Waist/hip ratio** - Measurement of the circumference of the waist versus the hips that helps indicate indicates the type of obesity and the risk for heart disease and diabetes.



## CHAPTER EIGHT ~ DIABETES

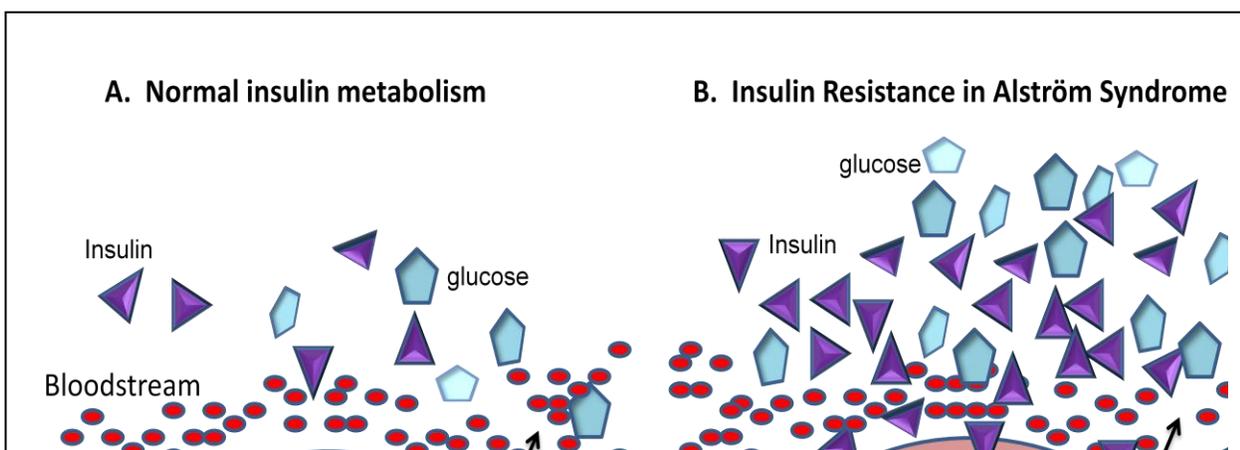
### Overview

One of the most important sources of energy in the body is **glucose** (the sugar that circulates in the bloodstream). It provides the main source of fuel for all of the tissues and organs. Blood glucose comes from several sources: dietary carbohydrates (what you eat), internal production (what is made inside the body) and the breakdown and release of stored sugar by the liver.

Hormones such as **insulin** and **glucagon** work together to maintain the proper balance of the blood glucose level (**normoglycemia.**) Secreted by islet cells in the pancreas, insulin acts to lower blood glucose concentration by reducing its production in the liver, as well as transferring it out of the blood to store as fat (**triglycerides.**) Conversely, the liver releases stored glucose into the bloodstream when it is needed.

Many situations can interfere with maintaining a proper balance, including inadequate insulin production in the pancreas, reduced effectiveness of the insulin itself, or excessive glucose production by the liver. **Type I diabetes** occurs when the cells in the pancreas cannot produce insulin.

### Insulin Resistance



LEGEND: Insulin resistance occurs when the normal amount of insulin secreted by the pancreas ( ) is not able to enter the cells through the receptor sites on the surface ( ). Think of it as a lock and key. Insulin is the key and the receptor site is the lock. Unable to allow insulin into the cells, your body can not provide them with glucose ( ). Your body produces more insulin which is unusable because it cannot enter the cells. Now the glucose and insulin stay in your blood stream resulting in hyperglycemia and hyperinsulinemia.

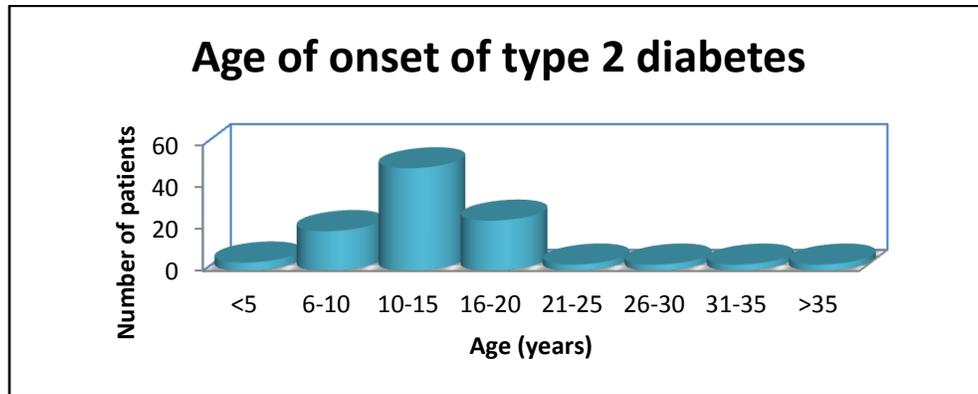


**Impaired fasting glucose, insulin resistance and hyperinsulinemia** are signs of an imbalance in glucose/insulin levels and predict the development of **type 2 diabetes**. To compensate for the body's resistance to the action of insulin and the resulting impaired fasting glucose, the pancreas tries to compensate by producing more and more insulin (hyperinsulinemia). Hyperinsulinemia is associated with obesity, water retention, **hypertension**, and elevated triglycerides (**hypertriglyceridemia**).

### ***Insulin Resistance and Diabetes in Alström Syndrome***

**Acanthosis nigricans** is seen in most children and adults with Alström Syndrome, regardless of whether they have diabetes. It is characterized by a darkening and thickening of the skin. Light-brown to black, velvety, rough areas usually first appear on the back and sides of the neck, under the arms, or near the groin. The condition is sometimes associated with being overweight, hyperinsulinemia, or insulin resistance, all of which are part of the clinical picture in Alström Syndrome. Insulin resistance and hyperinsulinemia constitute two of the earliest metabolic changes in Alström Syndrome. Both have been documented as early as age 2-4 years. Most children with Alström Syndrome eventually develop type 2 diabetes. Unlike adult-onset type 2 diabetes in the general population, in Alström Syndrome the onset occurs at a very early age and at an accelerated rate, often coinciding with the onset of puberty. However, there is a great deal of variability in the age of onset. Diabetes is present in nearly 70% of patients over the age of 6, with the average age of onset at 16 years. Interestingly, it has been noted that females with Alström Syndrome, who reach puberty at younger ages, also tend to develop

diabetes at a younger age. The age-range of onset of diabetes observed thus far in Alström Syndrome is 6 – 40 years.



#### *Signs and Symptoms of type 2 diabetes mellitus:*

- **Polydypsia** - excessive thirst
- **Polyuria** - excessive urine
- **Glycosuria** - glucose in the urine
- Fatigue
- Increased appetite
- Decreased resistance to infection, especially urinary-tract infections and yeast infections of the skin, mouth, or vagina.

#### *Detection and Diagnosis*

We know that if a child has Alström Syndrome, there is a strong chance that diabetes will develop, so careful monitoring of blood glucose is essential from an early age. This should include regular laboratory urine and blood evaluation to measure glucose, insulin, and **Hb1Ac** so that any necessary treatment can be started promptly. For a quick check to determine the presence of abnormal glucose levels, glucose detection strips can be purchased at most drug stores. Good glucose control decreases the chance of other complications that can occur in Alström Syndrome.

Hyperinsulinemia is detected by a simple blood test that measures the amount of insulin in the bloodstream. To evaluate impaired fasting glucose, the patient is asked to ingest a small amount of sugar, and the time it takes for the body to process and clear the blood glucose is monitored. Fasting glucose level between 6.1 and 7.0 mmol/L are abnormally high, and patients with glucose levels within this range are considered to have impaired fasting glucose. The diagnosis of type 2 diabetes is based on a consistently elevated fasting glucose, greater than 7.0 mmol/L or a level greater than 11mmol/L 2 hours after a 75gm glucose drink.

## ***Monitoring***

Self-monitoring is an extremely important component of management. Children should be educated on the use of a glucose meter, interpretation of the results, and how to modify treatment according to blood glucose levels. There are Braille and talking glucose monitors commercially available. The whole family should try to learn as much as possible about controlling diabetes and recognizing the signs and symptoms of complications.

## ***Treatment for Diabetes in Alström Syndrome***

**Glitazones** (Actos, Avandia) and **Glucophage** (Metformin) are known to be effective in improving glucose control in type 2 diabetes in Alström Syndrome by increasing sensitivity to insulin, but they act in different ways.

**Metformin**, decreases glucose production in the liver and increases its utilization in all tissues, thereby removing it from the plasma. At this time metformin appears to be the most commonly used treatment and is the drug of choice in the Alström population. The disadvantages of Glitazones are that they are expensive and can worsen hypertriglyceridemia and heart failure. Studies have shown that they reduce appetite, promote weight loss and can



reduce triglyceride levels. Glitazones do decrease the insulin resistance in the cells and can be used by Alström patients if cardiac and renal function is good, but must be avoided in the presence of active or treated heart and/or renal failure. These treatments should be discontinued when the serum creatinine concentration exceeds 200  $\mu\text{mol/L}$  or if cardiomyopathy is evident.

**Exenatide** (Byetta) is an injectable drug that reduces the level of sugar in the blood by mimicking hormones that are released into the blood by the intestines in response to food (**incretins.**) Exenatide has been tried in some patients and the response is often successful, but variable. Renal dysfunction is a contra-indication.

In some cases, patients with Alström Syndrome, over time, lose their ability to make insulin in the pancreas, so they must control their blood glucose by using injected insulin. Sometimes, it requires very high doses to maintain glycemic control.

## ***Recommendations***

Restricted calories, weight loss, and exercise have all been strongly advocated for the treatment of type 2 diabetes, and this is particularly important for people with Alström Syndrome, as uncontrolled glucose levels can cause damage to other organs in the body. Because we know that most children and young adults will develop type 2 diabetes, there are compelling reasons to institute these preventative steps early.

## ***Diet, Exercise and Weight Reduction***

Rigorously follow a healthy diet to reduce weight and limit refined sugars, fats, and carbohydrates. Increase fruits and vegetables (plant fiber.) In a study conducted with Alström Syndrome patients in the UK, low carbohydrate diets were effective in adults. However, long-term safety of very low fat diets has not been confirmed in Alström Syndrome. Weight reduction can be of enormous benefit and may result in normalization of fasting glucose levels and may delay the onset of overt diabetes. A dietitian or nutritionist should be consulted.

Even in overweight or obese patients, maintaining a regular exercise program can help prevent or delay the onset of diabetes and is an important part of controlling overt diabetes. In one large study in the general population over 6 to 14 years, there was a relative decrease of 30% to 50% in the development of type 2 diabetes among those who exercised regularly compared to those who were sedentary. This result was found in both men and women, and especially the obese subjects, so there is good reason to believe that this regimen can also benefit patients with Alström Syndrome.

## ***Frequently Asked Questions***

### ***FAQ: Is there a cure for acanthosis nigricans***

There is no “cure” for acanthosis nigricans. You cannot scrub it away. Retin A and salicylic acid are all prescriptions that may provide some improvement for this condition.

### ***FAQ: Are there different kinds of diabetes?***

*Diabetes mellitus* is the name given to a group of diseases characterized by an inability to properly store and use glucose. Diabetes is divided into different types: **type 1**, **type 2**, and **gestational**.



### ***FAQ: Why is it called “diabetes mellitus”?***

The name diabetes means “siphon or running through”; it was used by the Greeks 2000 years ago to describe the striking urinary volume excreted, and mellitus means ‘sweet’, referring to the excess sugar that is excreted in the urine.

### ***FAQ: Do all children with Alström eventually develop type 2 diabetes?***

The majority do. However, there is a wide range of ages when the first signs of diabetes are reported. Even children who do not yet have symptoms of diabetes should continue to vigilantly monitor blood glucose and HbA1c levels.

### ***FAQ: Is diabetes curable?***

No, but it is possible to achieve good control of blood sugars by diet, exercise, and medications.

***FAQ: What about non-drug therapies?***

There is good evidence that diet and exercise can delay the onset of type 2 diabetes in children with Alström Syndrome.

***FAQ: What kind of food should my child avoid in order to reduce the impact of insulin resistance and to postpone diabetes?***

In all circumstances, a child with Alström Syndrome should avoid over-eating, difficult though this may be. What is important is to reduce total calorie intake, while maintaining nutritional value. A low-calorie, low-fat and low-carbohydrate diet, combined with moderate physical exercise can help to moderate or diminish insulin resistance and postpone diabetes. Foods that increase triglycerides and the “bad” cholesterol, such as greasy or fatty food, red meat, and rich sauces should be avoided.

***FAQ: Are low carbohydrate diets such as the Atkins Diet or the South Beach Diet effective or appropriate for people with Alström Syndrome?***

Low carbohydrate diets have been advised for individuals with Alström Syndrome, but extremely low carbohydrate diet plans (<30%) have not been proven safe for long term use.

***FAQ: Is there any technology for visually impaired people that can help my teenaged child take responsibility for his own diabetes management?***

There is technology for the blind to monitor blood glucose levels, weight, and blood pressure – all of which are important in making your teenager independent. Improved tools for self-management suitable for the blind and visually impaired can allow many teens and adults with Alström Syndrome to take control of their own diabetes management.

## **SIDEBAR DEFINITIONS ~ DIABETES**

**Diabetes mellitus** – A metabolic disorder in which the body fails to make enough insulin or becomes resistant to insulin or both, resulting in high blood sugar levels.

**Exenatide** (Byetta) - A synthetic, man-made, hormone that resembles and acts like incretins (hormones that are secreted by the intestines that control appetite).

**Gestational diabetes** - Onset or recognition of glucose intolerance during pregnancy.

**Glitazones** (thiazolidinediones) - Drugs that work by lowering the entire body's resistance to insulin and sometimes taken with metformin and/or a sulfonylurea, requiring regular monitoring for potential liver and heart problems and increases in triglycerides.

**Glucagon** - A hormone produced by certain cells in the pancreas that acts directly on the liver and other tissues to stimulate the breakdown of stored glycogen and the release of glucose.

**Glucose** - Sugar, the major energy provider in the body.

**Glycated hemoglobin (HbA1c)** - A measurement taken from a blood sample that provides an evaluation of how much glucose the red blood cells have been exposed to over their lifespan (approximately 100-120 days) with normal levels ranging from 4-6% and levels of greater than 7% indicating poor control of diabetes.

**Glycosuria** - Presence of glucose in the urine, an indicator of an imbalance in the glucose/insulin ratio.

**Hyperglycemia (glycemia)** - High levels of blood glucose.

**Hyperinsulinemia** - High levels of insulin in the blood caused by the body's resistance to the actions of insulin and the compensatory increase insulin production by the pancreas.

**Hypertension** - High blood pressure.

**Hypertriglyceridemia** - Elevated levels of triglycerides (fats) in the blood.

**Impaired fasting glucose** - Also referred to as "glucose intolerance" and is characterized by fasting blood glucose levels above normal but below the diabetic threshold (6.1-7.0 mmol/L).

**Incretins** - Hormones that are secreted in response to glucose in the small intestine through the circulation to the pancreatic beta cells, causing them to secrete more insulin.

**Insulin** - A hormone produced and secreted by islet cells in the pancreas that acts directly on the liver and other tissues to regulate glucose level in the body.

**Insulin resistance** - A condition occurring when the tissues become less sensitive to insulin, resulting in an inability to use the body's own insulin to properly control blood glucose.

**Metformin (Glucophage)** - A drug that improves insulin sensitivity.

**Normoglycemia** - Normal blood glucose levels (3.8 - 6.0 mmol/L)

**Polydipsia** - Excessive thirst.

**Polyuria** - Excessive urine production.

**Triglycerides** - A major source of fat in the body and in foods.

**Type I diabetes** – Usually starting suddenly in young children when the beta cells in the pancreas are destroyed causing it to completely stop manufacturing insulin, leading to absolute insulin deficiency.

**Type 2 diabetes** (or generally non insulin-dependent diabetes, NIDDM) – Failure of one or more of the regulatory mechanisms that keep blood glucose levels within normal range, resulting in abnormally high glucose levels in the blood and urine.

The tint generally used for children with Alström Syndrome is BPI Burnt Orange #21600/26600. If your optician needs any assistance or more information, contact [Vogue30@vogueoptical.com](mailto:Vogue30@vogueoptical.com)

## CHAPTER NINE ~ VISION

### VISION

#### Overview of the Retina

The retina is the light sensitive tissue in the back of the eye. A retina consists of two main layers; the thin **retinal pigment epithelium (RPE)** and a thicker one called the **neural retina**.

neural layer is film in a When focused “takes the and the carried by nerve to The retinal contains of cells,

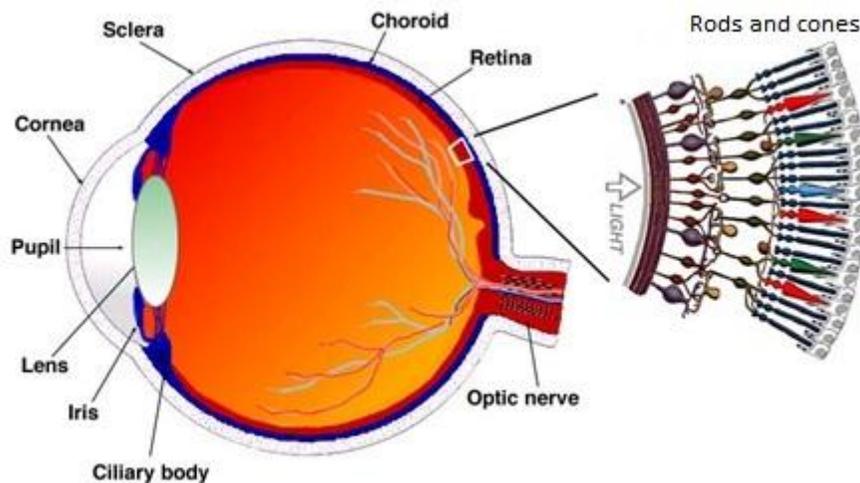


The retinal like the camera. light is on it, it picture,” signal is the optic the brain. neural layer millions called the

**photoreceptors**, which are able to respond to light with an electrical signal. **Cone cells**, about 6-

7 million concentrated in the central portion of the retina, contain light-sensitive pigments that enable us to see fine detail and color. About 120 million **rod cells**, absent from the center of the retina, but dense elsewhere, enable peripheral vision and vision in dim light or darkness. Rods are more than 1000 times more sensitive to light than cones. They cannot detect color, but they do perceive shades of gray, black, and white. Therefore, the human eye requires both rods and cones for normal vision. **Retinal dystrophy** is a general term used to describe a condition where there is degeneration of the cells in the retina.

### The Eye and Retina



*LEGEND: Neural retina. The photoreceptors, rods and cones, are the light-sensitive cells inside the retina. When these cells detect light coming into the eye, they send a message back to the brain, which, in turn, translates the message into what we see. Rods and cones are named because of the shapes of the cells.*

*With permission from Helga Kolb, MD, John Moran Eye Center, University of Utah. <http://webvision.med.utah.edu/>*

### ***Vision in Alström Syndrome***

The retinal dystrophy in Alström Syndrome is **congenital** (a condition they're born with.) Virtually all Alström children exhibit retinal dystrophy and associated vision problems within the first year of life. In Alström Syndrome, the cones are affected first, so the vision that Alström children experience in early childhood comes only from the rods. Often, parents fear that their infant or young child cannot see at all. However, vision appears to initially improve in the first few years of life, particularly if the child is given dark, red-tinted glasses. Unfortunately, although the progression of vision loss can be variable, all children eventually become blind or have severe vision impairment. According to patients, by the age of nine years, one-third (32%) of patients report becoming totally blind; 50% by age 12, and 90% by age 16.

### ***Signs and Symptoms***

The first symptom, usually noticed very early in infants (median age: 3 months) is **nystagmus**, a vibration or wobbling of the eyes that tends to decrease over time, but never totally disappears. One of the first signs, usually obvious by six months of age, is light sensitivity or **photodysphoria**. This happens because the lack of function in the cone cells causes the rods to become over saturated, especially in bright light. Squinting, blinking, and avoiding bright light are symptoms because the infant unconsciously tries to keep light from entering the eyes. As the retinal dystrophy progresses, the rods become less sensitive and the photodysphoria diminishes. This may initially be perceived as an improvement but is, in fact, associated with the disappearance of rod photoreceptors.

Kiefer



Hugo



Palmer



Pictured here are three different young boys at age three years. Dark or red tinted glasses can help to diminish the painful photophobia experienced by children with Alström.

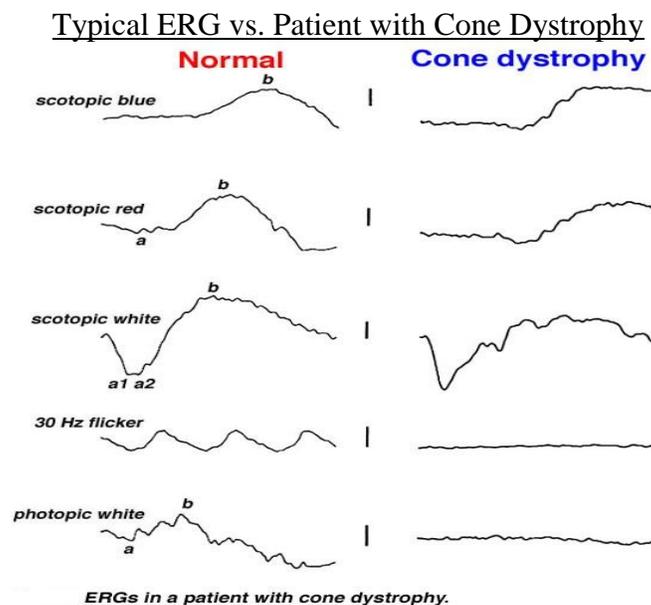
### *Detection and Diagnosis*

**The ERG:** When vision problems are first noticed, an ophthalmologist should test visual responses using an **electroretinogram** (ERG.) The ERG is the electrical potential generated by the retina in response to a brief flash of light. When performed before the age of 2 years, this test allows for a good characterization of the retinal dystrophy in Alström Syndrome. For young children, this often requires mild sedation. Any time a child might need sedation for a procedure, please ***be sure to advise the physician and anesthesiologist of the risk of possible sudden hypoxia.*** (See hypoxia warning in the respiratory chapter.)

The electrical response from the retina to either a bright or a dim flash in a darkened room can usually be easily measured in infants and very young children. However, because the retina in Alström Syndrome has few functioning cones to respond, the signal is often hard to detect. The solution is to place the electrode sensor directly on the cornea with a small contact lens, instead of on the lower eyelid, so that very small signals may be detected.

The signal will get smaller as the child's retina deteriorates and often will not be detectable even by a corneal electrode by about 4-6 years of age. Therefore, a *series* of ERGs are essential to demonstrate the progression that allows for a differential diagnosis from rod-monochromatism, a stationary, non-progressive disorder, with which Alström Syndrome is frequently initially confused. The major difference between rod-monochromatism and Alström Syndrome is that in Alström Syndrome the rods will also undergo a degenerative process and the rod function will eventually be lost. Later in the disease, about age 7-15, ERG signals (both rods and cones) are totally extinguished.

After a readable ERG signal can no longer be obtained, Alström Syndrome can be indistinguishable from the group of conditions called **Leber Congenital Amaurosis (LCA)**. Only time allows for a differential clinical diagnosis of Alström Syndrome as other cardinal features develop.



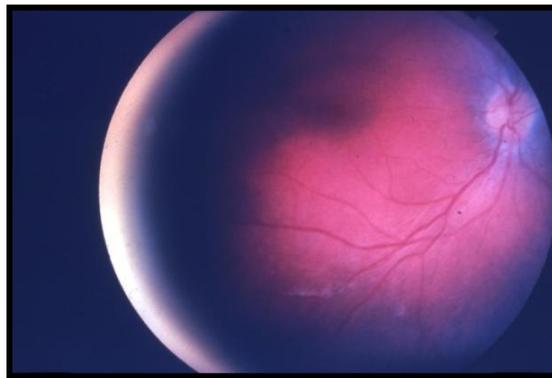
### ***Fundus Examination***

The **fundus**, the inner lining of the eye, can be photographed through the dilated **pupil** with specially designed cameras that produce a sharp view of the retina, the retinal blood vessels, and the **optic disc**. Photographs of the fundus are used to record the condition of these structures in order to document the changes in the retina over time.

In the early stages of Alström Syndrome, there are few distinguishing retinal features, and the diagnosis is never made from the fundus examination alone. Even though the ERG shows no recordable response, the fundus can look essentially normal. If subtle changes are observed in the fundus, they are indistinguishable from changes seen in other non-specific retinal dystrophies, i.e. Leber Congenital Amaurosis. Fundus photography is not a diagnostic tool, but it may rule out other diagnoses.

After several years, fundus abnormalities are more obvious. Typically one can observe the features of narrowed vessels, pale optic discs, poorly defined **macula** and abnormal RPEs. The retinal features evolve with age, and there is variation between individuals, but at all stages the fundus is not significantly different from cases of other retinal dystrophies.

Often, changes in the fundus are not easily visible because of **subcapsular cataracts**, especially with nystagmus present. About 39% of people with Alström Syndrome develop cataracts. The most likely cause of cataract formation is the substances released from the degenerating retina that damage the lens, causing it to become opaque from the back. Some patients have reported slightly improved vision after cataract surgery, but by the time cataracts develop, the retinal dystrophy has significantly progressed so cataract surgery will not “restore” any sight nor improve the underlying retinal degeneration.



*LEGEND:* The fundus of a 5 y/o male with Alström Syndrome. At this stage in this particular case there is no evidence of the abnormal pigmentation, which will eventually develop. *Photo courtesy of Isabelle Russell-Eggitt, Great Ormond Street Hospital, London.*

### ***Treatment***

Although a therapy has yet to be found for the retinopathy, early recognition of the visual problems is essential to ensure appropriate treatment of symptoms such as photodysphoria and reduced visual acuity and to help the child maximize his visual skills.

### **Recommendations:**

- If there is a question or an inconclusive diagnosis, obtain serial ERGs and **visual evoked response (VER)** testing and consult with other specialists in endocrinology and genetics.

- Try to “train” the infant by utilizing consistent strategies, like always announcing your intentions using the same phrase. Your child can then anticipate your actions.
- The severe photophobia can be relieved somewhat by the use of red-tinted glasses (or gray for some children.)
- Provide an IEP (individual education program) or “statementing” in the elementary grades to help the child gain the most from his early educational experience. Involve specialist vision teachers from an early stage.
- Make large print and other low-vision aids available to your child whenever possible. There is no harm and often a lot of educational benefit to making use of the sight your child does have early on, at the same time as proactively introducing Braille.
- Introduce Braille early to both the child *and yourself* to give the child an advantage, rather than trying to teach Braille after vision is lost.
- Help educators structure an individualized program by keeping them informed about your child’s level of vision *and the prognosis of vision loss*.



*LEGEND: A Representation of normal vision (left), early (middle) and late (right) visual defects in Alström Syndrome. Graphic courtesy of Francois Tremblay, Ph.D.*

## Artificial Retinal Implants: Could they be used in Alström Syndrome?

*Excerpted from Panoramic Views, March 2011.*

*Dr. Levin is a member of the ASI Scientific Advisory Board*

Alex V. Levin, MD, MHSc  
Julia A. Haller, MD  
Wills Eye Institute  
Thomas Jefferson University  
Philadelphia, Pennsylvania

One option for patients who have degenerating disorders of the retina would be the implantation of an “artificial retina”. Currently this terminology is used to refer to several different types of investigational electronic “chips”, composed of electrode arrays, that are implanted adjacent to the retina--either on its inner surface, or just beneath it, and either replace the degenerated photoreceptors of the diseased retina, or amplify the ability of damaged nerve cells to see. With the Argus Second Sight implant, for example, the world is viewed by a tiny video camera mounted on glasses which send these images wirelessly to the chip. The chip is hooked up directly to the nerve fibers on the surface of the retina. By converting these images into electrical impulses that the nerve fibers can read, the images are sent via the optic nerve to the brain. The other most-studied implant in humans is made by the company Retina Implant AG. Their product sits underneath the retina, directly replacing light receptors lost in retinal degenerative processes. The 3mm-by-3mm microchip has an array of approximately 1,500 photosensitive electrodes. Electrical power for the device is provided inductively through transmitter coils attached to the skin.

This technology will only work if the nerve fibers of the retina are still preserved. In fact, in many retinal degenerations, including that seen in Alström syndrome, these nerve fibers are likely still present as it is the underlying cells (photoreceptors) that are actually being destroyed by the genetic disease leaving the nerve fibers relatively unimpaired. By using an electronic chip, one is “bypassing” the degenerating part of the retina and taking advantage of those cells from the retinas which are preserved.

Retinal chip implantation is being conducted in several centers around the world including Wills Eye Institute. This technology is in its fairly early stages and is still an investigational (research) device. Early trials have been restricted to patients with extremely poor vision (light perception or no light perception). The chip itself, at this stage, is only able to see 20/200-20/400 at best. That means it would not at this point make sense to implant a chip in someone who sees better than 20/200. Many patients with the chip do get some ability to distinguish lights with some directionality, perhaps see a door frame which they can walk through, and see shadows or large objects more clearly. The risks of the chip (e.g. damage to the retina and/or eye) are still being evaluated. Like most research projects in their beginning phases, the research is confined to patients who have very clearly defined disease of the eye without disease of the rest of their body. One must first decide whether it’s safe for the eye before including patients who have other parts of their body that are not functioning well, particularly the brain. As Alström is a systemic disease that affects multiple part of the body, including patients with Alström would be a later stage of the research. At this time, we are not aware of any center that is implanting chips in patients with Alström syndrome.

Chip technology is advancing rapidly. As the quality of chips improves, the amount of vision obtainable with the chip will increase. It’s even possible that some day, electronic chips will be able to see better than the 20/20 of a normal eye!

## *Frequently Asked Questions*

### ***FAQ: What can be done to alleviate the painful light sensitivity?***

The pain and discomfort associated with photodysphoria can be moderated using devices developed to reduce the intensity of the light entering the eyes. Visors, photochromatic sunglasses, polarizing filters, and red colored glasses, overshields, or contact lenses (which have a spectral cutoff to allow only lower wavelengths of light to pass through) can provide some relief from the extreme pain and blindness in bright light.

### ***FAQ: Can my child's vision loss be treated or arrested?***

In Alström Syndrome retinal dystrophy begins in infancy. Sight loss is gradual and progressive, and no treatments are currently available to cure or prevent vision loss or slow its progression.

For the first time, my 5 year old daughter recognized the trees while driving down the road today, after getting her new glasses. Do you know what that means to a Momma like me...THE WORLD!!!!!!  
- Cayla

### ***FAQ: Should I tell my child that blindness will be the eventual outcome?***

“When to tell” is different for each child and for each family, but eventually the child must be told. It is more frightening to face loss of vision with no adult to discuss it with.

### ***FAQ: What can I do to help my child prepare for eventual blindness?***

Because it is well documented that children with Alström Syndrome will eventually lose their sight, it is beneficial to begin to learn Braille and white cane skills at an early age. Many young adults with Alström have had good experiences with the use of guide dogs, and this possibility should be considered for your teenage child. In addition, computer adaptive technology has maximized learning and communication, even at very young ages. For a comprehensive list of resources for the blind, see [www.Alström.org/families](http://www.Alström.org/families).

## SIDEBAR DEFINITIONS ~ VISION

**Cataract** - A cloudy or opaque area in the lens of the eye that prevents light rays from passing through the lens and focusing on the retina.

**Cone cells** - Concentrated in the center of the retina, about 6.5 million cones in each eye are responsible for color and detailed vision.

**Congenital** - A condition existing from birth.

**Electroretinogram (ERG)** - A test in which an electrode is placed on, or near, the cornea to measure the electrical responses of the rods and cones of the retina.

**Fundus** - The inner lining of the back of the eye.

**Leber Congenital Amaurosis (LCA)** - The general term for a group of autosomal recessive eye disorders characterized by moderate to severe vision abnormalities identifiable at birth or in the first months of life. (LCA is caused by a different gene than Alström Syndrome.)

**Macula** - The center of the retina containing the highest concentration of cone cells.

**Nystagmus** - An involuntary wobbling, jerking, or roving of the eyes.

**Optic disc** - The head of the optic nerve where the retinal blood vessels enter the eye.

**Optic nerve** - A flexible “cable” of nerve fibers connecting the eyeball to the brain which carries the electrical signals that the brain then interprets as visual images.

**Photodysphoria** - An extreme sensitivity to light, photophobia.

**Photoreceptors (rods and cones)** - The collective term for rods and cones in the neural retina, named as such because they are activated by light signals.

**Pupil** - The hole in the front of the eye through which light passes.

**Retina** - The layer of rods, cones, and the retinal pigment epithelium (RPE) found at the back of the eye.

**Retinal dystrophy** - A general term referring to abnormalities or degeneration of cells or tissues in the retina.

**Rod cells** – Cells in the retina responsible for the detection of movement, shapes, and light and dark. The rods cannot detect color, so vision obtained from rods is “black and white”.

**Rod monochromatism** - A non-progressive, recessive ocular condition characterized by loss of cone function, resulting in a total lack of color discrimination, photodysphoria, and congenital nystagmus, also known as congenital achromatopsia.

**Retinal Pigment Epithelium (RPE)** - A single layer of cells that lay on top of the photoreceptors, which perform multiple functions in the retina, including the transport of nutrients and fluid.

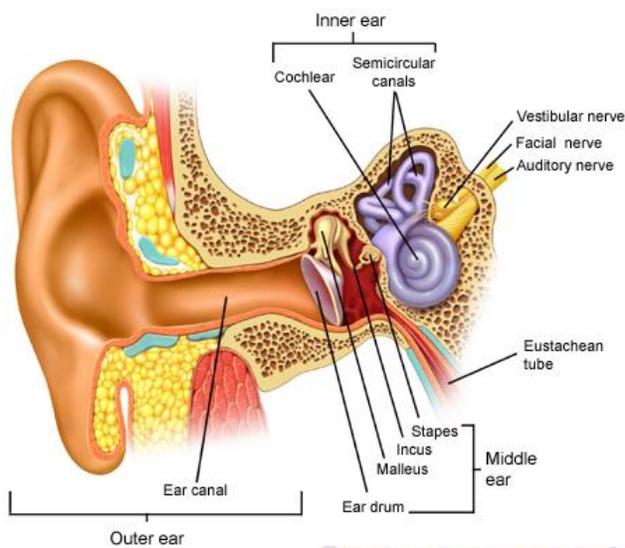
**Subcapsular cataract** - A cataract that develops slowly under the lens capsule, usually from the back.

**Visual Evoked Response (VER)** - Measures the response to a visual stimulus by placing electrodes on the back of the head, over the vision part of the brain.

## CHAPTER TEN ~ HEARING

### Overview

The ear is comprised of the *outer*, *middle*, and *inner* ear. The **pinna** (part of the outer ear) and ear canal funnel sound in the form of energy. Those sound waves and pressure changes to the **eardrum** cause it to vibrate. The vibrations of the eardrum travel through three small bones (**ossicles**) in the middle ear to reach the inner ear. The **cochlea** in the inner ear is lined with millions of sensitive hair cells that set up vibration patterns in a traveling wave and create electrical impulses along the **auditory nerve** that the brain interprets as sound.



### Hearing in Alström Syndrome

Alström Syndrome patients who have hearing impairment have **sensorineural** hearing loss rather than **conductive** loss. The hearing impairment is **bilateral** and slowly progressive and cannot be treated or prevented. Although differences in acuity exist, of the patients studied, 88% report some degree of hearing loss by age 7 and 34% have profound hearing loss by age 12. There is evidence that **vestibular** function, or balance, is abnormal in some Alström Syndrome patients.

Because hearing loss develops gradually and the onset is **post lingual**,

children typically do not experience speech problems often associated with deafness.

For an ear to work properly, the middle ear must be kept full of air. The **Eustachian tube** connects the middle ear to the back of the throat to help to equalize pressure. If the Eustachian tube becomes blocked, air cannot enter the middle ear. The cells lining the middle ear begin to produce a runny fluid that can get thicker as it fills the space. With fluid blocking the middle ear, less sound is able to pass through to the inner ear.

Although colds and ear infections are common in all children, Alström children, beginning in infancy, suffer from a higher than normal number of middle ear infections (**otitis media**) and post-infection fluid retention. Children with Alström Syndrome seem to be highly susceptible to **glue ear**. Although not proven, it has been suggested that they may have smaller Eustachian tubes, produce thicker mucus, or perhaps have a poorly functioning Eustachian tube. In any case, the presence of glue ear blocking sound transmission through the middle ear only serves to compound the existing problem of hearing impairment. As the children grow older, otitis media and glue ear tend to improve in some individuals.

### *Signs and Symptoms:*

- Difficulty discerning spoken words or asking you to speak louder.
- Difficulty talking over the phone.
- Turning a TV or radio too loud.
- Missing some words or whole phrases while in the classroom setting.
- Difficulty distinguishing female and children's voices.
- Ceasing to hear familiar sounds: birds' singing, foliage rustle, quiet music etc.
- Difficulty hearing telephone or doorbell.
- Difficulty hearing out of doors.



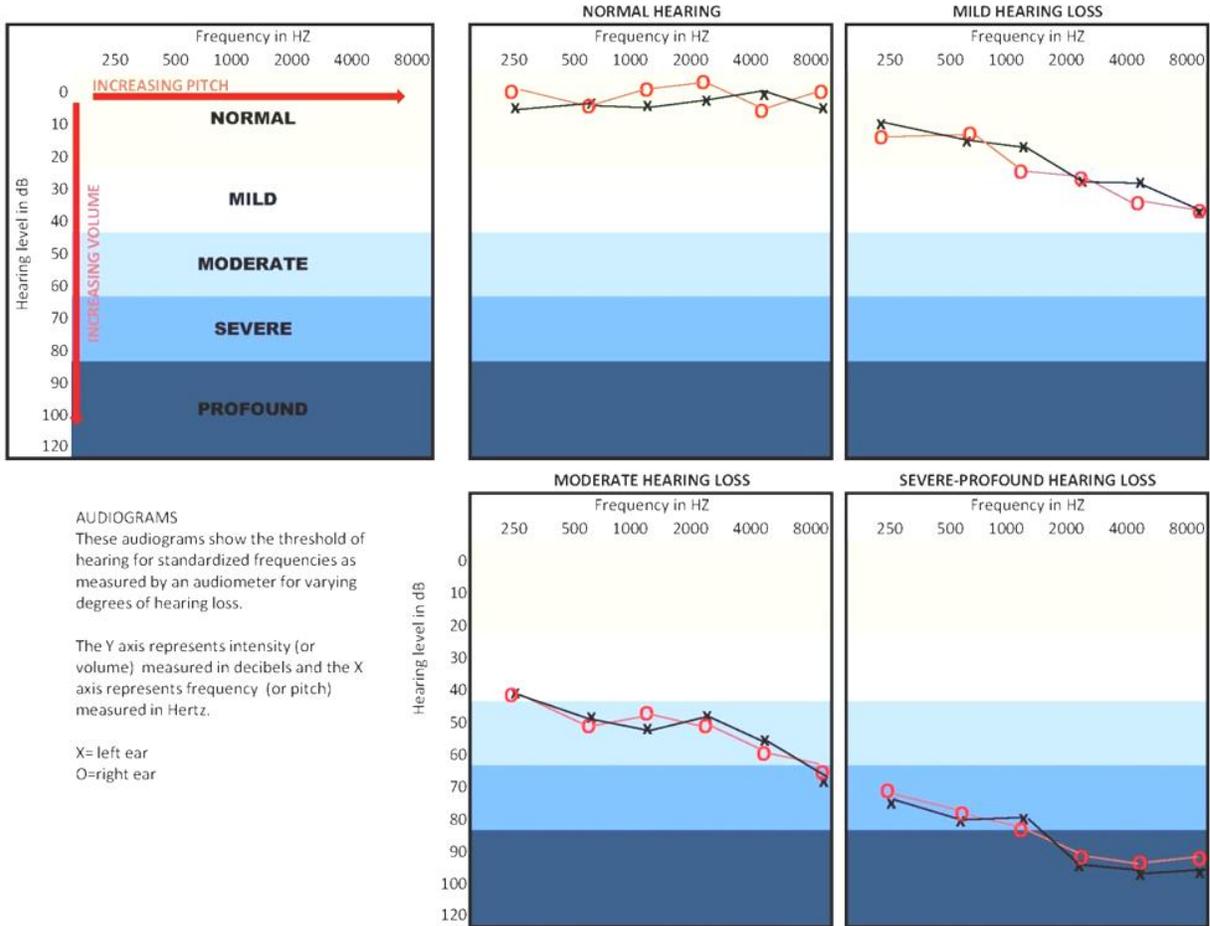
**Audiograms** typical in Alström Syndrome at pages. The audiogram has a downward sloping configuration, indicating symmetric deficits in both left and right ears. There is usually only a mild loss in the low frequencies with a mild-to moderate loss in the high frequencies both of which progress with age. Because presence and degree of hearing impairment is variable, if Alström Syndrome is strongly suspected, a normal audiogram should not rule out the diagnosis.

### *Detection and Diagnosis*

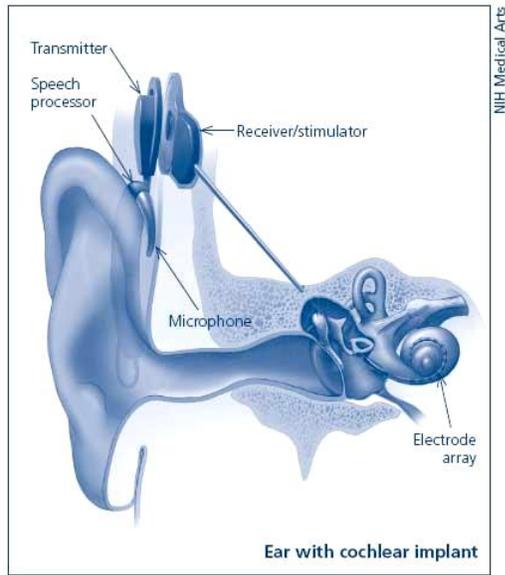
Even before hearing impairment is suspected, your child should be evaluated by an audiologist. **Pure tone audiometry** can determine the threshold at which different **frequencies** are discerned and evaluate hearing acuity.

Hearing is significantly impaired when loss exceeds 25 dB. Individuals with greater than 80 dB loss are profoundly deaf. progressive ages can be seen on the following

## Audiograms



**LEGEND:** Across the top are frequency numbers ranging from 125 Hz (a very low tone) to 8,000 Hz (a very high tone), while the series of decibel (dB) numbers along the left side represent how loud sound must be in order to be heard by the patient at each frequency. Marks near the top of the graph indicate better hearing and marks near the bottom of the graph indicate poorer hearing. Normal conversation usually occurs at approximately 55 dB.



NIH Medical Arts

## ***Treatment***

**Cochlear implants** have been successful in a number of people with Alström Syndrome. An implant consists of a microphone, a speech processor, a transmitter and receiver/stimulator, which receive signals from the speech processor and convert them into electric impulses and send them to different regions of the auditory nerve. An implant does not restore normal hearing, but it can give a deaf person a useful representation of sounds in the environment and help him or her to understand speech. A cochlear implant is very different from a hearing aid. Hearing aids amplify sounds so they may be detected by

damaged ears. Cochlear implants bypass damaged portions of the ear and directly stimulate the auditory nerve. Signals generated by the implant are sent by way of the auditory nerve to the brain, which recognizes the signals as sound. Hearing through a cochlear implant is different from normal hearing and takes time to learn or relearn. However, it allows many people to recognize warning signals, understand other sounds in the environment, and enjoy a conversation in person or by telephone.

## ***Recommendations***

Onset of hearing impairment in Alström patients can begin as early as 1.5 years with a median onset age of 9. Children with Alström Syndrome should have a routine hearing evaluation yearly. It is important to identify hearing deficits early and to make teachers aware of the hearing problems as they develop.

In Alström Syndrome, glue ear and other middle ear infections can last well into the early teen years and require constant medical care. Infections should be quickly treated to avoid compounding the hearing deficit. Many Alström children seem to have significant improvement in their glue ear after the insertion of **myringotomy tubes** or grommets. The tubes usually remain in place for six to nine months and then will fall out. If the fluid build-up recurs, another operation may be necessary to re-insert tubes. Some parents have found that cutting down on dairy products such as milk, cream and cheese has helped in reducing the production of mucus.

Most Alström Syndrome patients report significant improvement in hearing with the use of bilateral hearing aids such as **BTE**, **ITE** or **digital** aids. Digital hearing aids are the easiest to use because they adjust volume automatically. They are recommended for providing the best conditions for a child to hear and learn in the school setting.

## *Frequently Asked Questions*

### ***FAQ: Can hearing aids help?***

Significant improvement with the use of hearing aids is reported in 94% of children who use aids. However, hearing aids will not restore your child's hearing to completely normal levels. Follow the audiologist's suggestions and have reasonable expectations about what a hearing aid can and cannot do.

### ***FAQ: Do Alström Syndrome children go completely deaf?***

Generally not, although some people with Alström Syndrome become profoundly deaf, almost all retain some degree of hearing that enables them to function with use of bilateral hearing aids.

### ***FAQ: How do I find information about the new digital aids?***

Check the web pages from any of the digital manufacturers for more information. Look specifically for information on "power digitals." The best advice is to schedule an appointment with an audiologist and discuss these issues.

### ***FAQ: Are there any new technologies to help my child hear better in the classroom setting?***

Your audiologist might suggest the use of hearing aids with directional microphones, or hearing loop systems. Several companies like ComTeck, Easy Listener by Phonic Ear, and Danalogic Inc. have this kind of a circuit available. New companies and technologies are being developed at a rapid rate.

### ***FAQ: My child seems to have more sensitive hearing at certain pitches. Is that unusual?***

Some children perceive increased hearing sensitivity at lower frequencies.

## SIDEBAR DEFINITIONS ~ HEARING

**Audiogram** - The graphic record drawn from the results of hearing tests with an audiometer.

**Auditory nerve** - The “transmission line” from the hair cells in the cochlea of the inner ear to the brain.

**BTE (behind the ear)** - A hearing aid worn on the outside behind the ear - or a “conventional” hearing aid.

**Conductive hearing loss** - Occurs in the external auditory canal or in the bones of the middle ear.

**Bilateral** - Two-sided or affecting both sides.

**Cochlea** - Snail shaped structure, lined with millions of tiny hairs that are the sensory organ of hearing responsible for transmitting sound to the auditory nerve.

**Cochlear implant** - Small, complex electronic device that can help to provide a sense of sound to a person who is profoundly deaf or severely hard-of-hearing. The implant consists of an external portion that sits behind the ear and a second portion that is surgically placed under the skin.

**Digital aids** - Hearing instruments with digital circuits that can be precisely programmed to match the patient’s individual hearing loss at each specific frequency and offer improved clarity of sound, less circuit and background noise, and faster processing of sound.

**Eardrum (tympanic membrane)** - A small piece of tissue at the end of the ear canal that vibrates in response to sound waves or pressure changes.

**Eustachian tube** - The tube that equalizes pressure by connecting the middle ear, behind the eardrum, to the back of the throat.

**Frequency** - Cycles of sound waves per second that determine the pitch of a sound.

**Glue ear** - A thick, sticky fluid forming in the middle ear common among children that is often associated with middle ear infections.

**ITE (in-the-ear)** - Hearing aid placed within the ear.

**Myringotomy tubes** - Tiny plastic tubes that are placed in the eardrum during surgery allowing air to circulate in the middle ear and preventing fluid from building up.

**Ossicles** - The three tiny bones in the middle ear (malleus, incus, and stapes).

**Otitis media** - An infection of the middle ear, behind the ear drum that causes earache, swelling and redness.

**Pinna** - The flap of cartilage on both sides of the head that localizes the source of sound.

**Post lingual** - Occurring after child has learned language skills.

**Pure tone audiometry** - A test to measure the softest sounds that can be heard over a range of volumes (hearing threshold in decibels) at a series of increasing pitches (frequencies measured in Hertz).

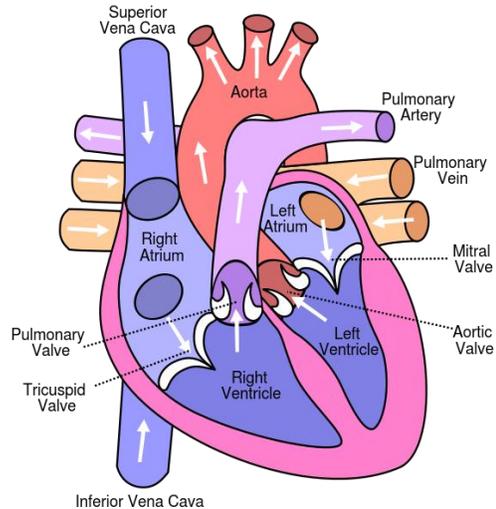
**Sensorineural hearing loss** - Can be a loss of hearing due to a lesion in the cochlea (*sensory*) or in the nerve itself (*neural*).

**Vestibular** - The organ of balance in the inner ear that transmits information about movement and position in space to the brain

## CHAPTER ELEVEN ~ CARDIO/PULMONARY

### Overview of the Heart

The heart is comprised of four chambers that act basically as a pump made of muscle. **Valves** connect the two lower chambers (**ventricles**) and two upper chambers (**atria**) to each other. The **pericardium** covers the heart and is designed to protect it. The heart pumps oxygen and oxygen-rich blood to all of the other organs in the body. The force producing this flow of blood comes from the contraction of the ventricles. The heart also has a complex electrical system, centered in the **sinus node**, which is responsible for synchronizing the contractions of the chambers of the heart.



Cardiomyopathy is a condition, often found in Alström Syndrome, that affects the heart muscle. There are different forms of cardiomyopathy. In “**dilated cardiomyopathy**” (DCM), the damaged heart muscle stretches and weakens, producing an enlarged or dilated heart that pumps poorly and cannot deliver the normal quantities of blood to the tissues and organs. Also, in a dilated heart, the cardiac valves may leak, resulting in a heart murmur. As the disease progresses, DCM can eventually affect both the left and right ventricles.

**Restrictive cardiomyopathy (RCM)**, the rarest form of cardiomyopathy, gets its name from the way it restricts the heart from stretching properly. It is a condition in which the walls of the ventricles are abnormally rigid and lack the flexibility to expand as they fill with blood. The rhythm and pumping action of the ventricles (**systolic** function) may be normal, but the ability of the heart to fill with blood (**diastolic** function) is abnormal. As a consequence of the inadequate heart function in either form of cardiomyopathy, DCM or RCM, a serious and potentially life-threatening condition known as **congestive heart failure** (CHF) can occur, because a reduced amount of blood leaves the heart and blood returning to the heart gets “backed up.” Fluid can also seep into surrounding tissues, causing **edema**.

### The Heart in Alström Syndrome

Alström Syndrome is unique in that there can be either DCM, RCM, or both conditions. Cardiomyopathy is now recognized as one of the cardinal features of Alström Syndrome. It occurs in approximately two-thirds of patients. Of those, the majority develop infantile dilated cardiomyopathy and CHF during their first year. This life-threatening episode of infantile heart failure can be one of the first symptoms to be noticed in babies, even before nystagmus or any problem with the eyes are observed. In some infants, the heart often appears to recover

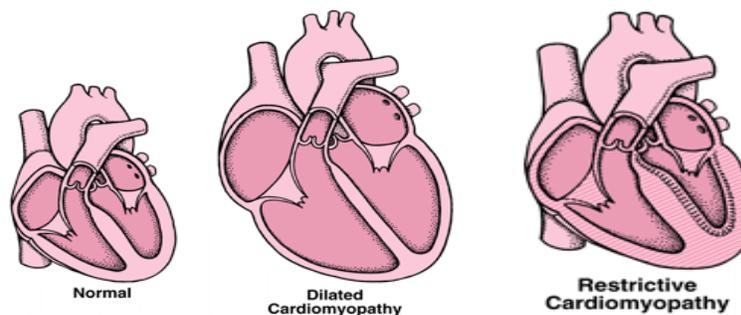
relatively quickly when treated with medications. Of those infants who had cardiomyopathy in infancy, over two-thirds report apparent recovery by the age of three years. Often these children can continue to have normal or “low normal” heart function for many years. It is now known, however, that a second episode of cardiomyopathy may ensue during childhood, adolescence, or adulthood and *those who experienced cardiomyopathy as infants do remain at risk for recurrence*. Patients with no previous history of cardiac dysfunction in infancy can also develop cardiomyopathy at any time. The condition may remain stable for many years or may deteriorate rapidly with resultant severe CHF. About one-third of patients have not reported any signs of cardiac problems, but the possibility remains that cardiomyopathy will develop in the future for these patients.

### ***Signs and Symptoms of Cardiomyopathy***

The symptoms of cardiomyopathy may develop slowly or they can occur very suddenly. At first, there may be only subtle signs. For example, parents of infants may observe decreased feeding or sweating with feeding, whereas in older children the only manifestation may be an inability to keep up with normal activities. Unusual fatigue may be noticed because the heart is weak and cannot pump an adequate supply of blood to the muscles. For instance, shortness of breath may occur with exertion (**dyspnea**.) As the condition worsens, dyspnea becomes more pronounced and may even occur while lying down or sleeping (**orthopnea**). Another sign may be edema, causing swelling in the feet, ankles and abdomen, swollen or distended neck veins, rapid weight gain, or a chronic cough.

In addition, when the heart does not function properly, **arrhythmias** causing extra heart beats **PVC’s**, dizziness, or **palpitations**, are common. Some rhythm disorders such as **atrial fibrillation/flutter** may result in deterioration over time.

### **An Illustration of Cardiomyopathy**



*LEGEND: Illustration of a dilated heart (as seen in DCM), and a heart with restrictive cardiomyopathy (RCM) compared to a normal heart (left). Adapted from Merck Manual, second edition*

### Symptoms in infants:

- Poor feeding, inability to eat
- Breathlessness
- Sweating with feeding

### Symptoms in children, adolescents and adults:

- Shortness of breath (dyspnea)
- Decreased activity tolerance, difficulty exercising
- Sudden weight gain of over 3 pounds (~1.4 kg) in a one week period
- Worsening cough
- Orthopnea or with an inability to breathe accompanied by panic when lying down flat
- Edema, swelling of feet or abdomen
- Unexplained fatigue
- Prolonged heart palpitations, skipped beats, or PVC's (pre-ventricular contraction)
- Sweating
- Persistent nausea, vomiting or inability to eat
- Spells of sudden dizziness or lightheadedness

### *Detection and Diagnosis*

It is important to note that because of the complicated clinical picture presented in Alström Syndrome, there is a risk of overlooking the symptoms of early CHF. In obese children, edema can be difficult to notice or totally undetectable. Furthermore, the effects of lack of exercise due to obesity and vision impairment can mask the shortness of breath and fatigue that may be symptomatic of CHF. Since many patients have respiratory problems, orthopnea and dyspnea may also be easily overlooked. It is important to consider the heart when respiratory problems occur.

Diagnosis of cardiomyopathy is based upon a number of tests that measure the functioning of the heart. The cardiologist may request a chest x-ray, by which the size of the heart can be estimated. **Electrocardiography (ECG/EKG)** is used to assess the electrical conduction system of the heart. An **echocardiogram (echo)** will likely also be required to determine the size or degree of enlargement of the heart and the pumping function by a number of methods including **fractional shortening** or **ejection fraction (EF.)** Occasionally, **heart catheterization** and heart muscle **biopsy** or **electrophysiology studies** may also be used as diagnostic aids.



Matthew had no sign of CHF as an infant, but developed sudden symptoms of heart failure at age 16.



Cheryl had CHF at five weeks of age. She had a complete recovery. At 22 years some signs of CHF reoccurred.



Chelsea had CHF at 4 weeks of age and had a full recovery until age 12 when symptoms appeared again and continued to worsen.



Samantha developed CHF at age 3 weeks, never fully recovered, but her symptoms were managed for thirteen years with medications.



Daniela is 46 years old and has never had any sign of cardiac failure.

### ***Treatment***

At present, there is no “cure” for the cardiomyopathy in Alström Syndrome and the damage to the heart cannot be fully reversed. The symptoms can be treated, but there can be a wide spectrum of outcomes. The goal of any treatment regimen is to reduce further damage to the heart and to help it pump as efficiently as possible and control the symptoms. With Alström Syndrome especially, great care must be taken to monitor the effects of cardiac medication on other vulnerable organ systems, such as the liver and kidneys. You should always inform your pharmacist and all specialists of any other medications that your child is taking because some drugs can adversely interact with each other. Medications are sometimes used to ease the workloads of the heart and to keep a regular heart rhythm.

Medicines used to treat CHF can include:

- **ACE inhibitors** ACE (Angiotensin Converting Enzyme) inhibitor drugs are proven to prevent progressive enlargement of the heart and counteract fluid retention. These drugs, also used to treat high blood pressure, have become the mainstay treatment for CHF. They facilitate the flow of blood from the heart by *decreasing* production of a hormone that constricts the arteries and raises blood pressure (Angiotensin II), and *decreasing* production of a hormone that causes the body to retain sodium and water (aldosterone). Examples of ACE inhibitors include: enalapril maleate (Vasotec), lisinopril (Prinivil, Zestril), captopril (Capoten) and others. ACE inhibitors can cause an irritating cough in about 20 percent of patients. Other side effects can include worsening kidney function. Therefore, careful monitoring with blood tests is essential.
- **Beta-blockers** are designed to regulate the hormone adrenalin. They can improve heart function, slow the heart rate, and reduce the work-load of the heart and may help prevent some heart rhythm problems. Examples of beta-blockers are: lopressor, toprol, metropolol, atenolol, bisoprolol, carvedilol (Coreg). Beta blockers may not be appropriate for children with asthma or some electrical problems with the heart.
- **Calcium channel blocker (or calcium blocker)** is a drug used to relax the blood vessel and heart muscle, causing pressure inside blood vessels to drop. It also can regulate heart rhythm.
- **Digoxin** is commonly used to control the heart rate. This drug, also referred to as *digitalis*, increases the strength of the heart muscle contractions, reduces heart failure symptoms, and improves the ability to function with the condition.
- **Diuretics** counteract fluid retention. They are occasionally referred to as “water tablets” because they rid the body of excess fluid by increasing urine production. Commonly prescribed diuretics include: bumetanide (Bumex), furosemide (Lasix) and others. The drugs also decrease fluid in the lungs, making it easier to breathe.
- **Warfarin** (Coumadin) is an anticoagulant drug that is used to prevent the formation of blood clots. When a patient is taking warfarin, the blood clotting time must be carefully monitored, and often blood tests must be done regularly. For this reason, physicians may elect not to prescribe this drug for very young children.
- **A-II (Angiotensin II) antagonists** – Losartan (Cozaar), irbesartan (Avapro), and valsartan (Diovan) work similarly to ACE inhibitors but are somewhat less likely to cause a persistent cough. Studies are in progress to evaluate whether they are as effective as ACE inhibitors.

## ***Recommendations***

Given the sudden onset and life threatening nature of CHF due to DCM in infancy, the increasing evidence of relapse after apparent recovery, and the high incidence of new RCM in older children, **ALL patients should have routine cardiac monitoring with evaluation by EKG and echocardiography every six months to one year, even if the child has been symptom-free.**

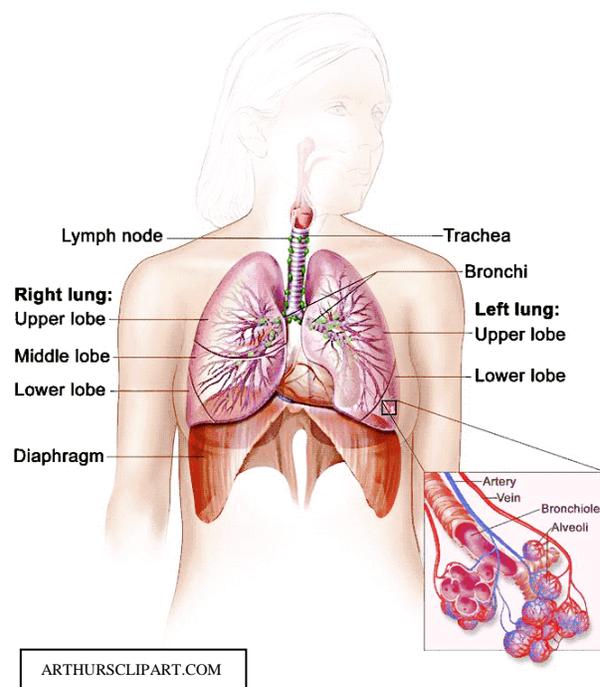
Always advise your physician that cardiomyopathy is a common feature of Alström Syndrome and report any sudden onset of symptoms.

If your child has CHF, important lifestyle changes can help relieve symptoms and prevent the condition from worsening. Restrict sodium (salt) to less than 3,000 milligrams (mg) daily. Monitor weight daily and notify your doctor if there is a rapid weight gain in a one-week period. It may indicate retention of fluid and medications may need adjusting. Engage in regular *moderate* cardiovascular exercise. Most importantly, if there is an obvious change in status or symptoms, see your cardiologist immediately. Do not wait!

## ***PULMONARY AND RESPIRATORY***

### ***Overview***

The lungs are comprised of millions of tiny airways. Oxygen is inhaled through the nose and mouth, down the **trachea** (windpipe,) through the two tubes called **bronchi** that branch off from the trachea, and then into the lungs. Within the lungs, the bronchial tubes branch into thousands of smaller, thinner tubes called bronchioles. These tubes end in bunches of tiny round flexible air sacs called **alveoli**. When inhaling, each sac fills up with air like a small balloon. Small blood vessels called **capillaries** run through the walls of the air sacs. When air reaches the alveoli, the oxygen in the air passes through the air sac walls into the blood in the capillaries and carbon dioxide is pulled out of the blood and sent back up the airway to be exhaled. The airways are surrounded by small bundles of muscles to help direct the flow of air. Sometimes the lining



Cheryl, as a pre-teen and young teenager, often ended up with "chest infections" which I knew were pneumonia. She has always had a rattling cough, and I knew the telltale signs of it very quickly worsening and turning into a high fever, nausea, vomiting, difficulty breathing. I had one doctor (her lung specialist actually) who disagreed with me that it was pneumonia and wanted to try her on the regular asthma meds (ventolin AND steroids) rather than antibiotic treatment and I hesitantly agreed to follow his treatment plan. Needless to say, it did NOT work and she ended up very, very sick, requiring antibiotics. We stopped seeing that specialist shortly afterwards.

I must back up my story a little bit. Whenever she began with these telltale signs, I would immediately contact her regular pediatrician who would see her. He would do a chest X-ray (which was mostly always inconclusive due to her obesity and the X-rays not penetrating well enough to get good clear pictures AND the fact that she could never take a large enough intake breath to fully expand her lungs - a fact that is very common with our children). Despite the ambiguity of the X-ray, the doctor could frequently hear "crackles" in her lung(s) which is usually a good sign of pneumonia, and he would prescribe antibiotics. The prescription was typically longer than the 7 or 10 day course. While on antibiotics, she would also use ventolin to help expand her airways. Steroids never did work on Cheryl, and only served to make her very cranky and irritable - understandably so. It has now gotten to the point that whenever I feel that things are starting to act up, I now immediately begin ventolin puffers. If this does not help within the first day or two, I contact her doctor who immediately prescribes an antibiotic to prevent pneumonia. Over the course of my experience with lung problems with Cheryl, and my knowledge and past experience of working with other Moms/Dads around the world, it is crucial to "follow your sixth sense" when it comes to your child's medical issues.

of the alveoli and the capillaries around them become damaged, leading to inflammation in the tissue wall between the air sacs of the lung. Normally, the tissue layer is very thin with a thickness of just a few cells. The cells in this layer then begin producing scar tissue in response to this damage. When alveoli are damaged, they can collapse and lose their ability to receive oxygen. Damaged capillaries leak fluid and cause edema in the lungs.

In chronic bronchitis, the lining of the airways is constantly irritated and inflamed, which causes the lining to thicken. Thick mucus can form in the airways, making it hard to breathe. If inflammation continues, the lungs, like any other parts of the body, become scarred as they try to heal themselves. When scarring occurs, much of the tissue in the lungs is replaced by scar tissue (**fibrosis**) that can interfere with the exchange of oxygen and carbon dioxide. When the lungs are impaired, more effort is needed to pump blood through them. Over time, the small air sacs (alveoli), together with their small vessels (capillaries), in the lungs can be damaged. Narrowing and constriction of the pulmonary arteries can occur as a result of low blood oxygen levels.

### ***Respiratory Problems in Alström Syndrome***

One of the most frequent complaints in the young child with Alström Syndrome is chronic respiratory illness, particularly in the first decade, but often persisting into adulthood. In Alström Syndrome both **restrictive lung disease**, characterized by reduced volume of air that is inhaled, and **obstructive lung disease**, characterized by an inability to fully exhale air from the lung, have been observed. The airways can be chronically inflamed, swollen, irritated, and hyper-reactive. At the same time, the bronchi swell, narrowing the airway, also producing thick mucus, further clogging the airways. Although not well understood, there have been some observations that the lungs of patients with Alström Syndrome are smaller

than normal. The symptoms range from frequent colds and flu, to asthma, chronic bronchitis, chronic sinusitis, and frequent bouts of pneumonia. Some of the older patients have received a diagnosis of **interstitial lung disease**, **COPD** (chronic obstructive pulmonary disease,) **bronchiectasis**, or **ARDS** (acute respiratory distress syndrome.)

Although the reason for this is not completely understood, patients with Alström Syndrome often have difficulty performing classic lung function testing, such as **spirometry**. It is often difficult for them to achieve a full inhaled breath, or to exhale fully.

Further study is required, because it is not clear whether the pulmonary problems in Alström Syndrome are related to deficits in the function of the **cilia** or to a scarring known as fibrosis, or to both.

## **HYPOXIA WARNING !!**

### **LOW OXYGEN SATURATION**

For patients with Alström Syndrome admitted to the hospital or outpatient facilities, even for routine minor surgery or infection, it is vitally important that medical and nursing staff be aware that hypoxia (dangerously low blood oxygen levels) can occur very rapidly in these patients. In some patients this has led to life-threatening heart/lung problems because of the reduced reserve capacity of their cardio-respiratory systems. Please be aware of the risk, and use all precautions for monitoring heart function and oxygen saturation until the patient is fully recovered and ambulatory.

Patients with Alström Syndrome may also be more prone to pulmonary edema, particularly if cardiomyopathy is present.

### ***Detection and Diagnosis***

The chest X-ray is usually the first test most patients undergo to evaluate lung problems. X-ray beams cannot pass as easily through inflammation and scarred tissue as through normal tissue, so scarring will look more "white" on an X-ray than normal tissue. The most common abnormal finding on the chest X-ray in patients with pulmonary fibrosis is a netlike appearance of straight or curved lines with or without small nodules superimposed on the lines. These abnormalities predominantly affect the lower lungs.

However, the presence of lung disease can be easily missed on a routine chest x-ray. Pulmonary fibrosis may look just like pneumonia and many other lung diseases. The extent of changes on the chest X-ray does not always correlate with the actual severity of the disease. As a result, some patients may require a computed axial tomography (CAT or CT) scan of the chest as well.

Pulmonary function tests (PFTs) measure how well the lungs work. Spirometry is usually the first test given. This measures how much air a patient can blow out in one second with complete exhalation. This value will be decreased if the lungs have a significant amount of fibrosis.

If pulmonary function tests or chest x-rays are abnormal and characteristic of interstitial lung disease, a biopsy or small sample of lung tissue is sometimes needed in order to make the diagnosis with certainty. This is often done by using a flexible fiber optic bronchoscope to do a procedure called **bronchoscopy**. With the patient sedated, a flexible scope is passed through the mouth and into the lungs. Several small biopsies are taken from the lung tissue and processed and examined under a microscope.

### ***Signs and Symptoms***

Symptoms usually develop gradually over months or years, and this chronic nature is what distinguishes pulmonary fibrosis in general from diseases with similar symptoms such as the common cold or flu.

On examination, fine "crackles" like the sound of Velcro may be heard in the lungs when the patient is inhaling. These crackles are usually heard in the lower lobes of both lungs. In addition, many patients may have shortness of breath but completely normal examinations. Pulmonary problems can be confused with congestive heart failure, which is another common condition in Alström Syndrome.

### ***Monitoring Recommendations***

Pulmonary function tests are a main tool used to diagnose lung problems. It is recommended that children with Alström Syndrome schedule an annual pulmonary evaluation. The easiest test is spirometry, or anemography. The child takes a deep breath and exhales as fast as possible. The test provides a graphic measurement of breathing, including breathing movements and breathing capacity. *It should be noted that some patients with Alström Syndrome have difficulties with performing traditional spirometry.*



Other tests that may be recommended:

- Chest X-ray
- DCLO - A diffusion capacity lung test is a specialized test that evaluates the thin membranes in the alveoli that allow for oxygen and carbon dioxide to be exchanged. The test requires that you inhale a small amount of carbon monoxide that is then measured in the red blood cells. A diminished DCLO may be the first test that picks up an indication of interstitial lung disease, when every other test is normal.
- FVC1/FVC ratio: FVC means forced vital capacity. It indicates the volume change from a full inhale to a full exhale. The results can distinguish between obstructive and restrictive lung disease.

Cigarette smoking has been associated with more progressive disease. No person with Alström Syndrome should ever smoke or be around second-hand smoke. Long-term exposure to other lung irritants, such as air pollution, chemical fumes, or dust, may also contribute to the lung dysfunction in Alström Syndrome.



B.J., after her successful heart transplant.

### ***Treatment***

Once scar tissue is laid down in the lung, no surgery or medication can remove or dissolve the scarring or reverse the damage to the lungs. It becomes a permanent part of the lung. There is no evidence that any treatment improves survival or the quality of life for patients with pulmonary fibrosis. Therefore, the goal of current treatments is to prevent the formation of this scar tissue in the first place.

## *Frequently Asked Questions*

### ***FAQ: If my child had cardiomyopathy as an infant, will there be a recurrence?***

There is significant risk of a recurring episode of cardiac dysfunction years after infantile cardiomyopathy. Regular monitoring should be continued, even after an apparent resolution of infantile DCM.

### ***FAQ: When should I have my child checked for signs of cardiomyopathy?***

Cardiac monitoring should DEFINITELY be an integral part of management since early recognition of cardiomyopathy and appropriate treatment can be crucial. Cardiac evaluation should be part of your child's annual physical examination, and if symptoms are present, consult your cardiologist immediately.

### ***FAQ: If my child has cardiomyopathy, what about exercise?***

Studies have shown moderate exercise helps the heart pump more efficiently, reducing the demands on the heart muscle, as long as it does not produce an increase in symptoms. Children with Alström Syndrome are usually able to participate in many forms of exercise including: swimming, dancing, cycling and walking.

### ***FAQ: What benefit would a pacemaker be?***

A pacemaker is a small electronic device, implanted in the chest, consisting of a battery and a small computer that regulates the rate of the heartbeat if the electrical system is not functioning properly. A pacemaker may increase heart function in some people by stabilizing the timing of the pumping of the heart. A pacemaker is not appropriate for every patient with Alström Syndrome, and a thorough evaluation by a physician will be necessary.

### ***FAQ: Is heart transplantation ever considered for patients with Alström Syndrome?***

Heart transplantation in Alström Syndrome patients has been successfully attempted a few times to date. There is potential for complications from use of anti-rejection drugs in patients with diabetes, kidney and liver problems. Although medical techniques and procedures have advanced in past years, this option is complicated by high pressure in the lungs, called pulmonary pressures. The decision for heart transplantation needs to be carefully considered, through discussion with the team of physicians treating your child.

***FAQ: How do Ventricular Assist Systems work?***

Ventricular Assist Systems, such as Heart Ware<sup>®</sup> is designed to help a patient's weakened heart pump blood by removing blood from the left side of the heart and pumping it into the aorta. The pump is placed inside the patient's chest, with a cable connecting the implanted pump to a battery/controller in a carrying case worn either around the patient's waist or over the shoulder.

***FAQ: What complications can develop from poor pulmonary function?***

Weakened lung function can cause dizziness, fatigue, fluid retention, and recurrent infections.

***FAQ: My child needs minor surgery and I am very worried about the low oxygenation warning. Should we avoid the surgery?***

You need to weigh the pros and cons. Is the surgery essential for the well-being of your child? If that is the case, you should make every effort to alert your child's surgeon and anesthesiologist to the risk of sudden low oxygenation and pulmonary edema.

***FAQ: Does the pulmonary disease progress?***

Yes, lung damage can progress in some patients to the point where the lungs cannot oxygenate the blood properly, which can then cause other organ systems to fail.

***FAQ: What do cilia have to do with lungs?***

The cilia in the cells of the respiratory tract sweep the mucous (which traps dust particles, bacteria and viruses) up and out of the respiratory passages to the pharynx where it is swallowed or coughed out. It is not yet clear how defects in cilia result in the fibrosis seen in so many of the organs in Alström Syndrome.

***FAQ: Can lung problems be treated with medication?***

Yes, in some cases drugs include corticosteroids and anti-inflammatory medicines.

***FAQ: What should I do when my doctor does not believe that lung problems are a part of Alström Syndrome?***

There are several medical papers that have documented the lung problems in Alström Syndrome. Contact the ASI office for copies of these papers.

***FAQ: How do we deal with friends and relatives who are heavy smokers?***

You should feel very comfortable and justified to state that second hand smoke and other irritants are significant risks for anyone with Alström Syndrome. Firmly insist that they smoke elsewhere.

## SIDEBAR DEFINITIONS ~ CARDIO/PULMONARY

**Acute Respiratory Distress Syndrome (ARDS)** - An acute, severe injury to most or all of both lungs.

**Alveoli** - Small air sacs in the lung.

**Arrhythmias** - A disruption of the heart's normal electrical impulses causing an abnormal or fluctuating heart rhythm.

**Atria** - The two upper chambers of the heart in which blood collects before being passed to the ventricles.

**Atrial fibrillation** - An abnormal rhythm, common in patients with DCM and often associated with deterioration of the condition.

**Bronchi** - The large air tubes leading from the trachea to the lungs that convey air to and from the lungs.

**Bronchiectasis** - A condition in which damage to the airways causes them to widen and become flabby and scarred.

**Bronchoscopy** – A procedure where an instrument (bronchoscope) is inserted through the nose or mouth that allows a physician to look for abnormalities and/or take tissue samples from the lungs.

**Capillaries** - Very small, thin vessels that connect arteries and veins.

**Cilia** - Tiny hair-like structures found on the lung lining, they filter out dust and propel mucus up and out of the lung with a synchronized wave-like motion.

**Congestive heart failure (CHF)** - The inability of the heart to efficiently pump out all the blood that comes to it which results in an accumulation of fluid in various parts of the body.

**COPD** (chronic obstructive pulmonary disease) - Progressive lung disease that makes it hard to breathe.

**Diastolic** - Refers to the time when the heart is in a period of relaxation and dilatation (expansion.)

**Dilated cardiomyopathy (DCM)** - An abnormal enlargement and weakening of the heart muscle.

**Dyspnea** - An unpleasant sensation of shortness of breath.

**Echocardiogram (echo)** - A non-invasive method to evaluate the size and functioning of the valves and chambers of the heart by using sound waves.

**Edema** - Fluid buildup at the ankles, belly or small of the back, caused by the weak pumping action of the heart.

**Ejection fraction** - A useful measure of left ventricular performance (pumping efficiency,) the normal range is 63-77% for males and 55-75% for females.

**Electrocardiogram (ECG/EKG)** - A routine test that records a picture of the heartbeat by measuring its electrical changes on a graph.

**Electrophysiology studies** - A catheter based diagnostic test to assess the electrical system of the heart.

**Fibrosis** - The formation of excess fibrous, or scar tissue, usually because of injury or long-term inflammation.

**Heart biopsy** – The removal of a small sample of the heart muscle using a catheter and a very small special cutting tool, which is guided to the heart.

**Heart catheterization** - A thin plastic tube or catheter guided through an artery or vein in the arm or leg and into the heart that measures blood pressure and how much oxygen is in the blood while also providing other information about the pumping ability of the heart muscle.

**Hypertrophic cardiomyopathy** - An abnormal growth of the heart muscle fibers making the heart thickened and stiff.

**Interstitial lung disease** - A group of lung diseases that affect the interstitium (the tissue and air space around the air sacs.)

**Obstructive lung disease** - The inability to fully expel air from the lungs that can be caused by fibrosis.

**Orthopnea** - A very unpleasant, panicky feeling of breathlessness and respiratory discomfort that occurs while the patient is lying down, compelling him to sit or stand up.

**Palpitations** - Abnormal heart rhythm (arrhythmia) that causes the heart to beat too quickly (tachycardia) or too slowly (bradycardia.)

**Pericardium** - The sac that covers the heart and protects it.

**Restrictive lung disease** - Characterized by reduced gas transfer and de-saturation after exercise, caused by inflammation or scarring of the lung tissue (interstitial lung disease.)

**Shortening fraction (Fractional shortening)** – A slightly different way of measuring left ventricle performance, the shortening fraction measures the change in the diameter of the left ventricle between the contracted and relaxed states.

**Sinus node** - Called the SA (sinoatrial) node, it is a small nodule of tissue that sits on top of the right atrium and controls the frequency at which the heart beats by conveying an electrical signal to another small nodule, the AV node, spreading the signal into the ventricles and causing them to contract.

**Spirometry** - One of a series of pulmonary function tests that measures air volume and flow rate.

**Systolic** - Refers to the contraction of the heart muscle and comes from the Greek *systole* meaning "a drawing together or a contraction."

**Trachea** - The tube that connects the nose and mouth to the lungs.

**Valves** - Connect the four chambers in the heart and regulate the flow of blood within and in and out of the heart.

**Ventricles** - The lower chambers in the heart that serve to pump blood through the arteries to other parts of the body.

**Ventricular ectopics or PVC's** – Occasional, sometimes annoying, single extra heartbeats that usually require no treatment.

**Ventricular tachycardia** - Rapid heartbeats often associated with a fall in blood pressure, symptoms of dizziness, breathlessness or fainting.

## CHAPTER TWELVE ~ HYPERTENSION

### Overview

The body has two loops of circulation – the systemic circulation that delivers oxygen and nutrients throughout the body, and the pulmonary system that pumps from the heart to the lungs. The right side of the heart receives the oxygen-depleted blood as it returns from the body and pumps this blood from the right side of the heart through the **pulmonary arteries** into the lungs. In the lungs, carbon dioxide is removed from the blood and oxygen is added. Blood contains a pigment called hemoglobin that carries the oxygen. The blood leaves the lungs and enters the left side of the heart, where the oxygen-rich blood is pumped to the body again.

Normally, the pressure in the pulmonary arteries is lower than **systemic blood pressure**, because less pressure is required for the right side of the heart to push the blood through the lungs. In contrast, the left side of the heart is more muscular because it has to push blood through the entire body against a much higher pressure.

Blood pressure is the force of blood pushing against the walls of the blood vessels. Blood pressure is measured in millimeters of mercury (mmHg) and the result is given as two separate numbers, for example, 110/70. The top number refers to **systolic pressure**, the pressure created when your heart beats. The lower number refers to the **diastolic pressure**, which measures the pressure inside the vessels when the heart is at rest. Blood pressure changes throughout the day depending on activity, diet, stress level and other factors. Normal blood pressure falls within a range according to age. Blood pressure is considered high (**hypertension**) if the systolic pressure is consistently over 140 or the diastolic pressure is consistently over 90.



### ***Pulmonary Hypertension (PHT)***

PHT is high blood pressure that occurs in the ‘loop’ between the heart and the lungs. It is a different measurement altogether from systemic blood pressure. It reflects the pressure the heart must exert to pump blood from the right side of the heart through the arteries of the lungs. Having sleep apnea and/or living at high altitudes can also cause pulmonary hypertension to worsen by lowering levels of oxygen in the blood.

### ***Hypertension in Alström Syndrome***

Not all patients with Alström Syndrome have high blood pressure. However, it is more common than in the normal population of young children. It is unclear whether hypertension itself is a part of the syndrome, or if it occurs as a result of other conditions found in Alström Syndrome (**secondary hypertension**) such as scarring and fibrosis in organs such as the lungs and kidneys.

Kidneys are important in the regulation of systemic blood pressure and damaged kidneys may account for at least some of the hypertension seen in patients with Alström. As discussed in the following chapters, the kidney damage in Alström Syndrome is characterized by scarring and the narrowing of passages within the kidney, which makes it more difficult for the heart to push blood through. Thus, blood pressure is increased. Damaged kidneys also may release hormones that raise blood pressure.

Hypertension can be especially serious in Alström Syndrome because it can have detrimental effects on vulnerable organ systems. For example, poorly controlled hypertension can be a major factor not only in deterioration of kidney function, but may also exert pressure on the heart. When something goes wrong with one organ or tissue in Alström Syndrome, there is often a ripple effect, creating problems for other organs or tissues.

### ***Pulmonary Hypertension (PHT) in Alström Syndrome***

Even as young children, many people with Alström Syndrome have PHT (also known as high pulmonary pressures.) There may be several reasons why this happens. Lung tissue and pulmonary blood vessel damage due to progressive fibrosis is well documented in Alström Syndrome. Pressure builds up and the heart works even harder to force the blood through. If the pressure is high enough over time, the right ventricle becomes thickened and enlarged, and right heart failure develops.

### ***Detection and Diagnosis***

Systemic blood pressure is measured using a blood pressure cuff, called a **sphygmomanometer**. A stethoscope is used to listen to the blood being pushed through the brachial artery of the arm. Once the sphygmomanometer is inflated, it cuts off the blood flow in the artery, leading to silence. As the cuff is deflated, the first sound heard denotes the systolic pressure in the artery. The diastolic pressure is measured when the silence returns.

Pulmonary blood pressure is measured in a number of ways. By listening through a stethoscope, doctors can hear certain characteristic heart sounds that occur when the right ventricle becomes strained. Chest x-rays can show the enlarged right ventricle and pulmonary arteries. The function of both the left and right ventricles is also evaluated with EKGs, echocardiography, and sometimes a **pulmonary arteriogram** or **cardiac catheterization**.

### *Signs and Symptoms*

There are usually no symptoms of systemic hypertension. Symptoms of PHT can be general fatigue and tiredness, breathing difficulty, dizziness, shortness of breath or light-headedness during activity. Fast heart rate and palpitations may also be present. As the condition progresses, there may be swelling in the ankles or legs, bluish discoloration of the lips and skin, and chest pains which may indicate the body is not circulating enough oxygen-rich blood from the lungs.

### *Monitoring Recommendations*

Children with Alström Syndrome should have their blood pressure checked at least annually if the results are normal, or every few months if the results are borderline or high. Those with PHT should also consider antibiotic therapy for significant respiratory tract infections. Getting a pneumococcal pneumonia vaccine and yearly flu vaccines is also recommended since these illnesses can be very serious in patients with Alström Syndrome. Be careful to avoid dehydration and excessive heat.

### *Treatment*

The treatment for systemic hypertension may include lifestyle, exercise and diet recommendations, such as weight loss, lowering sodium and fat intake, increasing consumption of fruits and vegetables (i.e. **DASH diet**) and increasing exercise. Additionally, there are established ways to control systemic blood pressure with medications such as Angiotensin Converting Enzyme (ACE) Inhibitors, Calcium Channel Blockers, or diuretics.

PHT is a more serious illness and will usually require separate treatment, which may include oxygen, agents to help the heart pump better, diuretics, and anticoagulants (blood thinners.) The long-term outlook for Alström patients with PHT has been poor, particularly with those who also have CHF (congestive heart failure.) New treatments coming on the market for PHT in the general population may lead to better results.

## *Frequently Asked Questions*

### ***FAQ: What does high blood pressure have to do with the kidneys?***

When there is even minor damage, the functioning of the kidney is diminished. This leads to sodium and water retention and increased blood volume, creating an increased demand on the heart.

### ***FAQ: What is the difference between systemic and pulmonary blood pressure?***

Pulmonary pressure refers to pressure in the pulmonary arteries, sometimes referred to as 'lung pressures' or 'right heart' pressure. Systemic blood pressure refers to the pressure in the arteries throughout the rest of the body.

### ***FAQ: Does hydration or weight have any influence on PHT?***

For the most part, hydration and weight have very little effect on pulmonary pressures. However, weight loss is usually recommended for control of systemic hypertension.



## SIDEBAR DEFINITIONS - HYPERTENSION

**Cardiac catheterization** - A test used to check blood flow in the coronary arteries, the pumping function of the heart, and blood pressure in the **heart's** chambers, it uses a thin wire catheter that is inserted through a blood vessel in the groin or arm to reach the heart.

**DASH diet (Dietary Approaches to Stop Hypertension)** - A diet based on fruits, vegetables, whole grains, and lean meats with limited fats and sugars.

**Diastolic pressure** - Pressure in the arteries when the heart is resting.

**Hypertension** - Usually defined as blood pressure consistently greater than 140/90 in adults, normal blood pressure for children varies with the size and age of the child.

**Pulmonary arteries** - Vessels that carry blood depleted of oxygen from the right side of the heart to the lungs.

**Pulmonary arteriogram** - A procedure that uses a special dye (contrast material) and x-rays to see how well blood flows through the lungs.

**Pulmonary hypertension (PHT)** - Abnormally high blood pressure in the pulmonary arteries.

**Secondary hypertension** - High blood pressure caused by another identifiable medical condition.

**Sphygmomanometer** - An instrument for measuring blood pressure in the arteries consisting of a pressure gauge and a rubber cuff that wraps around the upper arm and inflates to constrict the arteries.

**Systemic blood pressure** - The pressure exerted within blood vessels circulating blood throughout the body.

**Systolic pressure** - The pressure in the arteries when your heart is pumping.

## CHAPTER THIRTEEN ~ HYPERLIPIDEMIA & ATHEROSCLEROSIS

### Overview

**Hyperlipidemia** is an elevation of lipids in the bloodstream. Lipids are a broad class of fats that serve as a primary component of all cell membranes. They also store and transport fuel that supplies the energy for the body. Cholesterol and other fats cannot dissolve in the blood; they have to be transported in the bloodstream by special carriers of lipids and proteins called **lipoproteins**.

These fat-transporting molecules range in size from small, dense ones that are associated with heart disease, to light, fluffy ones that may prevent or protect against it. Three lipoproteins, referred to as plasma lipids, are routinely measured. **Low-density lipoprotein (LDL-cholesterol**, “bad cholesterol”) is the major carrier of cholesterol in the blood. **High-density lipoprotein (HDL-cholesterol**, “good cholesterol”) carries fat out of the bloodstream. **Triglycerides** are a type of fat present in blood that provide energy for the body.



When there is elevation of one or more classes of lipoproteins, the term **hyperlipoproteinemia** is used.

**Hypercholesterolemia** is the term for high cholesterol levels in the blood. **Hypertriglyceridemia** refers to high triglyceride levels in the blood.

Triglycerides play an important role. They make up most of the fat found in foods themselves and fat that circulates in the bloodstream. Triglycerides in the blood plasma are also derived from dietary sources like carbohydrates. Calories ingested in a meal not used immediately by tissues, are converted to triglycerides and transported to fat cells to be stored. When the body needs energy, hormones regulate the release of triglycerides from fat tissue.

Plasma triglyceride levels less than 200 mg/dL (or 2.25 mmol) are classified as normal.

When the triglyceride levels are increased, the HDL cholesterol levels tend to be lower than normal.

### *Hyperlipidemia in Alström Syndrome*

A common feature that can be seen early in Alström Syndrome is **hypertriglyceridemia** which is reported in more than 75% of patients. Often, the levels of cholesterol are within normal limits.

Some Alström Syndrome patients have experienced a rapid rise in triglycerides, reaching dangerous levels as high, or higher than 500 mg/dL (5.6mmol/L.) When this occurs, the patient can be at risk for developing **pancreatitis**.

The development of atherosclerosis and coronary artery disease has been documented recently in some older patients with Alström Syndrome. Atherosclerosis is a disease in which plaque, a waxy substance made of fat, cholesterol and other substances, builds up inside the arteries. Over time, plaque hardens and narrows your arteries.

There does *not* appear to be a correlation between the age of the patient, diabetes, liver or kidney function. There *does* appear to be a correlation between hyperinsulinemia and insulin resistance and hypertriglyceridemia.

***Signs and Symptoms***

There are no symptoms until the emergence of other problems that may be associated with hypertriglyceridemia, such as pancreatitis.



***Detection and Diagnosis***

Diagnosis of hypertriglyceridemia is made using a simple test that measures levels of lipids in the blood. Because lipid levels change throughout the day, rising and then falling after a snack or meal, they are usually measured in blood that’s drawn after a 12-hour fast.

***Treatment***

Hypertriglyceridemia in the presence of normal cholesterol levels can be challenging to treat. Usually, treatment begins with a lifestyle modification program. Cutting down on calories consumed, eating less fat, getting more exercise, and maintaining control of blood sugars are the main therapies. Severe hypertriglyceridemia (patients with triglyceride levels greater than 1,000 mg/dL (11.3 mmol/L) should begin drug therapy and be advised to make aggressive dietary changes. High dose statin (a lipid-lowering drug) treatment, maintaining hydration, and possibly fish oil can be considered to prevent pancreatitis. Fibric acid derivatives (fenofibrate, gemfibrozil, etc) are normally the drugs of choice, but patients must be monitored carefully because of the risk of liver toxicity. All these treatments must be given in accordance with current recommended safety guidelines with special emphasis on liver, renal, muscle, and cardiac function.

Currently, triglyceride levels in adults are categorized as:

Normal	Less than 150 mg/dL	1.70 mmol/L
Borderline-high	150-200 mg/dL	1.70 – 2.25 mmol/L
High	200 – 500 mg/dL	2.25-5.65 mmol/L
Dangerously high	>500 mg/dL	>5.65 mmol/L

## ***Recommendations***

Control of elevated triglycerides is extremely important because hypertriglyceridemia is associated with increased risk to the heart, and increased risk for acute pancreatitis. Statins, fibrates, niacin, and fish oil (alone or in various combinations) are effective when drug therapy is indicated.

## ***Frequently Asked Questions***

### ***FAQ: How is an excess of triglycerides harmful?***

Excess triglycerides can contribute to fatty liver (steatosis), atherosclerosis, and gall bladder problems. Extremely high triglycerides can put one at risk for acute pancreatitis.

### ***FAQ: My child has liver disease. Should we be cautious about triglyceride lowering drugs?***

Active liver disease, at any age, can be an absolute contraindication for use of statin, fibrate, or niacin.

### ***FAQ: What about triglyceride lowering drugs and kidney disease?***

In patients with chronic renal failure, statins should not be used.

## **SIDEBAR DEFINITIONS- HYPERLIPIDEMIA & ATHEROSCLEROSIS**

**High-density lipoprotein (HDL)** - The ‘good’ cholesterol.

**Hypercholesterolemia** - High cholesterol levels in the blood.

**Hyperlipidemia** - An elevation of fats or lipids in the blood.

**Hyperlipoproteinemia** - Characterized by abnormally elevated concentrations of specific lipoprotein particles in the plasma.

**Hypertriglyceridemia** - Excess triglycerides in the blood plasma.

**Lipoproteins** - Complexes of lipid and protein that circulate in the blood. They are named according to their density: high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL).

**Low-density lipoprotein (LDL)** - ‘Bad’ cholesterol can slowly build up in the inner walls of the arteries to form plaque and increase the risk for heart attack or stroke.

**Pancreatitis** - An inflammation of the pancreas, often caused by extremely high triglycerides.

**Plasma lipids** - Fats, including cholesterol and fatty acids, that are transported in the blood stream.

**Triglycerides** -A group of three fats, collectively called triglycerides, that are found naturally in the body, are used to store energy, and constitute much of the body’s stored fat.

## CHAPTER FOURTEEN ~ GASTROENTEROLOGY AND THE LIVER

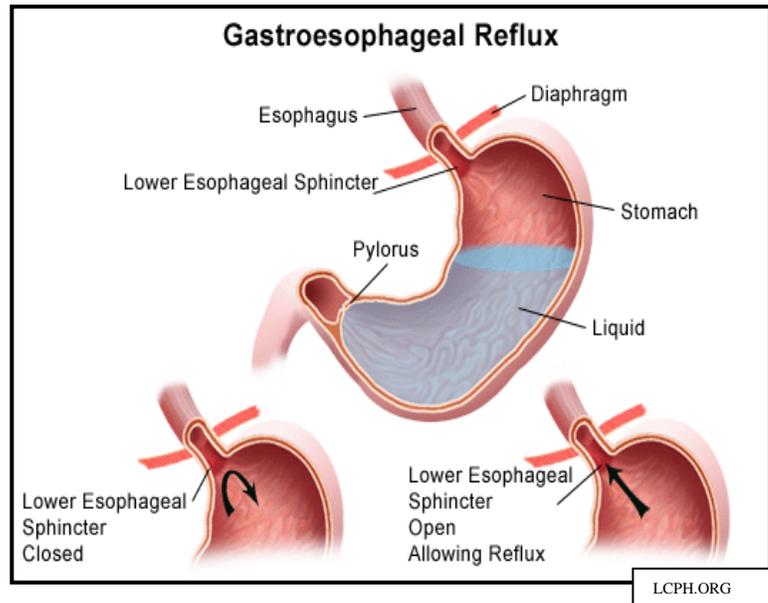
### GASTROINTESTINAL DISTURBANCES

#### Overview

The esophagus is the muscular tube that connects the throat to the stomach. At the lower end of the esophagus, where it enters the stomach, there is a muscular ring called the **lower esophageal sphincter (LES.)** The LES should remain tightly closed, except to allow food and liquid to pass into the stomach.

Heartburn occurs when the LES fails to close or opens at the wrong time. The term describes the return of acid and food from the stomach back into the esophagus.

Heartburn that is severe or that occurs frequently over a long period of time is known as **gastro-esophageal reflux disease (GERD.)** If GERD is untreated, there can be constant acid irritation to the lining of the esophagus.



#### *Gastro-Esophageal Reflux Disease in Alström Syndrome*

Occasional symptoms of GERD are fairly common in the general population (~10-20%.) Children and adults with Alström Syndrome may experience it more frequently, and with a degree of severity that it causes an impact on quality of life, especially in conjunction with other symptoms. Sometimes there is an association of GERD with asthma and frequent ear infections.

#### *Signs of Gastro-Esophageal Reflux in Infants:*

- Spitting up
- Wet burps
- Gagging or vomiting
- Sudden inconsolable crying, fussiness or colic

### ***Signs of Gastro-Esophageal Reflux in Older Children:***

- Bad breath
- Respiratory symptoms including apnea, choking, wheezing
- Persistent coughing or hoarseness – GERD is probably an aggravating factor
- Poor sleeping or frequent waking
- Refusal of food
- Sore throat, scarring or inflammation of the esophagus
- Ear, sinus, lung infections

### ***Detection and Diagnosis***

In severe cases, a doctor may prescribe a 24-hour probe or an upper GI endoscopy to assess any damage to the esophagus.



### ***Treatment***

A certain category of drugs called “proton pump inhibitors” are the main medications used to reduce stomach acid. These include Prilosec (omeprazole,) Prevacid (lansoprazole) and AcipHex (rabeprazole.) They are taken once or twice a day. Other brand-name acid reducing drugs such as Zantac, Pepcid, Axid, and Tagamet are also available. Reglan (metoclopramide) is a drug that can strengthen the LES. Review all medications with your child’s physician.

### ***Recommendations***

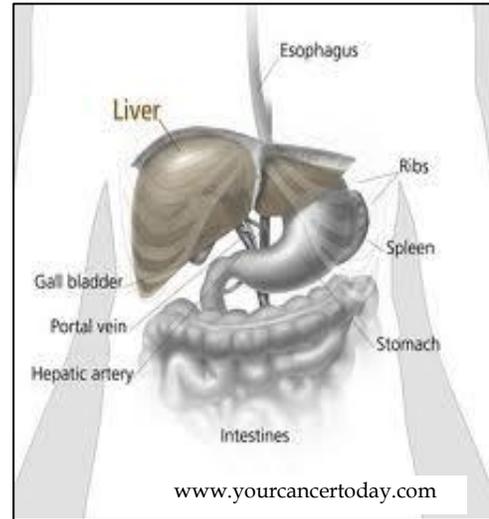
Generally GERD can be effectively controlled by an over-the-counter antacid. In addition, these are some tips to help alleviate symptoms and discomfort.

- Eat more slowly.
- Avoid eating anything within three hours before bedtime.
- Reduce consumption of high acid, fatty and fried foods, milk, chocolate, mints, caffeine, carbonated drinks, citrus fruits and juices, tomato products, pepper seasoning, alcohol, aspirin, and most pain medications.
- Eat smaller meals. Avoid tight clothing or bending over after eating.
- Elevate the head of the bed or mattress 6 to 8 inches. This helps to keep acid in the stomach.
- Lose weight.

## HEPATIC SYSTEM

### Overview

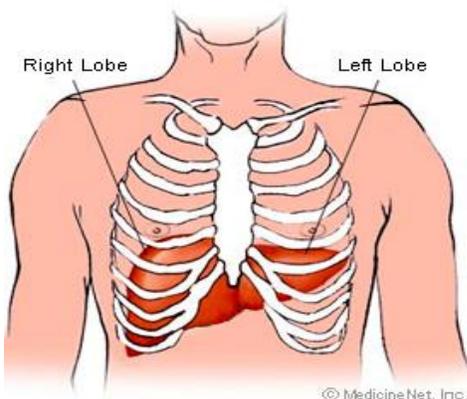
The liver, located in the upper right quadrant of the abdomen, is one of the largest organs in the body. Blood from the intestines and spleen flows through the liver to be cleaned, before returning to the heart. The cells of the liver, **hepatocytes**, metabolize the nutrients from the intestine and filter toxins from the body. About one quarter of a person's blood volume passes through the **portal vein** to the liver every minute. The cleansed blood leaves the liver through the **hepatic vein**. This is called **portal circulation**. The liver also receives some blood directly from the heart via the hepatic artery.



### Liver Dysfunction in Alström Syndrome

Nearly all patients with Alström Syndrome are at risk for some degree of liver involvement. However, liver problems in Alström Syndrome have a highly variable clinical course, and there are no guidelines that predict the prognosis. The initial abnormality in Alström begins with an accumulation of fat (mostly triglycerides) inside the liver cells. This fat accumulation is called **steatosis**. This accumulation of fat in liver cells is not the same as the fat cells (adipocytes) that constitute our body fat. Fatty liver is generally a harmless condition, which means that it, by itself, does not cause any significant liver damage.

Most children with Alström Syndrome will develop a fatty liver, but not all are at equal risk of developing substantial liver injury. Scientists do not yet know why some people with Alström will go on to develop serious liver complications while others will not. This varying susceptibility to liver disease, coupled with multiple, different liver disease-producing pathways, suggests that the development of liver disease is a multi-faceted process that is likely influenced by other factors such as modifier genes or environment.



A more serious stage of hepatic involvement that develops in a fraction of patients with Alström Syndrome is **non-alcoholic steatohepatitis (NASH)**, which involves steatosis as well as **inflammation** of the liver. In the term steatohepatitis, *steato* refers to fatty infiltration, while hepatitis refers to inflammation in the liver. The inflammatory cells can eventually destroy the liver cells and ultimately lead to scarring (**hepatic fibrosis**) and then irreversible, advanced scarring (**cirrhosis**.) Cirrhosis, where the normal liver cells are damaged and replaced by fibrotic scar tissue, is the last



and most severe stage in the hepatic spectrum for Alström Syndrome. When the liver fills with fibrotic tissue, blood flow resistance results in a “backup pressure” within the vessels that feed the portal vein. This backup pressure results in increased pressure in the portal vein (**portal hypertension.**) Additionally, if the blood flow through the liver is blocked by fibrosis, it can back up into the spleen and cause the spleen to also enlarge (**splenomegaly.**)

#### ***Portal Hypertension - Esophageal Varices:***

**Portal hypertension** is different from systemic high blood pressure. Most of the blood flowing through the liver comes from the portal vein. Portal hypertension occurs when there is reduced blood flow through the liver. When blood tries to pass through the liver, it meets resistance due to the fibrosis, and, therefore, must find another channel. The body diverts this blood through vessels surrounding the stomach and lower portion of the esophagus.

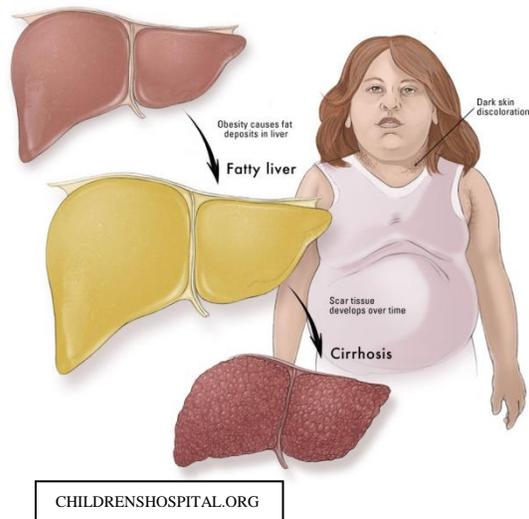
#### ***GI Bleeding***

As the pressure in the portal circulation increases, blood can be forced backward into the esophagus and stomach, causing swollen, distended, and weakened “varicose veins” known as **gastric or esophageal varices**. This is extremely serious because these veins have the potential to unexpectedly rupture and bleed into the stomach or gastrointestinal tract. In some cases, bleeding from esophageal or gastric varices can be sudden, massive, and life-threatening. If a bleed is from the gastrointestinal (GI) tract, it may cause nausea and bloody vomit with a “coffee grounds” appearance. There may be stools that are bloody, black or tarry in consistency.

***Alström patients with either “coffee grounds” vomiting, or black bloody stool should seek medical attention at the emergency room immediately. This is a life-threatening medical emergency!! MEDICAL CARE SHOULD BE SOUGHT IMMEDIATELY!!***

#### ***Ascites***

Ascites is an abnormal accumulation of fluid in the abdomen, often associated with liver disease and poor liver circulation. Two important causes of the production of ascites due to chronic liver disease are low levels of albumin in the blood and an increase in the pressure within the branches of the portal vein. Small amounts of fluid in the abdomen do not usually produce symptoms. Massive accumulations may cause rapid weight gain, abdominal discomfort and distention, shortness of breath and swollen ankles. Skin can stretch tightly across the abdomen if it contains large amounts of fluid.



## ***Hepatic Encephalopathy***

Hepatic encephalopathy is a very serious development that can sometimes occur as a result of severe liver disease. Ammonia generated by the breakdown of proteins in the intestine is not effectively removed by the failing liver. This causes the concentration of ammonia in the blood to increase. Subtle to very severe changes in mental functioning can result. Normal ammonia levels should be 5-69 mcg/dL.

## ***Signs and Symptoms***

There are usually no *early* signs of liver involvement. The liver may be enlarged and its edge might be felt below the rib cage. In later stages of liver disease, there may be abdominal pain or tenderness to the touch. An abnormally enlarged spleen will trap blood cells, which can also result in a drop in the **platelet** count.

Blood tests known as Liver Function Tests (LFTs) will determine if there are elevated **liver enzymes** that may be the first sign of a poorly functioning liver. These enzymes are normally contained within liver cells. If the liver is injured, the liver cells spill the enzymes into the blood, thus raising the enzyme levels, and signaling liver damage. Among the most sensitive and widely used are the **aminotransferases** (or transaminases.) They include the enzyme **aspartate aminotransferase (AST, also known as serum glutamic oxaloacetic transaminases, SGOT)**, and **alanine aminotransferase (ALT, which is also known as serum glutamic pyruvic transaminase (SGPT.))** (AST = SGOT and ALT = SGPT.)

## ***Detection and Diagnosis***



The diagnosis of liver disease in a patient with Alström Syndrome will be made from a combination of physical examination, laboratory testing and sometimes radiological ultrasound studies and biopsy. Blood tests are usually the first assessment of liver function.

Ultrasound (or liver sonogram) is also a widely used procedure to evaluate liver disease. The liver ultrasound may show evidence of steatosis, hepatomegaly, splenomegaly, or cirrhosis.

### ***Other Evaluations***

**Liver biopsy** provides critical information that none of the other tests can and is an important diagnostic test for Alström patients who have suspected chronic liver dysfunction. Liver biopsies are normally performed using a small needle through the skin. The patient is awake during the procedure, with a local anesthetic. Unfortunately, this procedure can be frightening, but it is the only way to clearly assess the status of the liver.

**Upper gastrointestinal endoscopy** may be recommended. A lubricated endoscope is placed down the throat and into the stomach so that the lining of the upper GI tract can be checked for varices.

### **Recommendations:**

- Weight loss.
- Better, tighter control of blood sugars.
- Low-fat diet.
- Exercise.
- Avoid alcohol.
- Immunization against hepatitis B and A to protect liver from other infections.

Primary care physicians *must be aware* of the potentially serious liver complications and be alert to early recognition, diagnosis, and treatment of chronic liver disease in any patient with Alström Syndrome.

### ***Treatments***

For a patient with Alström Syndrome who has progressive or worsening liver disease, there are several treatment options that may be tried.

The recommended diet for anyone suffering from liver disease is high in complex carbohydrate, low in protein, low in fat, and low in sodium.

- Medications: Drugs to reduce blood pressure. Diuretics to help relieve edema. Steroids to decrease inflammation.
- **Lactulose** decreases the absorption of protein from the intestine, and thereby further reduces the protein load to be handled by the liver, and removes ammonia from the bloodstream.
- Needle drainage reducing the ascites fluid accumulating in the abdomen.

Some potential treatments for enlarged veins in the esophagus or stomach (varices) are:

- **Endoscopic rubber band ligation** of varices.
- **Balloon compression (tamponade.)**
- **TIPS** (transjugular intrahepatic portosystemic shunting.)

Although, medicine has made great strides in organ transplantation, there have been no documented patients who have received a liver transplant thus far.

**Aminotransferases (ALT and AST)** are enzymes produced in the cells of the liver. The levels of ALT and AST in the blood are increased because hepatocytes are damaged or die and the enzymes leak out into the bloodstream.

**AST (SGOT)** is normally found in many tissues including the liver, heart, muscle, kidney, and brain. It is released into serum when any one of these tissues is damaged. For example, its level in serum rises with heart attacks and with muscle disorders. It is therefore not a highly specific indicator of liver injury.

**ALT (SGPT)** is, by contrast, normally found most concentrated in the liver. It is released into the bloodstream as the result of liver injury. It therefore serves as a fairly specific indicator of liver status.

**Alkaline phosphatase** - Originates mostly from liver and bone.

**Bilirubin** - The major breakdown product that results from the destruction of old red blood cells. It is removed from the blood by the liver, secreted into the bile, and passed into the intestine. In chronic liver disease, the serum bilirubin concentration is usually normal until a significant amount of liver damage has occurred.

**Albumin** - The major protein that circulates in the bloodstream. It is produced by the liver and secreted into the blood. Low serum albumin concentrations indicate poor liver function.

**Ammonia** – Concentrations in the blood provide an indication of liver function.

**Gamma-glutamyltransferase (GGT)** - One of the first tests important in detecting the early presence of liver disease. In Alström Syndrome, it's often one of the first enzymes to be elevated.

### *Frequently Asked Questions*

***FAQ: What are the long-term effects of medications for GERD on my child?***

Fortunately, it appears as though most medications used to treat GERD are quite safe. However, there is very little data on long-term use of these medications. As always, consult your physician before beginning *any* over-the-counter drug regimen.

***FAQ: Is there a connection between GERD and asthma?***

Epidemiological evidence for the GERD/asthma association suggests that about three-fourths of asthmatics in the general population, independent of the use of bronchodilators, have GERD, increased frequency of reflux episodes, or heartburn; and 40% have **gastric reflux esophagitis**.

***FAQ: How old are most children when liver complications develop?***

The liver complications that some patients with Alström Syndrome face can occur at any age. The earliest age that hepatic complications have been reported is 5 years.

***FAQ: Is the liver damage caused by other problems in Alström Syndrome?***

Steatosis is often associated with obesity. Although steatosis and steatohepatitis can sometimes worsen in patients with diabetes mellitus, Alström children can develop the problem well before the onset of diabetes. High triglycerides can also be a risk factor for steatohepatitis, but there does not seem to be a correlation with blood lipid levels in Alström patients.



***FAQ: Can other medications my child is taking damage the liver?***

Many different drugs are known to cause liver damage.

***FAQ: What about liver transplantation?***

To date there has been no experience with liver transplantation in Alström Syndrome. Because the procedure is so physiologically rigorous, significant cardiovascular or pulmonary disease may indicate that the patient is not a good candidate for hepatic transplantation. In general, contraindications include severe and uncontrolled infection, advanced cardiopulmonary disease, multisystem organ failure, and active substance abuse.



***FAQ: Does the herbal supplement milk thistle help the liver?***

Milk thistle is an herbal treatment that has been reported to be effective in the treatment of liver disease due to its ability to help the liver detoxify the body.

## SIDEBAR DEFINITIONS ~ GASTRO and THE LIVER

**Ascites** - An accumulation of fluid in the abdomen.

**Balloon Compression Tamponade** - This procedure involves the passage of a balloon through the nose to help compress the bleeding varices.

**Cirrhosis** - A general classification of liver disease characterized anatomically by widespread nodules in the liver combined with fibrosis. The fibrosis and nodule formation causes distortion of the normal liver architecture which interferes with blood flow through the liver. Cirrhosis can also lead to an inability of the liver to perform its biochemical functions.

**Endoscopic Band Ligation** - A rubber band is tied around the bulging veins to prevent ruptures or stop bleeding. This is considered the first line of treatment.

**Esophagus** - The passage extending from the mouth to the stomach

**Esophageal varices** - Distended, weakened, and blood filled veins in the esophageal wall caused by pressure in the portal vein, which have the potential to bleed into the esophagus.

**Gastric reflux esophagitis** - Esophagitis is inflammation of the esophagus, which can result in symptoms such as hoarseness, difficulty swallowing, and heartburn. Esophagitis is most commonly caused by acid reflux.

**Gastro-esophageal reflux disease (GERD)** - A backflow of acid from the stomach into the swallowing tube or esophagus. This acid can irritate and sometimes damage the delicate lining on the inside of the esophagus

**Gastrointestinal endoscopy** - An examination that is performed using an endoscope—a flexible fiber optic tube with a small camera at the end. The endoscope not only allows detection of gastrointestinal varices, but treatment, as well.

**Gastrointestinal (GI) tract** - Refers to the esophagus, stomach, small and large intestine.

**Hepatic** - Refers to the liver.

**Hepatic encephalopathy** - A condition describing the adverse effects of liver disease on the central nervous system. Symptoms may range from slight disorientation to coma.

**Hepatic vein** - The vein leading away from the liver through which the cleansed blood passes, leading back to the heart.

**Hepatocytes** - Cells in the liver.

**Hepatomegaly** - Enlarged liver.

**Inflammation** - The body's complex reaction involving a number of cellular and molecular components that can cause damage to surrounding tissues.

**Lactulose** - A synthetic sugar that reduces the amount of ammonia in the blood by drawing it out of the bloodstream and into the small intestine.

**Liver biopsy** - Sampling a small amount of liver tissue for microscopic examination by inserting a needle under the ribs and into the liver.

**Liver enzymes** - An initial step in detecting liver damage is a simple blood test to determine the presence of certain liver enzymes in the blood. Under normal circumstances, these enzymes reside within the cells of the liver. When the liver is injured, these enzymes are spilled into the blood stream.

**Lower esophageal sphincter (LES)** - A muscle that opens to let food pass into the stomach and closes to stop stomach acid and juices from backing up into the esophagus.

**Non-alcoholic steatohepatitis (NASH)** - Steatosis and liver disease that is not caused by excessive alcohol consumption.

**Platelet** - The smallest of the blood cells, which are involved in blood clotting.

**Portal circulation** - Pertains to the passage of blood in the portal vein, spleen, and gastrointestinal tract (GI tract).

**Portal hypertension** - Increased blood pressure in the portal vein and other connecting veins, usually caused by cirrhosis, fibrosis, or severe damage to liver cells. It may result in bleeding or ascites.

**Portal vein** - The vein that passes through the intestine to remove toxins and wastes and transport them to the liver.

**Sclerotherapy** - Drugs, intended to slow bleeding, are injected into the bleeding vein and sometimes into the surrounding area. The drugs cause clots to form and harden the vein in order to stop the bleeding.

**Steatohepatitis** - A term for a liver that contains fatty deposits and shows evidence of inflammation.

**Steatosis** - Fatty liver.

**Splenic vein** - The vein that drains the spleen.

**Splenomegaly** - Enlarged spleen due to increased pressure in the liver.

**Transjugular Intrahepatic Portosystemic Shunting (TIPS)** - *Transjugular*: Across the jugular vein; *Intrahepatic*: within the liver; *Portosystemic*: from the portal vein to the general circulation; *Shunt*: a channel for blood to flow. A major surgical treatment in which a tube is passed through the liver to help blood flow bypass the liver by connecting the portal and hepatic veins and thus reduce portal hypertension. This course of action is not trivial and must be done in a facility that specializes in the procedure.

**Varices** – Enlarged blood vessels which are prone to bleeding.

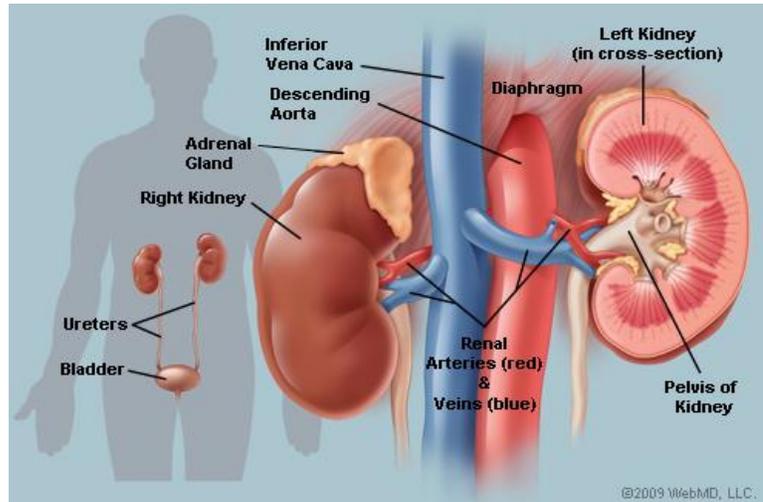
## CHAPTER FIFTEEN ~ NEPHROLOGY

### Overview

The kidneys are the two bean-shaped organs about the size of a fist that are located in the back part of the abdomen on either side of the spinal column just below the rib cage. The function of the kidneys is to remove liquid waste from the blood in the form of urine and to keep a stable balance of salts and other substances in the blood. The word “renal” refers to the kidneys.

Within the kidneys are more than a million tiny filtering units called **nephrons** which are responsible for removing toxins,

wastes, ingested water, and mineral salts from the bloodstream. Each nephron consists of a ball formed of small blood capillaries, called a **glomerulus**, and small tubes called a **renal tubules**. The glomerulus, the main filter of the nephron, allows water and soluble wastes to pass through to the renal tubules and to be excreted as urine. The filtered blood passes out of the glomerulus to be returned to circulation.



### Renal Dysfunction in Alström Syndrome

Kidney dysfunction (**nephropathy**) has long been known as a cardinal feature in Alström Syndrome. Most patients with Alström Syndrome will eventually develop symptoms of declining renal function that is caused by slowly progressive fibrosis in the glomeruli (**glomerulofibrosis**), an enlargement of the renal tubules, and a gradual destruction of the kidneys. Fibrosis within glomeruli (glomerulosclerosis) and between tubules (tubulointerstitial fibrosis) causes progressive loss of renal function. There is a gradual loss of the ability of the kidneys to excrete wastes, concentrate urine, and conserve the balance of salts in the body. Chronic renal failure usually occurs over a number of years as the internal structures of the kidney are slowly destroyed, resulting in the accumulation of fluid and waste products in the body, causing **azotemia** and **uremia**. Progression can range from mild kidney dysfunction to chronic kidney failure and may continue to **end-stage renal failure** (ESRD.)



### ***Signs and Symptoms***

In the early stages, there may be no symptoms. Development may be so gradual that symptoms do not occur until kidney function is significantly diminished. One of the first indications may be elevated levels of **creatinine** or **blood urea nitrogen (BUN)** in the blood.

Early stages of glomerulosclerosis may not cause any symptoms. The most important warning sign of glomerular disease is **proteinuria** (large or small amounts of protein in the urine,) which is usually discovered during a routine medical examination. However, the loss of large amounts of protein could cause swelling in the ankles or accumulation of fluid in the abdomen.

Scarring disrupts the filtering process of the kidneys, allowing protein to leak from the blood into the urine. Because glomerulosclerosis is just one of many possible causes of proteinuria, a kidney biopsy may be needed to determine if the cause is actually glomerulosclerosis. About 15 percent of people with proteinuria are diagnosed with glomerulosclerosis.

### **Initial Symptoms:**

- Elevated levels of creatinine and/or BUN
- Unintentional weight loss
- High blood pressure
- Protein in the urine (proteinuria)
- Blood in the urine (**hematuria.**) Urine may be pink or cola colored.
- General ill feeling: headache, fatigue.
- Generalized itching all over the body

### **Later Symptoms:**

- Increased or decreased urine output
- Edema may be obvious in hands and ankles, especially at the end of the day, or around the eyes when awakening in the morning
- Excessive need to urinate at night
- Easy bruising or bleeding: may have blood in the vomit or in stool
- Drowsiness, lethargy, or confusion
- Muscle twitching or cramps
- Seizures
- Breath odor
- Loss of appetite

### ***Detection and Diagnosis***

Urinalysis and blood chemistries provide information about kidney damage by indicating levels of protein and red blood cells in the urine. Blood tests measure the levels of waste products such as creatinine and urea nitrogen to determine whether the filtering capacity of the kidneys is impaired. Higher levels may be a sign that the kidneys are not working properly. As kidney disease progresses, the level of creatinine and BUN in the blood increases.

Sometimes changes that indicate chronic renal failure may be seen on renal or abdominal X-ray, abdominal ultrasound, CT scan or MRI. Additionally, a kidney biopsy can reveal the extent of the disease.

Since Alström Syndrome is known to affect the glomerulus of the kidney, causing problems at the cellular level, a kidney biopsy may be helpful in confirming the extent of kidney dysfunction. However, any surgical procedure comes with risk – particularly in Alström Syndrome, so be sure that the procedure is absolutely necessary before going forward with biopsy.

### ***Treatment***

There is no cure for the chronic renal failure in Alström Syndrome. However, treatment may control the symptoms, minimize complications, and slow the progression of the disease. Further, a group of blood pressure medicines called ACE inhibitors appears to give extra protection to the kidneys in patients with diabetes. (See further discussion on ACE inhibitors in a previous chapter.)

Fluid intake may be restricted, often to an amount equal to the volume of urine produced. Salt, potassium, phosphorus, and other **electrolytes** may be restricted in the diet to slow the build-up of wastes in the bloodstream. Modification of diet and blood pressure medication may be prescribed.

### ***Dialysis***

Scarred glomeruli cannot be repaired. When the kidneys fail to clear waste from the body, renal **dialysis** may be needed. Dialysis is the artificial process of getting rid of waste and unwanted fluid from the blood. There are two kinds of dialysis; hemodialysis and peritoneal dialysis.

In hemodialysis, the blood goes through a machine outside the body that has special filters. The blood comes out of the patient through a catheter (a flexible tube) that is inserted into the vein. Filters remove the waste products from the blood. The filtered blood then returns to the patient via another catheter. In order to make the insertion of the catheters possible, a blood vessel, usually in the arm, needs to be surgically enlarged. Hemodialysis usually lasts about 3 to 4 hours every three days.

In peritoneal dialysis, a sterile mineral/glucose solution is run through a tube into the abdominal body cavity. Waste products are naturally filtered out through the internal lining of the abdomen. The dialyzing liquid is then drained out through a tube and discarded. This

exchange, or cycle, is generally repeated several times during the day, and the procedure can usually be done at home.

Kidney transplantation has been successful in a number of persons with Alström Syndrome, although the regulations for a position on the transplant list differ from state to state (USA) and from country to country. Talk to your physician about steps that should be taken in advance preparation for dialysis in the future.

### ***Recommendations***

Renal function in patients with Alström Syndrome must be actively monitored for early signs of renal insufficiency and complications. Patients must be followed up regularly and appropriate treatments for arterial hypertension should be implemented immediately.

### **TESTS FOR KIDNEY FUNCTION:**

#### **Blood Tests:**

**Serum creatinine.** Creatinine is a waste product that comes from meat protein in the diet and also comes from the normal wear and tear on muscles of the body. Creatinine levels in the blood can vary, and each laboratory has its own normal range. In many labs the normal range is 0.6 to 1.2 mg/dL.

**Blood urea nitrogen (BUN).** Urea nitrogen also is produced from the breakdown of food protein. A normal BUN level is between 7 and 20 mg/dL.

#### **Urine Tests:**

Some urine tests require only a few ounces of urine. But some tests require collection of all urine produced for a full 24 hours. A 24-hour urine test shows how much urine your kidneys produce in 1 day. The test also can give an accurate measurement of how much protein leaks from the kidney into the urine in 1 day.

**Glomerular filtration rate GFR:** A test based on creatinine level, age, gender, and other factors that estimates the amount of blood that passes through the glomerulus each minute.

**Creatinine clearance:** A creatinine clearance test compares the creatinine in a 24-hour sample of urine to the creatinine level in the blood, to show how many milliliters of blood the kidneys are filtering out each minute (mL/min). In kidney failure, creatinine clearance decreases.

## *Frequently Asked Questions*

***FAQ: What age do Alström Syndrome patients normally exhibit declining kidney function?***

The age that kidney function begins to decline varies widely in Alström Syndrome.

***FAQ: What causes the renal failure in AS?***

Progressive changes in the kidneys' structure, called glomerulofibrosis or glomerulosclerosis, cause a reduced ability of the kidney to remove wastes from the blood.

***FAQ: Does renal failure occur because of diabetes?***

If uncontrolled diabetes causes sugar to stay in your blood instead of breaking down, it can act like a poison to organs. Damage to the nephrons from unused sugar in the blood is called diabetic nephropathy, but this is not thought to be the mechanism for renal disease in Alström Syndrome. However, it is important to keep blood sugars under control to avoid additional stress on the kidneys.

***FAQ: What is the connection between blood pressure and kidney function?***

High blood pressure can damage the small blood vessels in your kidneys so that the damaged vessels cannot filter poisons from your blood as they are supposed to.

***FAQ: Can certain medications cause damage to the kidneys?***

Some over-the-counter medicines can be harmful to the kidneys if taken regularly over a long period of time. Products that combine aspirin, acetaminophen, and other medicines such as ibuprofen have been found to be dangerous to the kidneys. Check with your doctor to make sure the medications your child is taking are not putting the kidneys at further risk.



## SIDEBAR DEFINITIONS ~ NEPHROLOGY

**Creatinine** - A metabolic (metabolism related) waste that is normally excreted as urine.

**Edema** - Swelling caused by the accumulation of fluid in cells and tissues including the feet, hands, abdomen, or face.

**Electrolytes** - Ions in the blood stream including sodium, potassium, chloride, and bicarbonate essential for normal function of cells and our organs.

**End stage renal disease (ESRD)** - A serious condition in which the kidneys fail to regulate water and chemicals in the body by ridding the body of wastes.

**Glomerulus (Plural: glomeruli)** - The glomerulus is the **main filter** of the nephron that consists of a mass of tiny tubes through which the blood passes, allowing water and soluble wastes to pass through and be excreted as urine.

**Hematuria** - Blood in the urine that may turn the urine pink or cola-colored.

**Nephrons** – Nephrons, numbering about 1 million in each kidney, are responsible for the actual purification and filtration of the blood.

**Nephropathy** - A slow deterioration of the kidneys.

**Proteinuria** - The presence of abnormally high amounts of protein in the urine, which may be a sign that the kidneys are not working properly.

**Renal dialysis (hemodialysis)** – A treatment usually conducted in a dialysis outpatient facility that involves removing and cleansing of waste products from the blood through a filter.

**Renal tubule** - The part of a nephron that leads away from a glomerulus.

**Urea** – A chemical produced when foods containing protein, such as meat, poultry, and certain vegetables, are broken down in the body.

**Uremia** - Accumulation of urea and other wastes in the blood that are normally eliminated through urination, which become toxic in large amounts and may occur without symptoms.

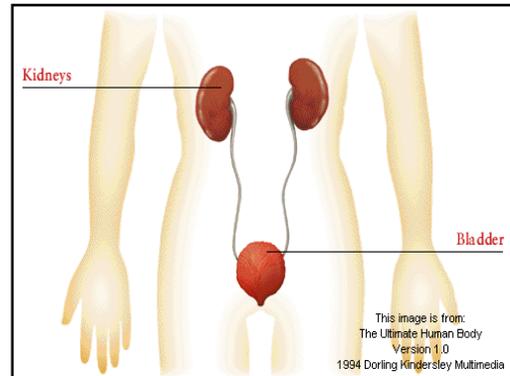


## CHAPTER SIXTEEN ~ UROLOGY

### Overview

The organs, tubes, muscles, and nerves that work together to create, store, and carry **urine** are called the urinary system. The urinary system includes two **kidneys**, two **ureters**, the **bladder**, two **sphincter muscles**, and the **urethra**. The urinary system removes a type of waste called **urea** from the body. The urinary system works with the lungs, skin, and intestines, all of which also excrete wastes, to keep the chemicals and water in the body balanced. Adults normally eliminate about a quart and a half of urine each day.

### The Urinary System



From the kidneys, urine travels down the two thin tubes called ureters to the bladder. Muscles in the ureter walls constantly tighten and relax to force urine downward and away from the kidneys. Small amounts of urine are emptied into the bladder from the ureters about every 10 to 15 seconds. If the urinary system is healthy, the bladder can hold up to 16 ounces (2 cups) of urine comfortably for 2 to 5 hours. Circular muscles called sphincters help keep urine from leaking from the bladder. Nerves in the bladder signal when it is time to urinate.

Normal urination involves communication between the brain and the excretory organs. The sensation to urinate becomes stronger as the bladder fills and reaches its limit. Nerves from the bladder send a message to the brain that the bladder is full, and the urge to empty the bladder intensifies. The brain simultaneously signals the bladder muscles to tighten, squeezing urine out of the bladder, and the sphincter muscles to relax, allowing urine to leave the bladder through the urethra. When all the signals occur in the correct order, normal urination occurs.

### *Urological Dysfunction in Alström Syndrome*

Patients with Alström Syndrome can experience varying degrees of urinary problems, with changing patterns of urinary dysfunction. One of the most common early patterns is recurrent urinary tract infections (UTI) or episodes of **cystitis** (bladder infections.) Minor symptoms include urinary urgency, difficulty initiating or poor flow, long intervals between voiding, incomplete voiding or urinary **retention**, and abdominal pain before or during urination.

Some patients go on to develop more severe complications such as marked frequency, urgency, **incontinence**, and significant **perineal** or abdominal pain.

Many children with Alström Syndrome, both males and females, report frequent UTI, painful urination, or incontinence. Other common complaints are excessive thirst (**polydipsia**) and urine production (**polyuria**.)

Urinary retention (the sudden inability to urinate, which causes pain and discomfort) is a common urological problem in Alström Syndrome with many possible causes. Chronic urinary retention refers to the persistent presence of urine left in the bladder after incomplete emptying.

Urethral strictures have also been described in the Alström literature. These occur when scar tissue forms in the urethra. The stricture blocks the urethra and may cause the urinary stream to slow to the point where the person cannot urinate.

### ***Signs and Symptoms:***

- Frequent UTIs.
- Voiding problems: Difficulty initiating urination, long periods between urination.
- Painful urination (**Dysurea**).
- Frequent and urgent need to urinate.
- **Incontinence.**
- **Stress incontinence.**
- Urinary retention (often without symptoms).

### ***Detection and Diagnosis***

Ultrasound is a non-invasive way to evaluate whether the bladder is emptying sufficiently. If there are symptoms that suggest a problem, the physician may recommend **urodynamic** tests to help evaluate the storage of urine in the bladder and the flow of urine from the bladder through the urethra. Most urodynamic testing focuses on the bladder's ability to empty steadily and completely. It can also show whether the bladder is having abnormal contractions that cause leakage or if there is remaining urine in the bladder (**postvoid residual or PVR**.) Urodynamic tests can range from simple observation to precise measurement using sophisticated instruments.

One such test measures the contraction of the bladder muscle as it fills and empties. The test takes about 30-45 minutes to perform. A small plastic tube called a catheter is inserted through the urethra into the bladder. The bladder is filled either with water or a gas. Another small tube is inserted into the rectum to measure the pressure put on your bladder when you strain or cough. Sometimes dye is used instead of water so that x-ray pictures can be taken when the bladder fills and empties, in order to detect any abnormalities in the function of the bladder.

### ***Treatment***

UTIs are treated with antibiotics. Drinking lots of fluids also helps by flushing out the bacteria. UTIs should be treated immediately, since reflux of infected urine can be the cause of permanent kidney damage. For difficulty in voiding, **self-catheterization** (clean-intermittent catheterization) can be taught. There are many causes and types of incontinence, and many treatment options. Treatments range from simple exercises to surgery.

### ***Recommendations – Monitoring:***

- Urinalysis every six months.
- Pay attention to urinary habits and report any concerns to your doctor.
- Drink plenty of fluids unless other health issues dictate otherwise.

## ***Frequently Asked Questions***

### ***FAQ: How would you know whether you have proteinuria or hematuria?***

Proteinuria may cause foamy urine. Blood may cause the urine to be pink or cola-colored (hematuria). Tests for both of these conditions can be run from a urine sample in the laboratory.

### ***FAQ: I am very reluctant to put my child through the invasive procedure of urodynamic testing. Is the discomfort of this test justified?***

Yes, if your child has symptoms. By evaluating the bladder, the physician may detect a problem before it becomes so serious it causes permanent damage to the kidneys or requires serious surgery. Parents can help enormously with this procedure by keeping a positive attitude. Do not tell the child that it will “hurt” or be “painful”. Instead, re-enforce the fact that it is mainly a pushing sensation that lasts only a few minutes. Your anxiety will only cause unnecessary anxiety for your child.

### ***FAQ: Should all people with Alström, even children, have a urological evaluation?***

There is no single “correct answer” to this question. It is generally agreed that any signs or symptoms of urological problems should be thoroughly investigated, and this often includes urodynamic testing or a scan of the bladder. The value of such evaluations in the absence of signs or symptoms of urological difficulties is not as clear. There should be an open discussion between a physician and the family about the risks and benefits of screening tests.

### ***FAQ: Does drinking cranberry juice help prevent problems?***

There is some evidence supporting the use of cranberry supplements to prevent UTI, although most available studies are of poor quality. There is no information about dosage and it has not been conclusively shown to be effective as a treatment. Cranberry juice contains sugar, so for people with Alström Syndrome, taking the supplement in capsule form would be better.

### ***FAQ: Do all adults with Alström eventually need to perform self-catheterization?***

No, only a small number of people with Alström have severe enough bladder/urinary dysfunction to require self-catheterization.

## SIDEBAR DEFINITIONS ~ UROLOGY

**Bladder** - A hollow muscular organ shaped like a balloon. It sits in the pelvis and is held in place by ligaments attached to other organs and the pelvic bones. The bladder stores urine, swelling into a round shape when it is full and reducing its size when empty.

**Clean Intermittent Catheterization (CIC)** - The bladder is drained every 6 hours by inserting a small tube through the urethra.

**Cystitis** - Infection in the bladder (*cysto* refers to the bladder).

**Detrusor** - The smooth muscle that forms the bladder.

**Detrusor urethral dysynergia** - The urethral sphincter muscle contracts and the bladder (detrusor) muscle also contracts at the same time, resulting in the obstruction of normal urinary flow.

**Dysuria** - Difficult or painful urination.

**Frequency** - The need to empty one's bladder frequently.

**Incontinence** - The inability to completely control the release of urine.

**Overflow incontinence** - A type of incontinence brought about because of incomplete emptying and a large amount of urine always being present in the bladder.

**Perineal** - The area between the vulva and anus in a woman, and between the scrotum and anus in a man.

**Polydipsia** - Excessive thirst over time. (This can also be an indication of diabetes.)

**Polyuria** - An increased need to urinate more frequently. (This too can be an indication of diabetes.)

**Post-void Residual** - The urine remaining in the bladder just after urination (a 20-50 cc residual amount normally remains).

**Retention** - The failure of the lower urinary tract to expel all the urine in the bladder.

**Sphincter** - A circular muscle that closes the urethra tightly like a rubber band around the opening of the bladder when voiding is not desired.

**Stress incontinence** - Losing urine when there is a sudden increase in pressure on the bladder, such as from a cough or sneeze.

**Stricture** - Scarring in the urethra that blocks urine flow.

**Ureter** - An 8-10 inch long tube that drains urine from the kidney to the bladder.

**Urethra** - The tube that carries urine from the bladder toward the outside of the body.

**Urgency** - The symptom of sudden onset of a strong need to urinate.

**Urodynamics** - The study of the mechanics of urinary bladder filling, emptying, and voiding.

**UTI** - Urinary tract infection.

**Void** - Urinate.

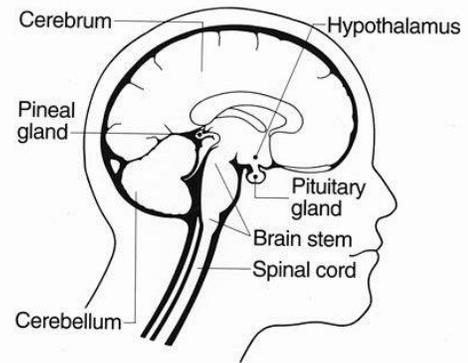
## CHAPTER SEVENTEEN ~ NERVOUS SYSTEM

### Overview

The primary function of the nervous system is to collect, process, store, control, and respond to information from the rest of the body and from the external environment. The brain receives information such as odors, light, sounds, and pain from the rest of the body. It interprets that information and then controls the body's response to it.

The nervous system is made up of the brain, the spinal cord, and nerves. The brain and spinal cord make up the central nervous system. The peripheral nervous system is made up of nerves which transmit information back to the brain. The autonomic nervous system is responsible for the bodily functions which are not under conscious control, such as heartbeat, digestion, breathing, maintaining blood pressure, and the release of hormones.

The brain is divided into sections: the cerebrum, the cerebellum, the diencephalon, and the brain stem. Each section is responsible for different functions of the brain (See definitions.)



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### Neurological Issues in Alström Syndrome

It is important to remember that, like many other clinical features of Alström Syndrome, not every child will experience neurological symptoms. However, some neurological manifestations are fairly common. It appears that at least 14% of children experience varying degrees of neurological involvement. If a child has symptoms, they usually begin in infancy or early childhood; however they may also develop later in life as well. The number of patients worldwide with Alström Syndrome is so small that information about the spectrum of symptoms is limited. However, more children and adults may have neurological issues than was previously thought. Much more study is needed to understand this unexplored aspect of Alström Syndrome that appears to affect nearly 15% of patients.

The following are neurological issues sometimes observed in Alström Syndrome:

- Abnormal pituitary (empty **sella turcica**)
- Autism spectrum disorder
- Abnormal **EEG**
- Abnormal **MRI**
- Seizures of varying type and severity
- **Hypersomnia** (excessive daytime sleep)
- **Hypotonia** (reduced muscle tone)
- Unexplained muscle pain (myalgia)
- **Ataxia** (lack of coordination)
- Frequent headaches
- Tics

## *Seizures*

In some people, the normal pattern of neurological activity becomes disturbed, causing strange sensations, emotions, and behavior or sometimes convulsions, muscle spasms, or loss of consciousness. Generalized seizures may cause loss of consciousness, falls, or massive muscle spasms, and there are several different types of generalized seizures.

The seizures are varied and usually begin in childhood. The cause of seizure activity is unknown. These seizures may develop because of an abnormality in brain wiring, an imbalance of nerve signaling chemicals, or some combination of these factors. There are several different classifications of seizures:

**Absence seizures** (petit mal) are the type most commonly seen in children with Alström Syndrome. Usually beginning in childhood or adolescence, a child may appear to be staring into space for a brief period of time, sometimes with repetitive movements such as lip smacking, abnormal mouth movements, or picking at clothing. During the seizure, responsiveness and awareness are impaired and the children usually do not know when they have had an episode. The children are usually completely alert immediately afterward.

**Tonic seizures** cause stiffening of muscles. **Clonic seizures** cause repeated jerking movements of muscles on both sides of the body. **Myoclonic seizures** cause jerks or twitches of the upper body, arms, or legs. **Atonic seizures** cause a loss of normal muscle tone, which may lead to falls or sudden drops of the head. **Tonic-clonic seizures** cause a mixture of symptoms, including stiffening of the body and repeated jerks of the arms or legs as well as loss of consciousness. **Focal seizures** occur when abnormal electrical activity is seen in only one half of the brain. All of these have been reported in a subset of our children.

### *Brain MRI Abnormalities*

MRI studies of a subset of people with the Syndrome have found irregularities in several regions of the brain, such as enlargement of the **brain ventricles** and **white matter** abnormalities. While these findings are intriguing, they are preliminary and require further study.

In some patients, there is enlargement or malformation of a structure in the head known as the sella turcica, a saddle-shaped depression that holds the pituitary gland located in the bone at the base of skull. In the case of “empty sella”, the malformed sella turcica is often either partially or completely filled with **cerebrospinal fluid**. As a result, the pituitary gland is often compressed and flattened so that the sella turcica appears empty. Most individuals with empty sella do not have any associated symptoms.

### *Detection and Diagnosis*

**Electroencephalograms (EEGs)** and brain scans are common diagnostic tests for seizures. The EEG is almost always abnormal during a seizure, but may be normal in between seizures. **Magnetic resonance imaging (MRI)** of the head is often performed as part of a general neurological work-up. A neurological examination assesses motor and sensory skills, the

functioning of one or more cranial nerves, hearing and speech, vision, coordination and balance, mental status, and changes in mood or behavior, among other abilities. Sometimes, a neurologist will order **computerized tomography (CT scan)** of the head, but areas of the brain are generally imaged using MRIs.

### ***Monitoring and Treatment***

If you observe unusual behavior in your child that might be even a small seizure, working with a pediatric neurologist is important. Seizures can often be treated with one or more anticonvulsant drugs.

## ***Frequently Asked Questions***

### ***FAQ: If my child has had a seizure, does it mean he has epilepsy?***

Having a seizure does not necessarily mean that a person has epilepsy. Only when a person has had multiple seizures is he or she considered to have epilepsy.

### ***FAQ: If my child has had seizures, will this be a life-long problem for him?***

Often, the seizure activity tends to go into remission or stop entirely as a child matures.

### ***FAQ: Will seizures impair learning for my child?***

The seizures do not seem to impair cognitive functions or development.

### ***FAQ: What should be done during a seizure?***

Stay calm. Do not restrict movement, but watch the child closely to prevent injury. Stay by the person's side until he or she is conscious.

### ***FAQ: What should be done after a seizure?***

Offer reassurance and comfort when the seizure stops. The child may likely be disoriented, confused, or sleepy. Sometimes a child will say something like, "I went away for awhile"...

### ***FAQ: How should teachers deal with 'absence seizures'?***

Depending on the frequency and intensity of the seizure, the student may face a range of consequences and reactions to the episode, including embarrassment, fear, rejection, and interference with the learning process. Every effort should be made to include a child with Alström in a full range of school activities.

## SIDEBAR DEFINITIONS ~ NERVOUS SYSTEM

**Absence seizure** - More common in children than adults, it's also known as a "petit mal" seizure. It involves a brief, staring spell (zoning out) and loss of conscious activity. There is usually no memory of the episode

**Ataxia** - Poor coordination of hands, arms, legs, or whole body, because parts of the nervous system that control movement and balance are affected.

**Atonic seizures** - Sometimes called "drop attacks" because muscles suddenly lose tone and/or strength, the child usually remains conscious, but the eyelids may droop, the head may nod, and the person may fall to the ground.

**Autonomic nervous system** - The portion of the nervous system concerned with the unconscious regulation of activity of cardiac muscle, smooth muscle, and glands that is controlled by the brain stem.

**Brain stem** - Divided into several distinct sections (midbrain, pons, and medulla oblongata) the brain stem regulates respiration, blood pressure, some reflexes, and the changes that happen in the body during what is called the "fight or flight" response.

**Brain ventricles** - Four communicating cavities within the brain that are filled with cerebrospinal fluid.

**Central nervous system (CNS)** - The part of the nervous system that consists of the brain and spinal cord.

**Cerebellum** - Located below and behind the cerebrum and attached to the brain stem, it controls motor function, the body's ability to balance, and the interpretation of information sent to the brain by the eyes, ears, and other sensory organs.

**Cerebrospinal fluid** - A fluid that is continuously produced and absorbed, and that flows in the ventricles within the brain and around the surface of the brain.

**Cerebrum** - The largest part of the brain, it contains sections called lobes that regulate memory, speech, the senses, emotional response, and more.

**Clonic seizures** - Rhythmic jerking movements of the arms and legs, sometimes on both sides of the body caused by rapid contraction and relaxation of the muscles.

**Computerized tomography scan (CT scan)** - A non-invasive and painless test that produces multiple cross-sectional images of the bone, soft tissue, and vessels.

**Diencephalon** - Sitting inside the cerebrum above the brain stem it contains the thalamus, hypothalamus, and epithalamus. It controls sensory function, food intake control, and sleep.

**Electroencephalogram (EEG)** - A non-invasive, painless test that measures and records the electrical activity of the brain.

**Focal seizure** - Sometimes called a partial or temporal seizure. It occurs when abnormal brain electrical activity remains in a limited area. The seizures may sometimes turn into generalized seizures, which affect the whole brain.

**Hypersomnia** - Excessive sleepiness, is a condition in which a person has trouble staying awake during the day and can fall asleep at any time.

**Hypotonia** - Decreased muscle tone.

**Magnetic resonance imaging (MRI)** - A test that uses a magnetic field and pulses of radio wave energy to take images of organs and structures inside the body, such as the brain.

**Myoclonic seizures** - Rapid, brief contractions or relaxations of a muscle that cause a sudden, jumpy movement.

**Peripheral nervous system** - Nerves in the body that lie outside the CNS (Central Nervous System).

**Pituitary** - A pea-sized gland, sometimes referred to as the "master gland", it is located at the base of the skull and secretes hormones that control hormone secretion from other glands throughout the body.

**Sella turcica** – A structure at the middle of the base of the skull that holds and protects the pituitary gland.

**Tonic seizures** - Brief seizures, usually lasting about 60 seconds or less, consisting of the sudden onset of stiffening in the muscles (neck, upper limbs, or thighs.)

**Tonic-clonic seizures** - Sometimes called 'grand mal' seizures, they are characterized by generalized stiffening of flexor or extensor muscles (the tonic phase), usually with loss of consciousness, followed by generalized jerking of the muscles (clonic activity.)

**White matter** - Located in the cerebellum, cerebrum, and spinal cord, it makes up roughly 60 percent of the total brain volume and contains nerve fibers, or axons, surrounded by a type of white colored fat called myelin.



## CHAPTER EIGHTEEN ~ GENETICS

*The capacity to blunder slightly is the real marvel of DNA. Without this special attribute, we would still be anaerobic bacteria and there would be no music.*  
~ Lewis Thomas (1913-1993)

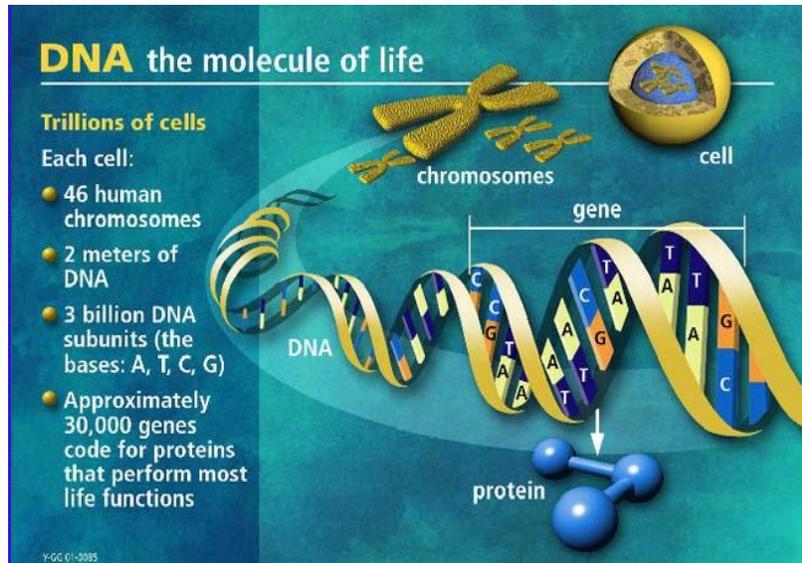


ILLUSTRATION OF A DNA MOLECULE Courtesy of Genetic Alliance.

### *The Nature and Function of Human Genetic Material*

The 46 chromosomes of the human body are made up of strings of thousands of genes. Genes are made of DNA, the “blueprint of human life.” It is the chemical responsible for storing and transferring all hereditary information in a cell. A DNA molecule consists of two chains wound around each other to form a **double helix**.

The structure resembles a twisted ladder, with the horizontal rungs made up of pairs of four chemical bases abbreviated A (Adenine,) T (Thymine,) C (Cytosine,) and G (Guanine.) Each rung of the ladder is made up of pairs of these bases, either A with T or G with C. The human body has approximately three *billion* base pairs (or six billion bases of DNA) in most cells. This is the **human genome**.

A **gene** is a segment of DNA containing fewer than 1000 to several million bases that contain a “recipe” for making a **protein**. The sequence of the bases (the order of the A’s, T’s, C’s and G’s) is different for every person and determines which molecules (usually proteins) will be made. Each person has a unique set of genes that are contributed randomly from each parent and paired at fertilization – half from the mother and half from the father.

The genes are carried on a set of 23-paired **chromosomes** (46 chromosomes, 23 from each parent), which are found in the nucleus of every cell. There are 22 numbered, or **autosomal** chromosomes (1-22) plus a pair of XX or XY chromosomes that determine gender. When fertilization occurs, one chromosome from each parent is paired. Therefore, the genes located on

the chromosomes will also be paired. The gene responsible for Alström Syndrome (*ALMS1*) is located at the top of chromosome 2.

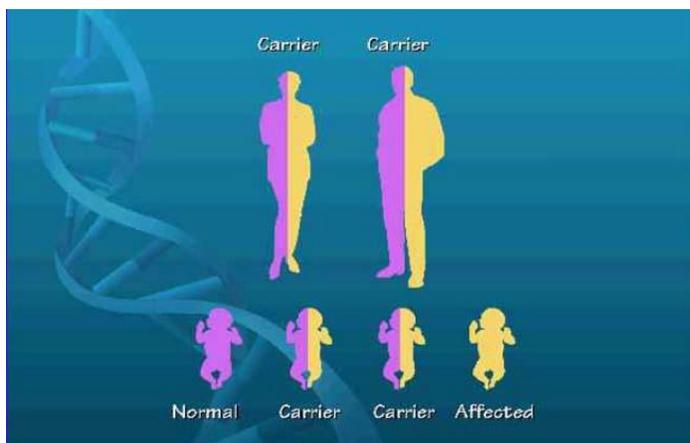
Variation in the DNA sequence, along with influences from the environment, accounts for all of human diversity, including diseases. It is the variation in the genes that causes differences in physical characteristics.

Most DNA variation is normal, but sometimes harmful changes occur in the DNA, causing or contributing to disease. Even a tiny change or “typographical error” (a wrong letter, an extra letter, or a missing letter) in the DNA sequence can have an impact on the function of the protein that is produced.

### ***How is Alström Syndrome Inherited?***

Alström Syndrome is a hereditary disorder caused by **mutations** in the *ALMS1* gene, usually passed down from each parent to the child. Everyone has two copies of every gene, including *ALMS1*; one copy is received from their mother and one from their father. The chromosomes are paired so there are 2 copies of each gene at every location, or **locus**.

The birth of a child with Alström Syndrome, in most cases, establishes both parents as **heterozygous** carriers. People who have only one copy of the defective gene don't show any signs of the disease, but, as “**carriers**”, can pass along a single copy of the mutation in *ALMS1* to their offspring. One parent alone cannot transmit Alström Syndrome to a child. In Alström Syndrome, both copies of *ALMS1* are altered in order to result in the disorder. We call this **recessive** inheritance because of this. The requirement for a “double dose” of the altered Alström gene explains why the syndrome is so rare. Every fertilization (combination of genes) is like a new deal from a very large, well-shuffled deck of cards. If both parents carry a single copy of the altered gene, all offspring will have a 25% risk of inheriting both altered genes and expressing the disorder. Fifty percent of their children may be carriers, and 25% may receive both ‘normal’ copies of *ALMS1*. Males and females are affected with equal probability (a 1:1 ratio).



### **Illustration of Genetic Inheritance of a Recessive Gene**

**LEGEND:** *If both parents are carriers of an autosomal recessive trait like Alström Syndrome, there is a 25% chance with each pregnancy that a child will inherit both abnormal genes and develop the disease. There is a 50% chance of a child inheriting only one abnormal gene from one of his parents (being a carrier). This does not necessarily mean that ¼ of the children of two carriers will be always be affected; it does mean that at conception each child has a one in four chance of inheriting the disorder and a 50:50 chance of being a carrier. (Courtesy of Genetic Alliance)*

## Genetics and Genealogy

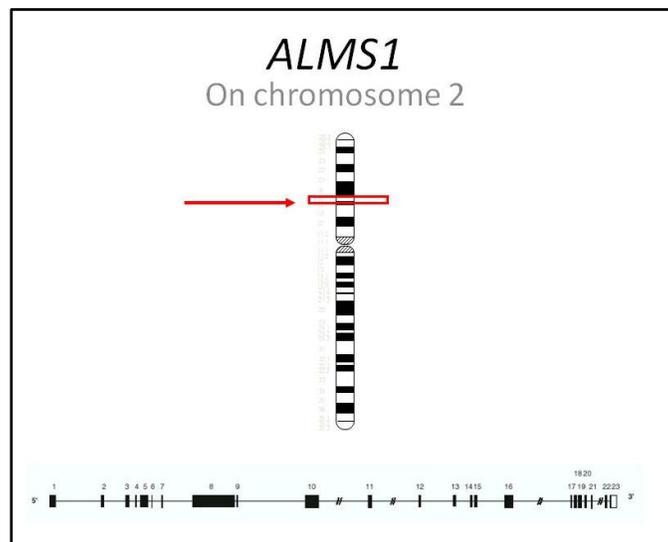
**Consanguinity** is a mating between two people who are genetically related to each other, even very distantly. In such cases, there is an increased likelihood that their genetic make-up will be similar, and they could each carry the same mutation in the same gene received from a common ancestor. Chances for such an unlikely combination are increased in culturally or geographically isolated populations where individuals live and marry within small communities. Such is the case with the Acadians, whose ancestors were a small number of early settlers of Nova Scotia. The genealogy of several Acadian families with Alström Syndrome who thought that they were not “related” has been traced back through 13 generations to one common ancestral couple who immigrated from France in the early 1600’s.

Alström Syndrome has also been identified in several other isolated populations that are not ethnically related to the Acadians, for example in Pakistan and Asia. However, we also know that Alström Syndrome is found world-wide among people of *all ethnicities and nationalities* and in families where there is no known or likely consanguinity.

### The Alström Syndrome Gene: *ALMS1*

Alström Syndrome is designated by the gene symbol *ALMS1*. *ALMS1* is located on the short arm (top half) of chromosome 2. In Alström syndrome, there is no reported **genetic heterogeneity**, which means that there is probably only one single gene that is responsible for Alström Syndrome. Remember, all of us have two copies of the “Alström gene” – it is only when there are two “mistakes” in the gene that Alström Syndrome occurs.

#### ILLUSTRATION OF CHROMOSOME 2



**LEGEND:** The area in red pinpoints the location of the *ALMS1* gene on the top arm of chromosome 2, called 2p13. The illustration below depicts the arrangement of the 23 exons, or “parts” of the *ALMS1* gene.

### **WHAT IS A GENETIC COUNSELOR?**

Genetic counselors are health professionals with specialized graduate degrees and experience in the areas of medical genetics and counseling. Genetic counselors work as members of a health care team, providing information and support to families who have members with birth defects or genetic disorders and to families who may be at risk for a variety of inherited conditions. They investigate the problem present in the family, interpret information about the disorder, analyze inheritance patterns and risks of recurrence, and then review available options with the family.

**Genetic counselors also provide supportive counseling to families**, serve as patient advocates and refer individuals and families to community or state support services. They serve as educators and resource people for other health care professionals and for the general public. Some counselors also work in administrative capacities. Many engage in research activities related to the field of medical genetics and genetic counseling.

*Adapted from the National Society of Genetic Counselors, Inc.*

### ***Mutations in ALMS1***

Some changes in the DNA sequence of the *ALMS1* gene do not cause any noticeable effects. Other types of mutations can alter the gene sequence in a number of ways that have significant effect on the *ALMS1* protein. It is possible to have many different kinds of changes in this large gene, and one parent could have one type of mutation, while the other parent carries another (different) type of mutation. There are now more than 180 different mutations spread across different locations in the *ALMS1* gene, and with new

techniques more are being identified every day. The types of mutations that have been found in *ALMS1* so far include:

- **frameshift mutation** - A mutation resulting from an addition or subtraction that is not an exact multiple of 3 base pairs in a coding sequence. From the point of the mutation onwards, the coding sequences are read out of phase and the resulting protein is usually damaged and unable to function. Insertion, deletion, and duplication of one or more bases can all be frameshift mutations.
- **missense mutation** - A change in the gene sequence that results in a different amino acid in the protein. The significance of many missense mutations is difficult to interpret.
- **nonsense mutation** - A genetic mutation in a base in the DNA sequence which signals premature termination of transcription of the protein, resulting in a shorter, unfinished protein product.

### ***Genetic Testing***

Genetic Testing for Alström Syndrome is available, but whether or not testing is pursued should be based on consideration of the individual's circumstances and concerns. Unfortunately, there are many circumstances where genetic testing is not useful or appropriate.

Even with the existing techniques, with reasonable effort, we are still not able to detect the *ALMS1* mutations in all Alström Syndrome patients. About 60-70% of the mutations can be found in a matter of a few weeks. An additional 30 % may be found after extensive examination of the gene which may often take months or even years. Expense can be an issue, as well. There are also mutations located in certain regions of the gene that cannot be thoroughly examined with

the current technology. Therefore, unfortunately, in some Alström Syndrome patients it is not yet possible to confirm the diagnosis in a genetic laboratory.

If you are considering having more children, you may be concerned that you will have another child with Alström Syndrome. In some cases, prenatal diagnosis may be possible if both *ALMS1* mutations are known for each parent in that particular family. There are two different procedures that can be performed at different stages of gestation. **Chorionic villus sampling (CVS)** is a procedure that is performed between 10-14 weeks gestation and involves sampling some of the cells in the placenta and performing genetic testing on those cells. The risk of miscarriage from this procedure is thought to be <1%. The second procedure, called **amniocentesis**, is performed between 16-20 weeks of gestation and involves sampling cells found in the amniotic fluid. The risk of miscarriage related to amniocentesis is very low.

At the present time, there is no way to determine with absolute certainty whether a person is a carrier unless they have had an affected child.

### ***Mouse Model for Alström Syndrome***

Mice live the equivalent of a human lifetime in one or two years and are very similar genetically and physiologically to humans. Mouse models are valuable for biochemical and physiological studies to study the disease progression and for testing potential drug treatments and other therapies. Mice enable us to study and hasten the understanding of Alström Syndrome in a fundamental way that simply is not possible in people.



CARL HENRY MOUSE

In 2004, the first mouse model for Alström Syndrome, *Alms1*<sup>-/-</sup>, was developed at The Jackson Laboratory. Testing has shown that this little mouse seems to exhibit most of the features that characterize human patients with Alström Syndrome. The first “Alström mouse” was dubbed “Carl Henry Mouse.”

### ***The Future of Genetic research***

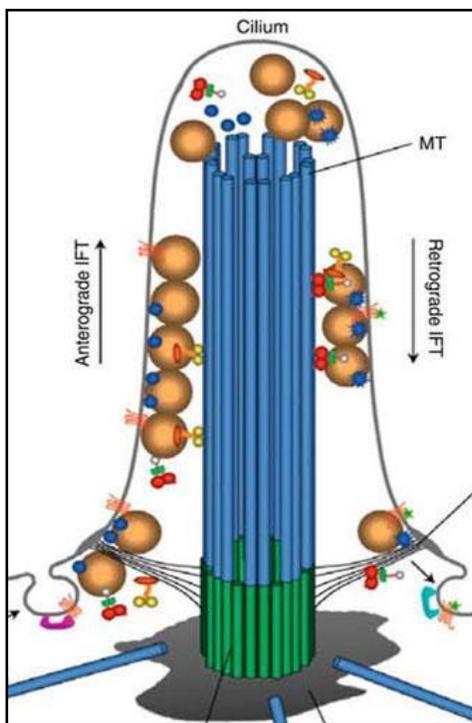
In 1997, Alstrom Syndrome was “**mapped**” to chromosome 2, which means that its chromosomal location was confirmed. In 2002, the actual gene, *ALMS1*, was discovered. Research scientists relied on blood and other tissue samples provided by patients and family members to achieve these milestones. However, finding the gene is only the first step in

understanding the disease process and in developing directed therapy for patients with Alström Syndrome.

The first major goal of current research programs is to understand the mechanism of ALMS1 (in other words, figure out what the gene does and how to fix it when it goes wrong).

Happily, research has entered an exciting phase of rapid progress. Sophisticated techniques such as Next Generation Gene Sequencing, as well as the ability to see and explore the smallest components of a cell with high-power microscopes and imaging capabilities is leading to vast amounts of information not accessible only a few years ago. With identification and funding of the right experts to develop and exploit the new techniques, it is ultimately hoped that an effective treatment, or cure, will result from this molecular genetic work.

### Alström Syndrome, A Possible Ciliopathy



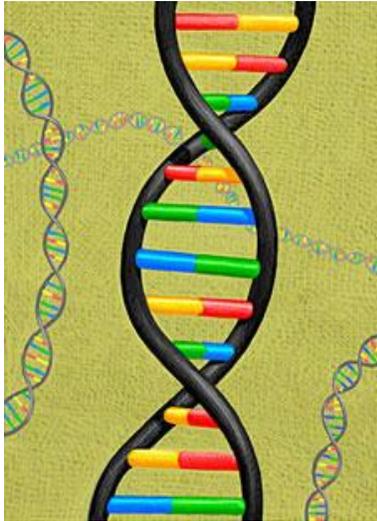
Although much is still unknown about the structure and function of motile and primary cilia, defective and dysfunctional cilia are now believed to underlie a number of devastating genetic conditions termed **ciliopathies**. Ciliopathies can affect multiple systems, causing retinal degeneration and blindness, hearing loss and glue ear, chronic respiratory infections, lung and airway congestion, kidney, liver, and heart disease, infertility, truncal obesity, diabetes, and skeletal abnormalities. Not all ciliopathies have the same clinical presentation, but they often share some major features in common. So, disorders such as Bardet-Biedl, Meckel-Gruber, and Joubert Syndrome, although very different in many respects, are all considered to be ciliopathies. It is suspected that Alström Syndrome falls into this classification of disorders because the Alström protein (ALMS1) is located in and near the **cilia**, and many of the clinical features resemble those of other ciliopathies.

Cilia are microscopic, hair-like structures (like small antennae) that extend from the surface of almost every mammalian cell at some point in their development. Cilia detect a variety of different stimuli outside the cell and control multiple signalling pathways within the cell. Thus, they are a vital part in the proper functioning of the human body, including cell cycle progression, proliferation, and development.

There are two types of cilia, which are structurally different, but which can also function either separately or together:

- **Motile** (or moving) cilia are found in the lungs, respiratory tract and middle ear. These cilia have a rhythmic waving or beating motion. They work, for instance, to keep the airways clear of mucus and dirt. They also help propel sperm.

- **Non-motile** or **primary** cilia were long thought to be evolutionary vestigial organs, but they are now known to play crucial roles in most organs by acting as ‘sensory antennae’ for cells, receiving signals from other cells or fluids nearby.



When proteins are synthesized in the cell body, they must be transported to the tip of the cilia to communicate with the cell’s environment. This elaborate process is called Intraflagellar Transport (IFT).

### ***The Importance of Cilia***

Cilia are found nearly everywhere in the human body, and new information about how they influence disease is emerging rapidly. These are only a few examples. They are inside photoreceptors of the eyes, connecting the inner segments in the retina to the outer segment. They move proteins made in the inner segment to outer segment. Malfunction of the cilia stops transport of vital proteins, and the photoreceptors die.

Motile cilia line the respiratory airways, to help clear mucus and dust. Sinusitis, rhinitis, bronchitis and otitis media have all been associated with motile cilia dysfunction in other ciliopathies.

Additionally, cilia are important during development of the heart. Flow of fluid is sensed by cilia leading to changes in cell growth. However, it is not clear how disruption of the function of cilia affects the unusual patterns of dilated cardiomyopathy found in Alström Syndrome.

### ***The Future of Alström Syndrome Research***

So far, there is no medical treatment that can cure Alström Syndrome or reverse or prevent all of its medical complications. Someday, with complete understanding of this gene, effective means of therapy *can be* developed.

*Schematic diagram courtesy of Queen Mary Hospital, University of London*

Although there is lack of knowledge of the basic mechanism whereby mutations in the *ALMS1* gene affect the body, the outlook is full of promise. In the coming years, researchers will undoubtedly identify the function and mechanism of *ALMS1* and begin to understand how it results in such a devastating clinical condition. With a comprehensive knowledge of the pathophysiology involved in Alström Syndrome, we will be well positioned to develop therapies that will intervene with precision and predictability on a molecular level. Without these therapies, medical management of Alström Syndrome is limited to the early detection of those complications which can be treated. As we know, anticipation of such problems and prompt intervention generally can improve the outcome of treatment.

## SIDEBAR DEFINITIONS ~ GENETICS

**Allele** - One of a pair of genes that occupy a specific position on a specific chromosome. Each person possesses only 2 alleles for each gene, receiving one of each pair of alleles from each parent.

**Amniocentesis** - Tests a sample of the amniotic fluid in the womb for genetic defects (the fluid and the fetus have the same DNA) by inserting a thin needle through the woman's abdomen and into the womb.

**Autosomal** - Occurring on one of the 22 numbered (non-sex) chromosomes.

**Chorionic villus sampling ( CVS)** - Performed by removing and testing with a fine needle for genetic abnormalities in a very small sample of the placenta during early pregnancy.

**Chromosome** - Thread-like structures made up of genes and other DNA that are tightly coiled within the nucleus of a cell. The nuclei of human cells normally contain 46 chromosomes, arranged in 23 pairs.

**Carrier** - An individual who is heterozygous for a recessive trait.

**Cell** - The basic structural unit of all living organisms. The central body of a cell is the nucleus which contains the inherited genetic material, DNA, arranged in thread-like structures known as chromosomes.

**Cilia** – Very small, microscopic hair-like projections from the surface of cell.

**Ciliopathy** – A broad category of diseases caused by structural or functional problems with cilia.

**Consanguinity** - A mating between genetically related individuals who share a common ancestor.

**DNA** - Deoxyribonucleic acid is a nucleic acid composed of long chains of molecules called nucleotides that contain nitrogenous bases (A adenine, G guanine, T thymidine. and C cytosine); A is always paired, with T, and G is paired with C.

**Founder effect** - A genetic trait or mutation occurring in one ancestral individual is passed through many generations.

**Gene** - The fundamental unit of heredity material (DNA) arranged along the lengths of chromosomes that codes for a protein. Different sequences and numbers of the AT and GC base pairs produce different genes.

**Genetic heterogeneity** - A given trait or disorder can be caused by several different genes.

**Heterozygous** - A carrier of one normal gene paired with its mutated allele.

**Homozygous** - A pair of identical alleles.

**Human genome** - The total possible array of genes carried by human beings.

**Locus** - The site or location of a particular gene on a chromosome.

**Mutation** - The process that produces an alteration in DNA or chromosomal structure.

**Phenotype** - The appearance or physical manifestations of the actions of a gene.

**Protein** - May be a structural constituent of a given tissue, an enzyme that causes a chemical reaction, or a hormone among other potential functions.

**Recessive** - A pattern of inheriting a genetic disorder. The result of inheriting two copies of a mutant gene, one from each parent.

## AFTERWORD

### A NEW BEGINNING

*The quality of your healthcare depends as much on you as on your doctor, on your being informed, on your asking the right questions, on your being your own best advocate.*

*~ Critical Condition - PBS Special*

Alström Syndrome is touching the lives of more and more people - those who live every day with its consequences and those who are working constantly to find better answers for people who have Alström Syndrome. The continuous accumulation and sharing of information forges new pathways for finding solutions. This Handbook is a first step. In the coming years, ASI-sponsored research and educational programs will focus on identifying the best combination of approaches for each child.

Piece by piece, using a myriad of research techniques and technologies, scientists are beginning to solve the puzzle. As research deepens our understanding, we approach a future where we can prevent and treat certain debilitating aspects of Alström Syndrome while we search for the cure. We will be able to make valid diagnoses, and treat each child effectively. This is the hope, the mission, and the vision!

**“Let us live the highest vision of what is possible.”**

*~ Inga Grace*

## Appendix I



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## Appendix II - QUICK REFERENCE PROFILE

These guidelines are a working document that reflects the state of our understanding at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

	All	Most	Some	A Few
Vision				
Nystagmus	X			
Photodysphoria	X			
Retinal degeneration	X			
Bilateral cataracts		X		
Attenuation of vessels		X		
Bilateral sensorineural hearing impairment		X		
Body type				
Short stature in adults		X		
Flat, wide feet		X		
Short stubby fingers		X		
Upper body obesity		X		
Endocrine				
Hyperinsulinemia / Insulin resistance	X			
type 2 Diabetes Mellitus		X		
Hypothyroidism			X	
Hyperthyroidism				X
Hypertriglyceridemia		X		
Hypertension		X		
Acanthosis nigricans	X			
Low HGH		X		
Low testosterone (boys)		X		
Hyperandrogenism (female)		X		
Gastroenterology (liver)				
Elevated transaminases	X			
Splenomegaly		X		
Hepatomegaly		X		
Portal hypertension			X	
Gastric reflux			X	

Renal (kidney)	X			
Elevated creatinine		X		
Proteinuria		X		
Hyperuricemia		X		
Cardiac		X		
Infantile cardiomyopathy			X	
Adolescent cardiomyopathy			X	
Developmental				
Delayed milestones		X		
Normal intelligence		X		
Sleep disturbances			X	
Absence seizures			X	
Pulmonary/respiratory				
Chest congestion		X		
Bronchiectasis			X	
COPD			X	
Asthma			X	
Urology				
Frequent UTI			X	
Incontinence			X	
Difficulty voiding			X	

## Appendix III.

### Alström Syndrome References

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## Appendix IV

### HANDBOOK GLOSSARY

**After each definition (in parentheses,) you will find the chapter each term is found in.**

**Absence seizure** - More common in children than adults, it's also known as a "petit mal" seizure which involves a brief, staring spell (zoning out) and loss of conscious activity usually with no memory of the episode. (17)

**Acute Respiratory Distress Syndrome (ARDS)** - An acute, severe injury to most or all of both lungs. (11)

**Adipose tissue**- A type of tissue that stores fat in cells. (7)

**Adipogenesis**- The process of producing and accumulating fat by the differentiation of fat cells (adipocytes) into fat tissue. (7)

**Adrenal** - Glands that sit on top of each of the kidneys and control metabolism and response to stress or fright. (15)

**Allele**- Each person possesses only 2 alleles (or alternative forms of genes which can be found at a locus) for each gene, and receives one copy from each parent. (18)

**Alveoli** - Small air sacs in the lung. (11)

**Amenorrhea** - The total absence or prolonged cessation of menstruation. (6)

**Amniocentesis** - Tests a sample of the amniotic fluid in the womb for genetic defects (the fluid and the fetus have the same DNA) by inserting a thin needle through the woman's abdomen and into the womb. (18)

**Androgen** - The generic term for any steroid hormone, such as testosterone, that stimulates or controls the development and maintenance of masculine characteristics. (6)

**Arrhythmias** - A disruption of the heart's normal electrical impulses causing an abnormal or fluctuating heart rhythm. (11)

**Ascites** - An accumulation of fluid in the abdomen. (14)

**Asperger syndrome** - Children with Asperger syndrome have difficulty with social interaction and communication, can have a narrow range of interests, have average or above average intelligence, and develop normally in the areas of language and cognition. Children with Asperger often also have difficulty concentrating and may have poor coordination.(3)

**Ataxia** - Poor coordination of hands, arms, legs, or whole body, because parts of the nervous system that control movement and balance are affected. (17)

**Atonic seizures** - Sometimes called "drop attacks" because muscles suddenly lose tone and/or strength, a child usually remains conscious, the eyelids may droop, the head may nod, and the child may fall to the ground. (17)

**Atria** - The two upper chambers of the heart in which blood collects before being passed to the ventricles. (11)

**Atrial fibrillation** - An abnormal rhythm, common in patients with DCM and often associated with deterioration of the condition. (11)

**Audiogram** - The graphic record drawn from the results of hearing tests with an audiometer. (10)

**Auditory nerve** - The “transmission line” from the hair cells in the cochlea of the inner ear to the brain. (10)

**Autism** - A complex neurodevelopment disorder, characterized by social impairments, communication difficulties, and restricted, repetitive, and stereotyped patterns of behavior. (3)

**Autism Spectrum Disorder** - A range of complex neurodevelopment disorders, which can include: impairment or difficulty with social interactions, communication problems, and restricted, repetitive, and stereotyped patterns of behavior. ASD varies significantly in nature and severity. (3)

**Autistic Spectrum** - Can range from classical autism, the most severe form, to other conditions along the scale, including milder forms known as Asperger syndrome, childhood disintegrative disorder, and pervasive developmental disorder. (3)

**Autonomic nervous system** - The portion of the nervous system concerned with the unconscious regulation of activity of cardiac muscle, smooth muscle, and glands that is controlled by the brain stem. (17)

**Autosomal** - Occurring on one of the 22 numbered (non-sex) chromosomes. (18)

**Axillae** - The underarms. (5)

**Balloon Compression Tamponade** - This procedure involves the passage of a balloon through the nose to help compress bleeding esophageal varices. (14)

**Bilateral** - Two-sided, or affecting both sides. (10)

**Bladder** - A hollow muscular organ shaped like a balloon sitting in the pelvis and held in place by ligaments attached to other organs and the pelvic bones, the bladder stores urine, swelling into a round shape when it is full and reducing its size when empty. (16)

**Body Mass Index (BMI)**- A mathematical formula to assess stature and body fat based on weight in kilograms divided by height in meters squared. ( $BMI = \frac{kg}{m^2}$ ) (7)

**Bone age** - A measure of the relative maturity of a child's skeletal system performed by x-raying several growth centers and comparing them to large numbers of other children of the same chronologic age. (6)

**Brain stem** - Divided into several distinct sections (midbrain, pons, and medulla oblongata) the brain stem regulates respiration, blood pressure, some reflexes, and the changes that happen in the body during what is called the “fight or flight” response. (17)

**Brain ventricles** - Four communicating cavities within the brain that are filled with cerebrospinal fluid. (17)

**Bronchi** - The large air tubes leading from the trachea to the lungs that convey air to and from the lungs. (11)

**Bronchoscopy** - A procedure where an instrument (bronchoscope) is inserted through the nose or mouth that allows a physician to look for abnormalities and/or take tissue samples from the lungs. (11)

**BTE** – “Behind the ear” hearing aid, or conventional hearing aid. (10)

**Buffalo hump** - The increased fatty tissue between the shoulder blades. (5)

**Capillaries** - Very small, thin vessels that connect arteries and veins. (11)

**Cardiac catheterization** - A test used to check blood flow in the coronary arteries, the pumping function of the heart, and blood pressure in the heart's chambers, using a thin wire catheter that is inserted through a blood vessel in the groin or arm to examine the heart. (12)

**Carrier** - An individual who is heterozygous for a recessive trait. (18)

**Cataract** - A cloudy or opaque area in the lens of the eye that prevents light rays from passing through the lens and focusing on the retina. (9)

**Cell** - The basic structural unit of all living organisms with the central body of a cell being the nucleus which contains the inherited genetic material, DNA, arranged in thread-like structures known as chromosomes. (18)

**Central nervous system (CNS)** - The part of the nervous system that consists of the brain and spinal cord. (17)

**Cerebellum** - Located below and behind the cerebrum and attached to the brain stem, it controls motor function, the body's ability to balance, and the interpretation of information sent to the brain by the eyes, ears, and other sensory organs. (17)

**Cerebrospinal fluid** - A watery fluid that is continuously produced and absorbed, and that flows in the ventricles within the brain and around the surface of the brain. (17)

**Cerebrum** - The largest part of the brain, it contains sections called lobes that regulate memory, speech, the senses, emotional response, and more. (17)

**Chorionic villus sampling ( CVS)** - Performed by removing and testing for genetic abnormalities in a very small sample of the placenta during early pregnancy, the sample, which contains the same DNA as the fetus, is removed by catheter or fine needle inserted through the cervix or by a fine needle inserted through the abdomen. (18)

**Chromosome** - Thread-like structures made up of genes and other DNA that is tightly coiled within the nucleus of a cell, the nuclei of human cells normally contain 46 chromosomes, arranged in 23 pairs. (18)

**Cilia** - Tiny hair-like structures found on the lung lining, they filter out dust and propel mucus up and out of the lung with a synchronized wave-like motion. (11)

**Cirrhosis** - A general classification of liver disease characterized anatomically by widespread nodules in the liver combined with fibrosis. The fibrosis and nodule formation causes distortion of the normal liver architecture which interferes with blood flow through the liver. Cirrhosis can also lead to an inability of the liver to perform its biochemical functions. (14)

**Clean Intermittent Catheterization (CIC)** - Draining the bladder every 6 hours by inserting a small tube through the urethra. (16)

**Clitoris** - A small, pea-shaped organ just above the urethra in females. (6)

**Clonic seizures** - Rhythmic jerking movements of the arms and legs, sometimes on both sides of the body caused by rapid contraction and relaxation of the muscles. (17)

**Cochlea** - Snail shaped structure, lined with millions of tiny hairs that are the sensory organ of hearing responsible for transmitting sound to the auditory nerve. (10)

**Cochlear implant** - Small, complex electronic device that can help to provide a sense of sound to a person who is profoundly deaf or severely hard-of-hearing. The implant consists of an external portion that sits behind the ear and a second portion that is surgically placed under the skin. (10)

**Computerized tomography scan (CT scan)** - A non-invasive and painless test that produces multiple cross-sectional images of the bone, soft tissue, and vessels. (17)

**Conductive hearing loss** - Occurs in the external auditory canal or in the bones of the middle ear. (10)

**Cone cells** - Concentrated in the center of the retina, about 6.5 million cones in each eye are responsible for color and detailed vision. (9)

**Congenital** - A condition existing from birth. (9)

**Congestive heart failure (CHF)** - The inability of the heart to efficiently pump out all the blood that comes to it which results in an accumulation of fluid in various parts of the body. (11)

**Consanguinity** - A mating between genetically related individuals who share a common ancestor. (18)

**COPD (chronic obstructive pulmonary disease)** - Progressive lung disease that makes it hard to breathe. (11)

**Creatinine** – A metabolic (metabolism related) waste that is normally excreted as urine. (11,15)

**Cryptorchidism** - The failure of one or both testes to descend. (6)

**Cystitis** - Infection in the bladder (cysto refers to the bladder.) (16)

**DASH diet (Dietary Approaches to Stop Hypertension)** - A diet based on fruits, vegetables, whole grains, and lean meats with limited fats and sugar. (12)

**Detrusor** - The smooth muscle that forms the bladder. (16)

**Detrusor urethral dysynergia** - The urethral sphincter muscle contracts and the bladder (detrusor) muscle also contracts at the same time, resulting in the obstruction of normal urinary flow. (16)

**Diabetes mellitus** – A metabolic disorder in which the body fails to make enough insulin or becomes resistant to insulin or both, resulting in high blood sugar levels. In Alström Syndrome, patients are resistant to the effects of insulin. (8)

**Diastolic** - Refers to the time when the heart is in a period of relaxation and dilatation (expansion.) (11)

**Diastolic pressure** - Pressure in the arteries when the heart is resting. (12)

**Diencephalon** - Sitting inside the cerebrum above the brain stem and containing the thalamus, hypothalamus, and epithalamus, it controls sensory function, food intake control, and sleep. (17)

**Digital aids** - Hearing instruments with digital circuits that can be precisely programmed to match the patient's individual hearing loss at each specific frequency and offer improved clarity of sound, less circuit and background noise, and faster processing of sound. (10)

**Dilated cardiomyopathy (DCM)** - An abnormal enlargement and weakening of the heart muscle. (11)

**Distal Splenorenal Shunt (DSRS)**- A surgical procedure connecting the main vein in the spleen to the left kidney vein. The procedure is done to lower blood pressure in the swollen vessels and limit bleeding. (14)

**DNA** - Deoxyribonucleic acid is a nucleic acid composed of long chains of molecules called nucleotides that contain nitrogenous bases ( A adenine, G guanine, T thymidine. and C cytosine). A is always paired, with T, and G is paired with C. (18)

**Dyspnea** - An unpleasant sensation of shortness of breath. (11)

**Dysuria** - Difficult or painful urination. (16)

**Eardrum (tympanic membrane)** - A small piece of tissue at the end of the ear canal that vibrates in response to sound waves or pressure changes. (10)

**Echocardiogram (echo)** - A non-invasive method to evaluate the size and functioning of the valves and chambers of the heart by using sound waves. (11)

**Edema** - Fluid buildup at the ankles, belly or small of the back, caused by the weak pumping action of the heart. Also, swelling caused by the accumulation of fluid in cells and tissues. In kidney failure, fluid may collect in the feet, hands, abdomen, or face. (11,15)

**Ejection fraction** - A useful measure of left ventricular performance (pumping efficiency). The normal range is 63-77% for males and 55-75% for females. If the left ventricle wall is thinned, a decrease in the ejection fraction is seen. (11)

**Electrocardiogram (ECG/EKG)** - A routine test that records a picture of the heartbeat by measuring its electrical changes on a graph. (11)

**Electroencephalogram (EEG)** - A non-invasive, painless test that measures and records the electrical activity of the brain. (17)

**Electrolytes** - Ions in the blood stream including sodium, potassium, chloride, and bicarbonate which balance of the electrolytes are essential for normal function of cells and our organs. (15)

**Electrophysiology studies** - A catheter based diagnostic test to assess the electrical system of the heart. (11)

**Electroretinogram (ERG)** - A test in which an electrode is placed on, or near, the cornea to measure the electrical responses of the rods and cones of the retina. (9)

**End stage renal disease (ESRD)** - A serious condition in which the kidneys fail to regulate water and chemicals in the body by ridding the body of wastes. (15)

**Endocrine** - A group of glands in the body that function to secrete hormones, and are regulated by “feedback control” from the target organs. (6)

**Endoscopic Band Ligation** - Considered the first line of treatment, a rubber band is tied around the bulging veins in the esophagus to prevent ruptures or stop bleeding. (14)

**Esophageal varices** - Distended, weakened, and blood filled veins in the esophageal wall caused by pressure in the portal vein, which have the potential to bleed into the esophagus. (14)

**Esophagus** - The passage extending from the mouth to the stomach. (14)

**Estrogen** - The hormone produced by the ovaries in response to LH and FSH which stimulates certain target tissues such as breast tissue, uterus, and fat cells, and is responsible for maintaining bone, brain, and lipid metabolism. (6)

**Eustachian tube** - The tube that equalizes pressure by connecting the middle ear, behind the eardrum, to the back of the throat. (10)

**Exenatide (Byetta)** - A synthetic, man-made, hormone that resembles and acts like incretins (hormones that are secreted by the intestines that control appetite.) (8)

**Expressive language delay** - Failure to develop speech, expressing thoughts and language abilities typical of other children in their age group, but often very capable of understanding what is being said to them. (3)

**Fallopian tubes** - Two tubes through which the ova travel to the uterus. (6)

**Fibrosis** - The formation of excess fibrous tissues or scar tissue, usually because of injury or long-term inflammation. (11)

**Focal seizure** - Sometimes called a partial or temporal seizure, it occurs when abnormal brain electrical activity remains in a limited area, sometimes turning into generalized seizures which affect the whole brain. (17)

**Follicle-stimulating hormone (FSH)** - A hormone that stimulates sperm production in the male and ovarian follicle development in the female. (6)

**Founder effect** – When a genetic trait or mutation occurring in one ancestral individual is passed through many generations. (18)

**Frequency** - Cycles of sound waves per second that determine the pitch of a sound. (10) The need to empty one's bladder frequently. (16)

**Fundus** - The inner lining of the back of the eye. (9)

**Gastric reflux esophagitis** - Esophagitis is inflammation of the esophagus, which can result in symptoms such as hoarseness, difficulty swallowing, and heartburn. Esophagitis is most commonly caused by acid reflux. (14)

**Gastro-esophageal reflux (GER)** - A backflow of acid from the stomach into the swallowing tube or esophagus, this acid can irritate and sometimes damage the delicate lining on the inside of the esophagus. (14)

**Gastrointestinal (GI) tract** - Refers to the esophagus, stomach, small and large intestine. (14)

**Gastrointestinal endoscopy** - An examination that is performed using an endoscope, a flexible fiber optic tube with a small camera that not only allows detection of gastrointestinal varices, but treatment as well. (14)

**Gene** - The fundamental unit of heredity material (DNA) arranged along the lengths of chromosomes that codes for a protein. Different sequences and numbers of the AT and GC base pairs produce different genes. (18)

**Genetic heterogeneity** – A given trait or disorder can be caused by several different genes. (18)

**Gestational diabetes** - Onset or recognition of glucose intolerance during pregnancy. (8)

**GHRH** - Released from the hypothalamus to stimulate release of GH. (6)

**Glitizones (thiazolidinediones)** - Drugs that work by lowering the entire body's resistance to insulin and sometimes taken with metformin and/or a sulfonylurea, requiring regular monitoring for potential liver and heart problems and increases in triglycerides. (8)

**Glomerulus (Plural: glomeruli)** - The glomerulus is the main filter of the nephron that consists of a mass of tiny tubes through which the blood passes, allowing water and soluble wastes to pass through and be excreted as urine.(15)

**Glucagon** - A hormone produced by certain cells in the pancreas that acts directly on the liver and other tissues to stimulate the breakdown of stored glycogen and the release of glucose. (8)

**Glucose** - Sugar, the major energy provider in the body. (8)

**Glue ear** - A thick, sticky fluid forming in the middle ear common among children that is often associated with middle ear infections. (10)

**Glycated hemoglobin (HbA1c)** - A measurement taken from a blood sample that provides an evaluation of how much glucose the red blood cells have been exposed to over their lifespan (approximately 100-120 days) with normal levels ranging from 4-6% and levels of greater than 7% indicating poor control of diabetes. (8)

**Glycosurea** - Presence of glucose in the urine, an indicator of an imbalance in the glucose/insulin ratio. (8)

**Gonadotropins** - A collective name for the pituitary hormones that stimulate the genital organs to produce the sex hormones. (6)

**Growth Hormone (GH)** - The most abundant hormone produced by the pituitary gland, that affects energy, bone and muscle growth and strength, brain function, fat and glucose metabolism, physical and mental health, especially during adolescence. (6)

**Gynecomastia** - The enlargement of the male breast due to proliferation of glandular tissue. (6)

**Heart biopsy** - The removal of a small sample of the heart muscle using a catheter and a very small special cutting tool, which is guided to the heart. (11)

**Heart catheterization** - A thin plastic tube or catheter guided through an artery or vein in the arm or leg and into the heart that measures blood pressure and how much oxygen is in the blood, it also provides other information about the pumping ability of the heart muscle. (11)

**Hematuria** - Blood in the urine which may turn the urine pink or cola-colored. (15)

**Hepatic** - Refers to the liver. (14)

**Hepatic encephalopathy** - A condition describing the adverse effects of liver disease on the central nervous system with symptoms that may range from slight disorientation to coma. (14)

**Hepatic vein** - The vein leading away from the liver through which the cleansed blood passes, leading back to the heart. (14)

**Hepatocytes** - Cells in the liver. (14)

**Hepatomegaly** - Enlarged liver. (14)

**Heterozygous** - A carrier of one normal gene paired with its mutated allele. (18)

**High-density lipoprotein (HDL)** - The 'good' cholesterol. (13)

**Hirsutism** - The appearance of hair in females where it should not normally be, for example facial, chest or back hair in females possibly due excess male hormones called androgens, primarily testosterone. (6)

**Homozygous** - An individual with a pair of identical alleles. (18)

**Hormones** - Chemicals released into the blood-circulation that stimulate other hormones or specific cell functions. (6)

**Human genome** - The total possible array of genes carried by human beings. (18)

**Hypercholesterolemia** - High cholesterol levels in the blood. (13)

**Hyperglycemia (glycemia)** - High levels of blood glucose. (8)

**Hyperinsulinemia** - High levels of insulin in the blood caused by the body's resistance to the actions of insulin and the compensatory increase insulin production by the pancreas. (8)

**Hyperlipidemia** - An elevation of fats or lipids in the blood. (13)

**Hyperlipoproteinemia** - Characterized by abnormally elevated concentrations of specific lipoprotein particles in the plasma. (13)

**Hyperostosis frontalis interna** - Overgrowth of the frontal bone of the skull, usually bilateral (both sides) and symmetrical, it is harmless and of no clinical significance. (5)

**Hyperphagia**- Abnormally increased appetite for, and consumption of food, thought to be associated with the hypothalamus in the brain. (7)

**Hypertension** - Usually defined as blood pressure consistently greater than 140/90 in adults, normal blood pressure for children varies with the size and age of the child. (8,11)

**Hypertriglyceridemia** - Excess triglycerides in the blood plasma. (13)

**Hypertrophic cardiomyopathy** - An abnormal growth of the heart muscle fibers making the heart thickened and stiff. (11)

**Hypogonadism** - Underdeveloped genital system manifested by deficiencies in production of eggs and sperm and/or the secretion of gonadal hormones. (6)

**Hypothalamus** - Plays a key role in growth and sexual development and also regulates appetite, metabolism, body temperature, mood, and other functions affected by Alström Syndrome. (6)

**Hypothalamus** - The part of the brain that receives stimulation from neurons and releases signaling chemicals that target the pituitary gland causing it to inhibit or release pituitary hormones. (6)

**Hypothyroidism** - An inadequate production of the thyroid hormone, thyroxine, that can result in slowed metabolism. (6)

**Hypotonia** - Decreased muscle tone. (17)

**Ideal body weight**- An estimate of what your healthy weight is, taking into account gender, height, and size of your frame. (7)

**IGF-I (Insulin-like Growth Factor 1 or Somatomedin C)** - A protein synthesized by the liver and circulated in the blood in response to growth hormone stimulation that stimulates growth in cells and tissues. (6)

**Impaired fasting glucose**- Also referred to as “glucose intolerance” and is characterized by fasting blood glucose levels above normal, but below the diabetic threshold. (6.1-7.0 mmol/L) (8)

**Incontinence** - The inability to completely control the release of urine. (16)

**Incretins**- Hormones that are secreted in response to glucose in the small intestine through circulation to the pancreatic beta cells, causing them to secrete more insulin. (8)

**Inflammation** - The body's complex reaction involving a number of cellular and molecular components that can cause damage to surrounding tissues. (14)

**Interstitial lung disease** - A group of lung diseases that affect the tissue and air space around the air sacs. (11)

**Islet cells** - Specialized cells in the pancreas that produce insulin. (8)

**Insulin**- A hormone produced and secreted by islet cells in the pancreas that acts directly on the liver and other tissues to regulate glucose level in the body. (8)

**Insulin resistance**- A condition occurring when the tissues become less sensitive to insulin, resulting in an inability to use the body's own insulin to properly control blood glucose. (8)

**ITE (in-the-ear)** - Hearing aid placed within the ear. (10)

**Kyphosis** - A convex, forward curvature of the upper spine producing a "hump" when viewed from the side. (5)

**Labia** - The inner and outer lips of the vagina. (6)

**Lactulose** - A synthetic sugar that reduces the amount of ammonia in the blood by drawing it out of the bloodstream and into the small intestine. (14)

**Leber Congenital Amaurosis (LCA)** - The general term for a group of autosomal, recessive eye disorders characterized by moderate to severe vision abnormalities identifiable at birth or in the first months of life. [LCA is caused by a different gene than Alström Syndrome.] (9)

**Leydig cells** - Cells in the testes that release hormones called androgens. (6)

**Lipodystrophy**- The loss of adipose tissue in selected areas of the body, usually associated with insulin resistance, hyperglycemia, hyperlipidemia, and other metabolic disturbances. (7)

**Lipoproteins** - Complexes of lipid and protein that circulate in the blood, they are named according to their density: high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL.) (13)

**Liver biopsy** - Sampling a small amount of liver tissue for microscopic examination by inserting a needle under the ribs and into the liver. (14)

**Liver enzymes** - An initial step in detecting liver damage that is a simple blood test to determine the presence of certain liver enzymes in the blood. (Under normal circumstances, these enzymes reside within the cells of the liver. When the liver is injured, these enzymes are spilled into the blood stream.) (14)

**Locus** - The site or location of a particular gene on a chromosome. (18)

**Low-density lipoprotein (LDL)** - 'Bad' cholesterol can slowly build up in the inner walls of the arteries to form plaque and increase the risk for heart attack or stroke. (13)

**Lower esophageal sphincter (LES)** - A muscle that opens to let food pass into the stomach and closes to stop stomach acid and juices from backing up into the esophagus. (14)

**Luteinizing hormone (LH)** - Secreted by the pituitary gland and acting directly on the testes or ovaries to stimulate production of gonadal hormones (androgens and estrogens.) (6)

**Macula** - The center of the retina containing the highest concentration of cone cells. (9)

**Magnetic resonance imaging (MRI)** - A test that uses a magnetic field and pulses of radio wave energy to take images of organs and structures inside the body, such as the brain. (17)

**Menarche** - The onset of menstruation, the periodic shedding of the lining of the uterus.(6)

**Metformin (glucophage)**- A drug that improves insulin sensitivity. (8)

**Mutation** - The process that produces an alteration in DNA or chromosomal structure. (18)

**Myoclonic seizures** - Rapid, brief contractions or relaxations of a muscle that cause a sudden, jumpy movement.(17)

**Myringotomy tubes** - Tiny plastic tubes that are placed in the eardrum during surgery allowing air to circulate in the middle ear and preventing fluid from building up. (10)

**Nephrons** - The nephron is responsible for the actual purification and filtration of the blood. About one million nephrons are in the cortex of each kidney. (15)

**Nephropathy** - A slow deterioration of the kidneys. (15)

**Non-alcoholic steatohepatitis (NASH)** - Steatosis and liver disease that is not caused by excessive alcohol consumption. (14)

**Normoglycemia**- Normal blood glucose levels. (8)

**Nystagmus** - An involuntary wobbling, jerking, or roving of the eyes. (9)

**Obstructive lung disease** - The inability to fully expel air from the lungs that can be caused by fibrosis. (11)

**Optic disc** - The head of the optic nerve where the retinal blood vessels enter the eye. (9)

**Optic nerve** - A flexible “cable” of nerve fibers connecting the eyeball to the brain which carries the electrical signals that the brain then interprets as visual images. (9)

**Orthopnea** - A very unpleasant, panicky feeling of breathlessness and respiratory discomfort that occurs while the patient is lying down, compelling him to sit or stand up. (10)

**Ossicles** - The three tiny bones in the middle ear (malleus, incus, and stapes.) (10)

**Otitis media** - An infection of the middle ear, behind the ear drum that causes earache, swelling and redness. (10)

**Ovarian cysts** - Generally harmless fluid-filled sacs which are similar to blisters, common among girls with Alström Syndrome. (6)

**Ovaries** - The female gonads that store eggs and produce estrogens and progesterone that influence secondary sexual characteristics and reproduction. (6)

**Overflow incontinence** - A type of incontinence brought about because of incomplete emptying and a large amount of urine always being present in the bladder. (16)

**Palpitations** - Abnormal heart rhythm (arrhythmia) that causes the heart to beat too quickly (tachycardia) or too slowly (bradycardia.) (11)

**Pancreas** - A glandular organ, located behind the stomach and adjacent to the liver, which produces and secretes enough insulin to maintain normal blood sugar levels. (8)

**Pancreatitis** - An inflammation of the pancreas, often caused by extremely high triglycerides. (13)

**Parathyroid** - Four glands that lie on top of the thyroid gland which act on bones, kidneys, and intestines to reabsorb calcium. (6)

**Pedunculated** - Elevated, as on a stem (peduncle) or stalk. (5)

**Pericardium** - The sac that covers the heart and protects it. (11)

**Perineal** - The area between the vulva and anus in a woman, and between the scrotum and anus in a man. (16)

**Peripheral nervous system** - Nerves in the body that lie outside the CNS (Central Nervous System.) (17)

**Pervasive developmental disorders (PDD)** - A range of conditions that involve delays in the development of many basic skills, most notably the ability to socialize with others, to communicate, and to use imagination. (3)

**Phenotype** - The appearance or physical manifestations of the actions of a gene. (18)

**Photodysphoria** - An extreme sensitivity to light, photophobia. (9)

**Photoreceptors (rods and cones)** - The collective term for rods and cones in the neural retina, named as such because they are activated by light signals. (9)

**Pinna** - The flap of cartilage on both sides of the head that localizes the source of sound. (10)

**Pituitary** - A pea-sized gland, sometimes referred to as the "master gland", it is located at the base of the skull and secretes hormones that control hormone secretion from other glands throughout the body. (17)

**Plasma lipids** - Fats, including cholesterol and fatty acids, that are transported in the blood stream. (13)

**Platelet** - The smallest of the blood cells, which are involved in blood clotting. (14)

**Polydactyly** - More than five fingers or five toes. (5)

**Polydipsia** – Excessive thirst over time. [This can also be an indication of diabetes.] (8,16)

**Polyuria** – An increased need to urinate more frequently. [This too can be an indication of diabetes.] (8,16)

**Portal circulation** - Pertains to the passage of blood in the portal vein, spleen, and gastrointestinal tract (GI tract.) (14)

**Portal hypertension** - Increased blood pressure in the portal vein and other connecting veins, usually caused by cirrhosis, fibrosis, or severe damage to liver cells which may result in bleeding or ascites. (14)

**Portal vein** -The vein that passes through the intestine to remove toxins and wastes and transport them to the liver.(14)

**Post lingual** - Occurring after a child has learned language skills. (10)

**Post-void Residual** - The urine remaining in the bladder just after urination (a 20-50 cc residual normally remains.) (16)

**Progesterone** - Female sex hormone that induces thickening of the lining of the uterus. [If fertilization does not take place, the secretion of progesterone decreases and menstruation occurs.] (6)

**Protein** - May be a structural constituent of a given tissue, an enzyme that causes a chemical reaction, or a hormone among other potential functions. (18)

**Proteinuria** - The presence of abnormally high amounts of protein in the urine, which may be a sign that the kidneys are not working properly. (15)

**Pulmonary arteries**-Vessels that carry blood depleted of oxygen from the right side of the heart to the lungs. (12)

**Pulmonary arteriogram** - A procedure that uses a special dye (contrast material) and x-rays to see how well blood flows through the lungs. (12)

**Pulmonary hypertension (PHT)** - Abnormally high blood pressure in the pulmonary arteries. (12)

**Pupil** - The hole in the front of the eye through which light passes. (9)

**Pure tone audiometry** - A test to measure the softest sounds that can be heard over a range of volumes (hearing threshold in decibels) at a series of increasing pitches (frequencies measured in Hertz.) (10)

**Receptive language delay** - A problem understanding and processing words and sentences. (3)

**Recessive** - A pattern of inheriting a genetic disorder, the result of inheriting two copies of a mutant gene, one from each parent. (18)

**Renal dialysis (hemodialysis)** - A treatment used to remove waste products such as creatinine and urea and additional fluid from the blood, after the kidneys have stopped functioning. [The procedure, which involves removing and cleansing the blood through a filter, can be conducted in a dialysis outpatient facility.] (15)

**Renal tubule** - The part of a nephron that leads away from a glomerulus. (15)

**Restrictive lung disease** - Characterized by reduced gas transfer and de-saturation after exercise, caused by inflammation or scarring of the lung tissue (interstitial lung disease.) (11)

**Retention** - The failure of the lower urinary tract to expel all the urine in the bladder. (16)

**Retina** - The layer of rods, cones, and the retinal pigment epithelium (RPE) found at the back of the eye. (9)

**Retinal dystrophy** - A general term referring to abnormalities or degeneration of cells or tissues in the retina. (9)

**Retinal Pigment Epithelium (RPE)** - A single layer of cells that lay on top of the photoreceptors, which perform multiple functions in the retina, including the transport of nutrients and fluid. (9)

**Rod cells** - They are responsible for the detection of movement, shapes, and light and dark and cannot detect color, so vision obtained from rods is “black and white.” (9)

**Rod monochromatism** - A non-progressive, recessive ocular condition characterized by loss of cone function, resulting in a total lack of color discrimination, photodysphoria, and congenital nystagmus, also known as congenital achromatopsia. (9)

**Sclerotherapy** - Drugs, intended to slow bleeding, are injected into the bleeding vein and sometimes into the surrounding area which cause clots to form and harden the vein in order to stop the bleeding. (14)

**Scoliosis** - A lateral (sideways) curvature of the spine into a C or S-shaped configurations when viewed from behind. (5)

**Secondary hypertension** - High blood pressure caused by another identifiable medical condition. (12)

**Secondary Sex Characteristics** - Physical traits that distinguish males and females but are not a functioning part of the reproductive system, such as beards in males. (6)

**Sella turcica** - A saddle shaped structure at the middle of the base of the skull that holds and protects the pituitary gland. (17)

**Sensorineural hearing loss** - Can be a loss of hearing due to a lesion in the cochlea (sensory) or in the nerve itself (neural.) (10)

**Shortening fraction (Fractional shortening)** - The shortening fraction is a slightly different way of measuring left ventricle performance which, instead of measuring and ratio-ing blood volumes, measures and ratios the change in the diameter of the left ventricle between the contracted and relaxed states. (11)

**Sinus node** - Called the SA (sinoatrial) node, it is a small nodule of tissue that sits on top of the right atrium and controls the frequency at which the heart beats by converging an electrical signal to another small nodule, the AV node, spreading the signal into the ventricles and causing them to contract. (11)

**Spermatogenesis** - The development of sperm cells in the testes. (6)

**Sphincter** - A circular muscle that closes the urethra tightly like a rubber band around the opening of the bladder when voiding is not desired. (16)

**Sphygmomanometer** - An instrument for measuring blood pressure in the arteries consisting of a pressure gauge and a rubber cuff that wraps around the upper arm and inflates to constrict the arteries. (12)

**Spirometry** - One of a series of pulmonary function tests that measures air volume and flow rate. (11)

**Splenic vein** - The vein that drains the spleen. (14)

**Splenomegaly** - Enlarged spleen due to increased pressure in the liver. (14)

**Steatohepatitis** - A term for a liver that contains fatty deposits and shows evidence of inflammation. (14)

**Steatosis** - Fatty liver. (14)

**Stress incontinence** - Losing urine when there is a sudden increase in pressure on the bladder, such as from a cough or sneeze. (16)

**Stricture** - Scarring in the urethra that blocks urine flow. (16)

**Subcapsular cataract** - A cataract that develops slowly under the lens capsule, usually from the back. (9)

**Subclinical hypothyroidism** - High TSH levels but still normal T4 levels with no apparent symptoms. (6)

**Syndactyly** - Fused fingers or toes. (5)

**Systemic blood pressure** - The pressure exerted within blood vessels circulating blood throughout the body. (12)

**Systolic** - Refers to the contraction of the heart muscle and comes from the Greek systole meaning "a drawing together or a contraction." (11)

**Systolic pressure** - The pressure in the arteries when your heart is pumping. (12)

**Testes** - Male gonads, located in the scrotum, that produce testosterone. (6)

**Testosterone** - Produced by the testes and responsible for masculinization, hair growth, muscle development, and influences sexual desire. (6)

**Thyroid** - A large endocrine organ, located in the neck, which functions mostly to control metabolism. (6)

**Thyroid hormone (TH)** - Consists of Thyroxine (T4) and triiodothyronine (T3), which are secreted into the bloodstream from the thyroid gland in response to stimulation from the pituitary hormone TSH. (6)

**Tonic seizures** - Brief seizures, usually lasting about 60 seconds or less, consisting of the sudden onset of stiffening in the muscles (neck, upper limbs, or thighs.) (17)

**Tonic-clonic seizures** - Sometimes called 'grand mal' seizures, they are characterized by generalized stiffening of flexor or extensor muscles (the tonic phase), usually with loss of consciousness, followed by generalized jerking of the muscles (clonic activity.) (17)

**Trachea** - The tube that connects the nose and mouth to the lungs. (11)

**Transjugular Intrahepatic Portosystemic Shunting (TIPS)** - Transjugular: Across the jugular vein; Intrahepatic: within the liver; Portosystemic: from the portal vein to the general circulation; Shunt: a channel for blood to flow. A major surgical treatment in which a tube is passed through the liver to help blood flow bypass the liver by connecting the portal and hepatic veins and thus reduce portal hypertension. This course of action is not trivial and must be done in a facility that specializes in the procedure. (14)

**Triglycerides** - A group of three fats collectively called triglycerides, that are found naturally in the body and that are used for energy. (8,11)

**Truncal obesity**- Fat concentrated around the waist and upper body. (7)

**TSH (thyroid stimulating hormone)** - A hormone produced by the pituitary gland which acts on the thyroid gland to stimulate more thyroxine production when levels drop. (6)

**Type I diabetes**- Usually starting suddenly in young children when the beta cells in the pancreas are destroyed, causing it to completely stop manufacturing insulin leading to absolute insulin deficiency. (8)

**Type 2 diabetes (or generally non insulin-dependent diabetes)**- Failure of one or more of the regulatory mechanisms that keep blood glucose levels within normal range, resulting in abnormally high glucose levels in the blood and urine. (8)

**Urea** - Produced when foods containing protein, such as meat, poultry, and certain vegetables, are broken down in the body. (15)

**Uremia** - Accumulation of urea and other wastes in the blood that are normally eliminated through urination, which become toxic in large amounts and may occur without symptoms. (15)

**Ureter** - An 8-10 inch long tube that drains urine from the kidney to the bladder. (16)

**Urethra** - The tube that carries urine from the bladder toward the outside of the body. (16)

**Urgency** - The symptom of sudden onset of a strong need to urinate. (16)

**Urodynamic** - The study of the mechanics of urinary bladder filling, emptying, and voiding. (16)

**Uterus** - The pear-shaped reproductive organ from which women menstruate and where normal pregnancy develops. (6)

**UTI** - Urinary tract infection. (16)

**Vagina** - The passage that connects a woman's outer sex organs with the cervix and uterus. (6)

**Valves** - Connect the four chambers in the heart and regulate the flow of blood within and in and out of the heart.(11)

**Varices** - Enlarged blood vessels which are prone to bleeding. (14)

**Ventricles** - The lower chambers in the heart that serve to pump blood through the arteries to other parts of the body. (11)

**Ventricular ectopics or PVC's** - Occasional single extra heartbeats that usually require no treatment. (11)

**Ventricular tachycardia** - Rapid heartbeats often associated with a fall in blood pressure, symptoms of dizziness, breathlessness or fainting. (11)

**Vertebrae** - Individual bones that make up the spine. (5)

**Vestibular** - The organ of balance in the inner ear that transmits information about movement and position in space to the brain. (10)

**Virilization** - Virilization is the appearance of masculine sexual characteristics, such as acne, deepening of the voice, baldness and increased muscle mass. (6)

**Visual Evoked Response (VER)** - Measures the response to a visual stimulus by placing electrodes on the back of the head, over the vision part of the brain. (9)

**Void** - Urinate. (16)

**Waist/hip ratio** - A measurement of the circumference of the waist and upper body. (7)

**White matter** - Located in the cerebellum, cerebrum, and spinal cord, it makes up roughly 60 percent of the total brain volume and contains nerve fibers, or axons, surrounded by a type of white colored fat called myelin. (17)