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Cystinuria Support Network News

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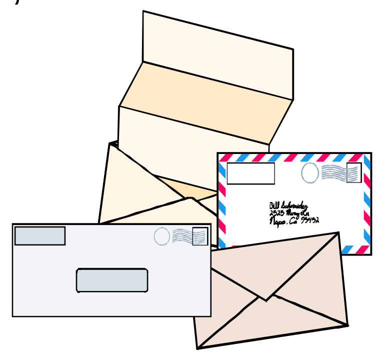
From the Editor

The *Cystinuria Support Network,* a Mutual-Aid Support Network, has been developed to provide a resource for putting individuals in touch with each other for support and practical advice. Since no one can understand the issues like those who are sharing the same experience, this Network will allow us to come together with our strengths, hopes and concerns to offer support and understanding to each other.

The Cystinuria Support Network in no way endorses any drug or treatment that is reported to you and should not be regarded as a substitute for personal, professional medical advice. It is our wish only to provide information and encourage you to always check any treatment with your physician.

When my two and a half year old daughter was diagnosed with Cystinuria almost five years ago, I searched high and low for additional information about Cystinuria and some kind of support network. What we needed more than anything was to be able to talk with someone who understood first hand what we were experiencing. It was extremely difficult to find support or information about the practical issues of dealing with Cystinuria in our daily lives. I was finally put in touch with several other individuals with Cystinuria through the networking services of the National Organization for Rare Disorders (NORD) and the Research Trust for



Metabolic Diseases in Children (RTMDC) and I found the contacts invaluable. So, after thinking about it for quite some time, I decided to start the ***Cystinuria Support Network****. I began my letter writing campaign exactly one year ago and I have to say that it has been a lot of work but tremendously rewarding. I have talked to many people who have told me how they have longed to be in touch with someone else who has Cystinuria and I have been so glad to be able to give these people a long list of names of people that they can call or write.*

It is very exciting for me to be publishing the first newsletter of the ***Cystinuria Support Network****.I was not sure what type of information the participants in this network would be interested in. I did not get much response to my requests for ideas. So I set out to solicit articles written by professionals willing to address some of the areas of concern or confusion that had come up in my conversations with people in the network. You will notice that some of the articles contain duplications of information that is covered in another article; however, each and every one contains some unique and valuable information.*

Therefore, this newsletter tends to be a bit heavier on the medical information side than may be found in future newsletters. What I would like to see is a newsletter that helps to bring all of the participants in this network closer together. As the group continues to grow it becomes impractical, if not impossible, for you to contact each and every participant. Yet I believe we all have so much to share with each other. This newsletter will be used to share information from each of you. I would love to publish some "personal profiles" or your story about your life with Cystinuria. This would give the other participants an opportunity to get to know you. I would also like to see a column develop where a person could post a certain issue or concern they have, and the following newsletter could list responses to this concern by other members of the group or medical professionals.

But, as I have said before, I want this group to be whatever the participants want it to be and I am open to any and all suggestions and ideas. I hope you enjoy this first newsletter and learn something new from reading it.

Jann L.

The Genetics and Inheritance of Cystinuria

Written by Darci Lise Sternen, M.S.
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With thanks to Linda A. Ramsdell for assistance with editing.

Cystinuria is a genetic metabolic condition. Cystinuria is known to be inherited in an autosomal recessive pattern. What does "autosomal recessive" mean? Let's start from the beginning with a crash course in genetics...

People are made up of millions of tiny parts called "cells". These cells compose our skin, blood and all the parts of our bodies. Within each cell are instruction that tell the cell how to function: this information is our genetic material of "genes". Humans have two copies of each gene, inheriting one copy of each gene from both his/her parents. That's why we look a little like each of our parents.

Sometimes one or both copies of a gene have changes that can cause a disease in a person: these changes are called "mutations". An individual has Cystinuria when <u>both</u> copies of the "Cystinuria gene" have a mutation. A person is called a Cystinuria "carrier" if just <u>one</u> Cystinuria gene copy has a mutation and the second copy does not. In these individuals, the one functional Cystinuria gene copy can compensate so the person does not have Cystinuria. Since individuals who have Cystinuria have mutations in <u>both</u> copies of their Cystinuria gene, we can assume that they inherited these from their parents, who are carriers. This inheritance pattern seen in Cystinuria is termed "autosomal recessive".

As mentioned earlier, parents give one copy of every gene to each of their children. If a parent is a carrier for Cystinuria there is a 1/2 (50%) chance to pass on the mutated Cystinuria gene copy and a 1/2 (50%) chance to pass on the functional Cystinuria gene copy to each pregnancy. If <u>both</u> parents are carriers the probability for each pregnancy to have Cystinuria is 1/4 (1/2x1/2=1/4). The chance for each pregnancy to be a carrier is 1/2. The chance for a pregnancy to be unaffected is 1/4.

Going into a little more detail...how does a gene mutation cause a genetic condition such as Cystinuria?

Genes determine how the body cells make proteins. Proteins are composed of building blocks called amino acids. Basically, genes are the blueprints that the cells read to know in what order the amino acids are put together and ultimately, how each protein is made.

The Cystinuria gene has not yet been identified. It is believed though that one or more mutations of this gene result in an amino acid sequence change and subsequent protein dysfunction. The Cystinuria protein is thought to be involved in the transport of cystine and other amino acids across cell membranes in the kidneys and intestines. The end result of the improper cystine transport is stone formation in the kidneys.

So there you have the "basic" genetics of Cystinuria (but unfortunately in this case "basic" does not mean "simple"!!) Ultimately we hope to find the exact gene mutation in order to understand the mechanisms involved in Cystinuria. With this information perhaps a treatment can be found.

As new information is being learned, individuals with Cystinuria and/or their family members may wish to meet with a genetic counselor or genetics professional to discuss current information about the inheritance and medical aspects of Cystinuria.

How Cystinuria Occurs

Written by Lisa A. Ruml, M.D.
Mineral Metabolism Section
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Dallas, Texas

Cystinuria is an amino acid, one of the building blocks of proteins. Cystinuria is an inherited condition in which the kidney is unable to remove cystine from the urine. Cystine is present in large amounts in the urine and is not very soluble; thus, it tends to clump together and form stones. This is the only problem that patients with Cystinuria will have, but it can cause major problems. There are varying levels of severity, with some patients excreting relatively small amounts of cystine, and some excreting huge amounts.

Cystinuria is inherited in a recessive fashion, meaning that two abnormal genes are needed for Cystinuria to be present. For this to occur, a patient must receive a copy of the abnormal gene from each parent. Having only one abnormal gene creates no problems at all, as the level of cystine is too low to become insoluble in the urine (both parents will have an abnormal gene, but do not have Cystinuria). People with one abnormal gene are called “carriers” for Cystinuria.

It is not yet known exactly what the abnormality is in the kidney that results in the high cystine levels in the urine. It is thought that there is a special protein molecule on the outside of a kidney cell that is responsible for binding the cystine and bringing it into the cell. If the gene responsible for making the protein molecule is absent or defective in some way, the protein that is produced by the gene would be unable to bind to the cystine and the cystine would remain in the urine.

Is It Possible to Find a Cure for Cystinuria?

Written by Lisa A. Ruml, M.D.
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Work is being done to try to identify the gene responsible. A protein molecule that binds cystine in certain animals has been found, but it is not known if there is a similar protein in humans. Our institution in Dallas has begun to look for the abnormality. We have begun collecting blood samples from patients with Cystinuria and their family members so that we can study the DNA and, it is hoped, find the gene responsible. This will be the first step toward finding a way to cure the disease with possible future genetic therapy.

The more samples we can analyze, the easier it will be to isolate the gene. We are currently collecting samples from families in the Texas/Oklahoma/Arkansas/Louisiana area, but we plan a national expansion in the future. I would be pleased to talk to any families that are willing to participate by allowing us to get blood samples for our lab. Our office number is (214) 648-2466 and is open from 9:00-5:00 Central Time.

The Search for the Gene that Causes Cystinuria

Written by Dr. Giora Katz

Cystinuria is a hereditary disease, which means that if your parents or other relatives have it, you then have a higher chance of having it than another person who does not have a relative with Cystinuria. It also means that the disease comes from the body and not by infection or environmental changes.

A person with Cystinuria cannot absorb the amino acid cystine from their urine while it is being secreted in the kidney, and also from the food we ingest in our intestine. In spite of this, the body does not lack cystine because it produces as much as it needs. The cystine that leaks in the urine produces crystals which unite to form stones. People without Cystinuria absorb all the cystine from their urine before it has a chance to crystallize.

Our body is composed of cells. Within each cell we have a nucleus which carries our genetic characteristics. The genetic characteristics are arranged within 23 pairs of chromosomes. The special thing about the genetics of Cystinuria is that the place on the chromosome, called the gene, that controls the absorption of cystine can be defective in three different ways. It also has to be defective on both pairs of chromosomes that carry it. In cases where it is defective on both sides, the person has Cystinuria. If only one chromosome is defective and its counterpart is normal, the person will not have Cystinuria but he can transmit the defective gene to his/her children. If one of them marries another person with the same situation, and their child takes from each of them the defective gene rather than the good gene, this child will have Cystinuria because both chromosomes of this pair are defective.

Until now we have been able to trace the three types of genes that cause Cystinuria by measuring the amount of cystine that a very small piece of bowel, taken from a Cystinuria patient by biopsy, can absorb in a test tube. By defining the various types we were able to consult patients about their chances of having Cystinuria, or of transmitting Cystinuria to their offspring. Sometimes there is no family history and the patient represents the first one in the family with Cystinuria. This first case phenomenon usually happens because the chance of marrying someone with a Cystinuria gene is small and then the chance that both parents will give their child the Cystinuria gene instead of its healthy pair is 50% for each, or one in four. The gene for Cystinuria is there but it shows up infrequently so nobody remembers another family member from the past with Cystinuria. Among certain closed circles the incidence of Cystinuria is very high, for example, Jews who come from Libya. They have been isolated from other Jews for a long time and since they had to marry only Jews according to their religion, they married within a small community. Consequently, the gene became very common and was not diluted by marrying outside people who may not have the gene.

Dr. Elon Pras is an Israeli physician who works in the National Institute of Health at Bethesda, Maryland. He used his acquaintances with Libyan Jews to obtain blood and urine samples from all members of some large Libyan Jewish families. He checked them all to determine who had Cystinuria. Then he checked their blood cells and obtained from them their chromosomes. He knew these people also had a rare hereditary disease called Familial Mediterranean Fever and he found that many had both diseases at the same time. Based on observation and knowing that this Fever is inherited through chromosome 16, he started comparing chromosome 16 from healthy and Cystinuric individuals in his Libyan Jewish group of patients. The logic was sound but the results were disappointing. Another group of researchers told Dr. Pras that they had found a protein which is produced in the kidney and helps absorb cystine. They traced the production of this protein to the very chromosome that gave the cell the instructions how to produce it. This is chromosome number 2. Dr. Pras directed his attention from chromosome 16 to chromosome 2. He took all the number 2 chromosomes from 113 people of 17 families, broke it up in a special way so the broken parts became comparable among the number 2 chromosome from the various people. Knowing who was Cystinuric and who was not, he was able to identify the specific location of the gene on chromosome 2.

This is important because it is the first step that may one day lead us to a situation in which we can benefit from the advances in genetic manipulation, thus getting rid of the defective gene or replacing it with a good one instead. This possibility is still far ahead but so was the moon in 1960. Since then we have walked on the moon and genetic engineering has made huge progress.

In the meantime, please do not forget to drink plenty and take your medication so you will have good functioning, stone free, kidneys when the great day of gene replacement comes!!

Dr. Giora Katz was born, raised and educated in Jerusalum. While working at Hadassah Medical School he was involved with the introduction of the first ESW machine there and this began his association with and interest in Cystinuria patients.

I originally contacted Dr. Katz after finding his name listed as one of the collaborators on an article titled "Localization of a gene causing Cystinuria to Chromosome 2p". I wrote to him at Hadassah Medical Center in Jerusalem, Israel. He is currently doing a fellowship in Florida and wrote to me when he got to the U.S. telling me he had brought with him the names of 50 Cystinuria patients from Israel and he was enthusiastic about this network. However, we decided that the language barrier would be difficult so he is currently working with one of his patients to set up an Israeli Cystinuria Support Network. These two groups could then share translated newsletters and other items of interest.

Understanding the Numbers !!

Written by Lisa A. Ruml, M.D.
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While it is simple enough to understand that Cystinuria occurs because the urine has too much cystine in it, it can be quite another matter to figure out what the various numbers and units for cystine levels may mean, especially when different physicians and laboratories report cystine values in different ways. The situation may become even more complicated when physicians begin talking about cystine concentration as opposed to daily excretion rates.

Diagnosis: The actual diagnosis of Cystinuria is an accepted standard and refers to a specific level of cystine per gram of creatinine. A person is said to have Cystinuria when the urinary cystine is greater than 250 mg per gram of creatinine. Creatinine is a normal byproduct of everyday metabolism which is disposed of through the kidney. Because creatinine varies depending on a person's size (so that children have much lower urine creatinine compared with adults), it is used as a correction factor to allow diagnosis in all ages.

The level of cystine is reported in two ways, the amount put out in the urine per day and the amount of cystine per liter of urine. The two are used in similar ways. When a physician is trying to determine the risk of forming a stone, it is preferable to know the cystine concentration in the urine; that is, the amount of cystine per liter of urine. Cystine is soluble at low concentrations, but insoluble at higher concentrations. In general (and there are differences between individual patients), cystine solubility ranges from 190-400 mg per liter when the pH of the urine is 7.0. It is slightly less soluble at lower pH values. We generally try to aim for a cystine level of less then 250 mg per liter when adjusting medication dosage. As you can see, if a person drinks increasing amounts of fluid, he of she can lower the concentration of the cystine, perhaps even into the normal range.

Another way of measuring cystine is with daily amounts excreted in the urine. This level is commonly used as it is a good way of measuring the response to a therapy. Because total volumes will vary from day to day, the total concentration may change, though the total amount of cystine may not. Total cystine is reported either in milligrams (mg) per day or in millimoles (mmol) per day. Both measure total cystine, but use different units. There are 240 mg in one mmol of cystine. For example, if a person excretes 1000 mg of cystine in one day, that is equal to 4.16 mmol of cystine per day (1000/240). To convert mmol of cystine to mg, you need only multiply the number of mmol by 240. Occasionally, cystine is reported in micromoles per day, which is the number of mmol multiplied by 1000.

The Treatment and Prevention of Cystine Stones by Forced Hydration and Strong Urinary Alkalinization

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INTRODUCTION: Increased urinary dilution (from forced hydration) and strong urinary alkalinization (from oral alkalinizing agents) are two of the most effective methods for the treatment and prevention of cystine kidney stones (calculi). Neither of these modalities reduces the total urinary excretion of cystine; that appears to be relatively stable for each cystinuric individual. Rather, increasing urinary dilution *reduces the concentration* of urinary cystine (I.e., the amount of cystine contained in each milliliter of urine while the total output of cystine remains unchanged). By contrast, urinary alkalinization *increases the solubility* of urinary cystine (I.e., the amount of cystine that can be dissolved in each mL of urine without it precipitating out of solution to form cystine crystals, sand, gravel and stones). These therapeutic effects on cystine concentration and solubility are complementary. Not only can they decrease cystine stone formation, but, if applied with sufficient vigor over sufficient time, can even dissolve large cystine calculi--a process accelerated by lithotripsy which cracks cystine calculi and increases their (therapy-exposed) surface area.

The benefits of forced hydration and urinary alkalinization are obtained with wide safety margins. Forced hydration has no serious adverse effects while with urinary alkalinization serious risks are minimal. In treating Cystinuria, a wide safety margin is particularly appreciated because the only other established method of treating Cystinuria is with penicillamine and Thiola, drugs which carry high risks of serious allergy and toxicity. (For simplicity, in this article, the generic drug penicillamine--brand names Cupramine and Depen--will be referred to by their generic appellation. Thiola, the only brand available for the generic variously known as alpha-mercaptoproprionylglycine, tiopronin and MPG, will be referred to by its brand name.) The action of penicillamine and Thiola is to *decrease the total urinary excretion of cystine*. Since the stone-inhibiting benefits of forced hydration-alkalinization are complementary to the cystine reductions from penicillamine and Thiola, a strongly applied regimen of the former may entirely replace the more toxic agents or at least permit reduction in their dosage. This is of particular importance for patients with proven intolerance of penicillamine or Thiola, or who are in fear of their adverse effects, E.g., patients who already have reduced kidney function, or women who desire pregnancy. In fact, cystinuric women under treatment with penicillamine or Thiola who become pregnant can frequently have these agents discontinued and go through pregnancy treated only by forced hydration and urinary alkalinization--albeit under an extreme burden voiding frequency.

INTENSITIES OF CYSTINURIA: The frequency and severity of kidney-stone formation vary widely in cystinurics. Some patients experience very frequent sand and gravel and form at least two to three cystine stones per year, sometimes huge in size ("staghorn" calculi). Others form only one or two small calculi over decades. By combining data of 24-hour-urinary cystine excretions, the urine-solubility characteristics of cystine, and clinical experience correlating these parameters with stone formation rates, the following broad classification of Cystinuria intensity can be suggested: (1) Generally insignificant (I.e., cystine stones rarely form): up to 150 mg/day; (2) Mild: 150--400 mg/day; (3) Moderate: 400--800 mg/day; (4) Moderately severe: 800--1,200 mg/day; (5) Severe: 1,200--2,000 mg/day; (6) Very severe: over 2,000 mg/day.

In general, the greater the 24-hour-urine excretion of cystine, the greater the cystine stone problems. Variations from this rule, however, include the following situations:

(1) Obstruction in the urinary tract can induce intense cystine stone formation behind the obstruction even though the total urinary excretion of cystine may be only modest; obstruction has this stone-inducing effect for all types of kidney stones, not just cystine.

(2) Without current explanation, some patients with fairly unimpressive urinary cystine concentrations (E.g.,only 200 mg/liter), who in theory should have ceased forming cystine calculi, nevertheless avidly continue to do so. In contrast, some subjects with urinary cystine concentrations as high as 800 mg/liter only rarely experience stone events.

(3) When numerous retained cystine calculi are present--with an extensive cumulative surface area--percolating high volumes of dilute, strongly alkalinized urine over these stone surfaces dissolves cystine which is then added to the total urinary cystine excretion. Such increments in cystine excretion, however, reflect successful therapy and do not increase the stone formation rate. (However, in such patients it may be impossible to calculate the true "baseline" urinary cystine excretion until they are rendered stone free, or the regimen of hydration and alkalinization is temporarily discontinued.)

For reasons that are unclear, increased sodium intake can significantly elevate urinary cystine excretion and exacerbate cystine stone formation, in some subjects more than others. Restriction of methionine-containing foods (milk, meat, eggs, etc.) results, in most patients, in a small decrease in total urinary cystine excretion. Usually, the cystine decrement is neither clinically significant nor worth the (considerable) efforts involved; in rapidly growing children the requisite protein restrictions can even lead to nutritional deficiencies. However, because some patients lower their cystine outputs more dramatically than others, advanced protein restriction--with close monitoring of its hoped-for cystine reductions--is worth a brief trial in patients who prove refractory to other measures.

CYSTINE SOLUBILITY IN URINE: It has been observed that if the urinary concentration of cystine is approximately 300 mg/liter, or less, new calculi generally do not arise, nor already formed stones enlarge. If the urinary concentration of cystine is much below 300 mg/liter, calculi may even slowly dissolve (although this usually requires concomitant strong urinary alkalinization.) If the urinary concentration of cystine is above 300 mg/liter, cystine calculi may form, or enlarge--the higher the cystine concentration, the more rapid the process. A urinary concentration of 300 mg/liter may be regarded as the "clinical saturation point" for cystine. The clinical message from this data is that, if at all possible, the urinary concentration of cystine should be kept at, or below, 300 mg/liter. For the rare patients who continue to form cystine calculi at unexpectedly low cystine concentrations (E.g., even as low as 200 mg/liter), therapy should be directed at strong urinary alkalinization and keeping urinary cystine concentrations at even lower levels.

URINARY DILUTION AND FORCED HYDRATION: Clearly, it is not the total cystine excretion which determines whether or not cystine calculi will form but the urinary cystine *concentration*. E.g., even if the cystine output of a patient were (a huge) 2,000 mg per day, if the concentration of cystine in the urine could be diluted down to 200 mg/liter--I.e., by forcing enough water ingestion to form 10 liters of urine per day--cystine calculi would be unlikely to form. In contrast, if the urinary cystine output of a patient were only 400 mg/day, but only 1 liter of urine per day were formed, the resultant urinary cystine concentration (I.e., 400 mg per liter, or twice that in the previous example) might be sufficient to initiate stone formation.

Since to stop cystine calculi in most patients it is sufficient to dilute urinary cystine concentration down to 300 mg/liter, for a patient with a daily cystine excretion of 600 mg this would mean forcing a 24-hour urine volume of 2 liters (2,000 ml, or about 2 quarts). For a patient with a daily cystine excretion of 1,200 mg, achieving the protective cystine concentration would necessitate a 24-hour urine volume of 4 liters, etc. In such a subject, to achieve the even safer (lower) cystine concentration of 200 mg/liter, a daily urine volume of 6 liters would be required--a formidable undertaking!

For cystinurics who require such huge daily urine volumes, it is advisable to consume at least 2 large glasses of water every 2 hours during the day, with 2 more glasses upon retiring to force voiding at least twice during the night, coupled with ingestion of another glass of water at each nocturnal awakening. It may take several months of patient effort until such an onerous regimen is adapted to--with an ability to readily fall back to sleep being a significant asset in this regard. As a rule of thumb, the urine should be kept "very light in color," approaching that of tap water, making it a habit to observe this aspect with each voiding--and increasing the amount and/or rate of water consumption *no matter what it might already be* if the urine color remains too dark. (Maintain awareness that coloring dyes in medications, or capsules, may also darken urine.)

INSENSIBLE WATER LOSSES: *Protection against cystine stone formation comes not from how much liquid is drunk, but from how much urine is passed*. Under different circumstances, different amounts of liquid will be required to achieve protective volumes. Most ingested water is excreted from the body as urine. However, significant additional losses of water from the body occur via sweating, evaporation from skin surfaces, excretion as liquid stool, and as moist air exhaled during respiration. These are called "insensible losses," and can readily mount to 1,500 ml/day--or much more if environmental temperatures are high, or fever, heavy sweating, diarrhea, or deep rapid respirations are present (as during illness.) Thus a cystinuric who requires a daily urine volume of 4,000 mL might readily have to drink 5,500 ml of water per day to reach this goal--and perhaps double this amount if insensible water losses are very pronounced (E.g., as in vigorously playing tennis, with heavy associated sweating, during very warm weather.)

POTENTIAL ADVERSE EFFECTS FROM FORCED HYDRATION: Adverse effects from forced hydration are primarily of a nuisance type, but may be very perplexing. Large urine volumes force frequent, highly inconveniencing voidings. Indeed, certain professions may be rendered almost impossible by this aspect, E.g., mailmen, policemen, sterile-gowned surgeons, etc. Commuting via public transportation without adequate bathroom facilities can become nightmarish. Nocturnal voiding forces frequent awakening and some patients cannot fall back to sleep, resulting at times in near ruinous daytime fatigue, with job loss or falling asleep at the wheel. The small bladder capacities of men with prostatism, and women in their last trimester of pregnancy, exact particularly cruel penalties. However, serious medical risks from forced hydration are vanishingly rare. In general, one need not fear drinking "too much water" since normal kidneys can excrete up to 20--22 liters per day of an ingested water load. Rarely, a patient ingesting a large water load who is also on thiazide diuretics, high dosages of nonsteroidal antiinflammatory drugs (E.g., Naprosyn, Advil, Aleve, etc.), or a very-low sodium diet, may retain water and experience a drop in serum sodium with resultant muscle cramps and headache. Patients with advanced renal disease should also observe special precautions. On balance, however, the advantages of forced hydration in preventing cystine stones far outweigh any downside risks especially when the alternatives are a concentrated stone-forming urine, or potentially toxic drugs such as penicillamine or Thiola.

SIGNIFICANCE OF URINARY PH: Urinary pH signifies the degree of acidity or alkalinity of the urine: the lower the number, the more acidic the urine; the higher the number, the more alkaline the urine. Because of limits on the degree of urinary acidity or alkalinity which can be generated by human kidneys, urine pH ranges only from 4.5 to 8.0. As approximate definitions, urine pHs of 4.5--5.5 are regarded as highly acid; 5.5--6.5 as mildly acid to neutral; 6.5--7.0 as neutral to mildly alkaline; and 7.0--8.0 as strongly alkaline. All pH measurements are based upon a logarithmic scale (i.e., a mathematical system of 10 being multiplied upon itself) as in an earthquake-measuring scale. In a logarithmic system, small-appearing differences signify huge mathematical increments: E.g., with a pH increment of only 2 units, a urine pH of 7.0 is *one-hundred* times more alkaline than a pH of 5.0, and with a further pH increment of only 0.3 units, a urine pH of 7.5 is *twice again* as alkaline as a urine pH of 7.2.

EFFECTS OF PH ON CYSTINE SOLUBILITY: At urine pHs below 6.5, the solubility of cystine is only 300 mg/liter. At pH 6.5, cystine solubility starts a very slow rise--barely perceptible until pH reaches 7.0 when it has risen to 400 mg/liter. By pH 7.5, however, cystine solubility has climbed to 600 mg/liter and starts to elevate even more rapidly. By pH 8.0 it has climbed to over 1,000 mg/liter, with some graphed results suggesting even more dramatic elevations. (Note: at urine pH 9.0, the solubility of cystine reaches 1,400 mg/liter which would be incredibly useful for dissolving cystine stones. Although urine pH cannot rise above 8.0 via any oral alkalinizing regimen, certain chemicals at pH 9.0--10.0 (solutions of THAM and sodium hydroxide) can be infused directly into the collecting system of the kidneys--where cystine stones collect--via percutaneously introduced catheters. At medical centers specializing in these techniques, such "superalkalinization" can be safely maintained for several days at a time, rapidly dissolving cystine stone fragments.) Cystine calculi dissolve only very slowly when exposed to dilute-alkaline urine because dissolution only occurs from stone surfaces, which are limited. Even though lithotripsy commonly is not successful in breaking up cystine stones so that they pass from the urinary tract, lithotripsy treatments can introduce myriads of cracks into a large cystine stone. This vastly increases the total surface area of the stone over which dilute-alkaline urine can percolate, grossly accelerating the rate of stone dissolution.

Viewing the benefits of urinary alkalinization benefits in reverse, at urine pH 8.0, marked solubilization of cystine is present; at pH 7.5, cystine solubilization is rising rapidly; at pH 7.2, although the solubility increments from alkalinization are measurable, they are of only minimal clinical significance; at pH 6.8--7.0, urinary alkalinization is largely a waste of time for cystinurics. Physicians who are not familiar with the ultra-steep slope of cystine's solubility curve at pH 7.5 may not counsel cystinuric patients correctly about pH matters. One reason for this is that for the much more common (and familiar-to-physicians) condition of uric acid kidney stones, a urine pH of 6.0--6.5 is all that is required for protective solubilization, and a sustained urine pH of 8.0 is deemed undesirable.

MEASURING URINE pH: To monitor urine pH in cystinurics, a fine grade of urine pH-testing strip paper should be used that can distinguish readings in the 7.0--8.0 range. Nitrazine pH-testing paper has the advantage of being widely available. Its drawbacks, however, include its considerable expense (frequently over $30.00 per roll), and a top pH reading of only 7.5. An inexpensive but high quality urine pH-testing paper, which has proven sufficiently accurate clinically, is available from Micro Essential Laboratories in New York. This pH paper starts its readings at 6.0 and progresses, by increments of 0.2--0.4 pH units, to a top reading of pH 8.0. (Write for: pH paper; range 6.0--8.0; Catalog# 345; Micro Essentials Laboratories, Inc.; 4224 Avenue H; Brooklyn, New York 11210; $12.00 for two rolls. Management requests no telephone orders, please.)

HOW INGESTED ALKALI ALKALINIZES URINE: Alkalinizing agents ("alkali") work by neutralizing body-fluid acids, with the "excess" alkali "spilling" out through the kidneys to alkalinize the urine. The acids in body fluids arise both from dietary sources (I.e., ingesting "acidifying foods," E.g., red meats, or acidic liquids) and from the body's internal metabolism (I.e., cellular activities, E.g., muscle cells during exercise). Alkali can be ingested as alkalinizing foods (E.g., vegetables), ingested as drug store-origin chemicals (E.g., sodium bicarbonate, or Alka-Seltza), produced internally by the kidneys, or "borrowed" from the alkali-rich skeleton.

Both acids and alkali are measured in units termed milliequivalents (mEq). One mEq of any alkali neutralizes one mEq of any acid, and vice versa, whether in a test tube or the body. An average adult produces internally about 70 mEq of acids per day. Since this acid is generally more than is needed to neutralize the body's usual alkali load, the "excess acid" spills into the urine, acidifying it down to a pH 4.5--5.5 Therefore, to strongly alkalinize such urine (raise its pH to 8.0) this individual would have to introduce into his/her body about 70 mEq of alkali, either ingested as alkalinizing food or drug store-origin sodium bicarbonate. (Renal and bone originating alkali are not calculated in this simplified example.) Although such an alkali load would neutralize the body's acid load, it would not yet alkalinize the urine. To do this, the subject would have to ingest slightly more alkali (I.e., in "excess" of what was required to neutralize the acid load) which would then "spill" into the urine, alkalinizing it. The more excess alkali taken, the more rapid the urinary alkalinization, and the higher the resultant urine pH, until the maximum of 8.0 was reached.

The amount of alkali required for this "alkali-acid titration" is not fixed. Rather, it will vary with rates of cellular metabolism, diet (E.g., vegetarian vs. meat-eating), loss of alkaline fluids from the body (E.g., as in alkali-rich diarrhea), or the ingestion of drug store-origin alkali over the preceding several days. Therefore, for a cystinuric to attain the desired degree of urine alkalinity, a "guesstimated" amount of alkali is taken and urine pH measured after about 30--60 minutes (to allow for absorption, metabolic processing and urinary excretion of the "excess" alkali). If the chosen dosage of alkali does not sufficiently elevate urine pH, a larger amount is chosen for the next dose. Frequently, over time, less and less alkali is required to produce the desired degree of urinary alkalinization as alkali stores within the body (probably in the skeleton) progressively build up.

Acetazolamide (Diamox) alkalinizes the urine by a different mechanism: Acetazolamide blocks the kidneys' reabsorption of bicarbonate causing bicarbonate to spill into the urine, strongly alkalinizing it. Acetazolamide also blocks the kidneys' reabsorption of sodium, water and potassium causing large losses of these substances--I.e., acetazolamide is a strong diuretic. Acetazolamide is particularly useful for nocturnal alkalinization of urine in patients who cannot, or do not want to, awaken to maintain forced hydration, and in patients who cannot tolerate high sodium loads E.g., patients with hypertension, edema, or heart problems.

AVAILABLE URINARY ALKALINIZING AGENTS: Urinary alkalinizing agents include: (1) those that are sodium-based; (2) those that are potassium-based; (3) the drug acetazolamide. Examples of sodium-based alkalinizing agents, and their common dosage forms, include: (1) sodium bicarbonate tablets, (generic only, 0.324 gm or 3.7 mEq; 0.648 gm or 7.5 mEq); (2) BICITRA oral solution (sodium citrate and citric acid; each mL is equivalent to 1 mEq of bicarbonate). Examples of potassium-based alkalinizing agent include: (1) POLYCITRA-K CRYSTALS (potassium citrate and citric acid, 30 mEq per packet for solution in water); (2) K-Lyte tablets (potassium citrate-bicarbonate, 25 mEq or 50 mEq per tablet for solution in water); (3) UROCIT-K (slow-release potassium citrate in a wax-matrix tablet, 5 mEq and 10 mEq per tablet). Diamox (acetazolamide) is available in extended-release caplets of 125, 250 and 500 mg.

REGULATING THE ALKALINIZATION REGIMEN: An average cystinuric patient, under average conditions of diet and exercise, requires about 15--20 mEq of an alkalinizing agent to elevate urine pH to 7.5, perhaps 25--30 mEq to reach 8.0. If this amount of alkalinizing agent does not elevate the urine pH to the requisite range (I.e., probably signifying that the body had a larger-than-expected acid load to be neutralized), a larger dose should be administered at the next chosen dosing interval and/or the interval between dosages should be shortened. After an alkalinizing agent elevates urine pH, that elevation will remain for a highly variable duration (E.g., 15 minutes to 6 hours), depending, again, upon the rate of the body's acid loading from diet and internal metabolic acid production.

For some examples, if the alkalinization target were an 8.0 urine pH for merely a 2 hour period, then a single dose of about 15--20 mEq of the chosen alkalinizing agent would likely be sufficient. If the alkalinization target were a urine pH of 8.0 on an around-the-clock basis, then 25--30 mEq three or four times per day would likely be required. The exemplified dosages are on the light side. If a target urine pH elevation is not achieved, be prepared to increase the dose of alkalinizing agent (perhaps markedly), or shorten dosing intervals, or both. Conversely, if a target urine pH is readily achieved, test if the amount of alkalinizing agent utilized was really necessary by lessening its dose or lengthening dosing intervals, etc. Lastly, recall that the longer, and more frequently, a subject takes alkalinizing agents, the easier alkalinizing the urine becomes (as internal alkaline stores build up).

HOW LONG AND HOW FREQUENT THERAPY?: Although approximate guidelines can be suggested, clinical results are the final judge. If over a 6 to 12 month period a given hydration-alkalinization regimen prevents cystine stone formation, or actually dissolves stones, it is likely sufficient and, if the regimen were burdensome, can perhaps (gingerly) be lightened. If stones are not prevented, or dissolved, the hydration-alkalinization regimen must be intensified, or, if the regimen were already maximized, complementary therapy should probably be added (E.g., penicillamine or Thiola), probably on a permanent basis. E.g., for a patient with mild-moderate-intensity Cystinuria (E.g., cystine excretion of about 400 mg/day), with no cystine calculi, where the goals of therapy are primarily prophylactic, maintaining the hydration-alkalinization regimen for merely 2 to 4 hours per day, or perhaps even every other day, is probably sufficient. (This may be analogized to a prophylactic "Roto-Rooter" treatment.) However, if numerous or large cystine calculi are present, and the goal of hydration-alkalinization is stone dissolution, the regimen should optimally be maintained around-the-clock for months at a time, perhaps even permanently. This would be especially true, E.g., for a woman planning pregnancy, or a stone-forming cystinuric planning a trip abroad to undeveloped regions, both being instances where it would be desirable to enter the endeavor with a stone-free urinary tract.

POTENTIAL ADVERSE EFFECTS FROM URINARY ALKALINIZATION: Serious adverse effects from alkalinizing agents are very uncommon provided some minimal precautions are observed. Minor adverse effects are common but can be minimized by appropriate monitoring and regimen modifications.

POTENTIAL ADVERSE EFFECTS FROM SODIUM PREPARATIONS: Sodium bicarbonate frequently gives rise to increased gas formation in the stomach which may lead to excessive belching and chest discomfort. It can also induce lower intestinal bloating and diarrhea. Because of its buffered characteristics, Bicitra is far less problematic than sodium bicarbonate in terms of gastrointestinal tolerance. (Indeed, it is also far less irritating to the gastrointestinal tract than any of the potassium-based agents.) In patients with heart problems or advanced kidney disease, however, sodium-containing agents can induce sodium retention resulting in edema or lung congestion. Sodium loading can also exacerbate hypertension and induce excessive thirst. And all alkalinizing agents can induce over accumulation of bicarbonate in the body (I.e., metabolic alkalosis) with confusion, cramps, weakness, and symptoms of low blood calcium (muscle spasms)--especially in the face of any dehydration and renal disease. Close physician's guidance is necessary if any of these conditions are present, suspected, or develop.

At sustained high urine pH, starting at about 7.3, and becoming more pronounced at 8.0, calcium phosphate salts (apatite) in the urine are much less soluble. Apatite stones can form in the urinary tract and "ring calcifications," I.e., calcium encrustations can form around foreign bodies including catheters, stents and cystine kidney stones. These complications occur more readily in patients who already have low urine citrate values (urinary citrate helps keeps calcium in solution and helps prevent calcium stones or encrustations from forming or enlarging).

Although apatite stone formation, and ring calcifications, are a theoretical risk from any intense, sustained alkaluria, in our experience we have noted it only in association with sodium-based alkalinizing agents. Although we don't fully understand the basis for this advantage of potassium over sodium-based agents, it may be because potassium citrate elevates protective urinary citrate more than does sodium bicarbonate. Also, sodium loading sweeps calcium out through the kidneys elevating urinary calcium--much more in some subjects than others--while potassium-based alkalinizing agents do not possess this disadvantage. Elevated urinary calcium (hypercalciuria) increases the potential for calcium stones formation, and ring calcifications at high urine pHs. (The action of sodium citrate in this regard is not known; as a sodium-based agent it likely also induces hypercalciuria; but, as a citrate salt, it may elevate protective urinary citrate as much as the potassium citrate preparations.)

To monitor whether intense alkalinization therapy is inducing the complication of calcium kidney stones, or calcium encrustations in the urinary tract, it is wise to obtain X-rays of the abdomen every 1--2 months when starting the regimen, then, if no problem has arisen, less frequently; radiation-free sonographic evaluations, although more expensive, may be substituted. If calcification-type complications do not develop within the first 6 months of intense urinary alkalinization, it is unlikely that they will do so in the future provided the regimen is not significantly altered. If calcium stones, or calcium encrustations, are induced by urinary alkalinization, it is best to switch to a potassium-based alkalinizing agent, if tolerated. If this cannot be effected, one might consider drastically lowering dietary phosphate intake, probably coupled with the use of oral aluminum-based phosphate binders, I.e., a Schorr regimen. The Schorr regimen decreases apatite stone formation in the urinary tract, perhaps by grossly lowering urinary phosphate concentrations, or perhaps by the apatite-inhibiting effects of aluminum being excreted in the urine. Lastly, since sodium loading can increase urinary cystine excretion, in patients with refractory, problematic cystine stones, sodium loading should be avoided unless it has been demonstrated not to significantly elevate urinary cystine.

POTENTIAL ADVERSE EFFECTS FROM POTASSIUM PREPARATIONS: Potassium-based alkalinizing agents also can cause stomach and intestinal gas formation but far less frequently than sodium-based agents. However, potassium agents frequently irritate the gastrointestinal lining causing gastritis, "heartburn," and diarrhea, especially in patients with an underlying G.I. sensitivity. These bothersome GI side effects can be mitigated somewhat by taking the preparations only at mealtimes, or by taking lower dosages at more frequent intervals.

The only potentially serious adverse effect from potassium-based alkalinizing agents is *potassium retention (I.e., hyperkalemia.) When marked, or arising suddenly, potassium retention can be fatal.* Potassium retention from potassium alkalinizing agents is a risk in the following situations: (1) Whenever kidney function is very depressed, or when urinary tract obstruction is present; (2) Rarely, some older diabetics may unexpectedly experience difficulty with excreting potassium; (3) When a potassium-taking patient is concurrently being treated with drugs that inhibit renal excretion of potassium. These include certain diuretics (E.g.,Dyazide, Aldactone, Midamor), and "ACE inhibitors" (E.g., Vasotec, Capoten, etc.) In this regard, the ACE-inhibitor, captopril (Capoten) is to be particularly feared because it is sometimes used, and in very high dosage, to treat Cystinuria as a substitute for penicillamine and Thiola (in subjects allergic to the latter.) Captopril can be a very effective drug to lower urinary cystine, at least for a few months, but any cystinuric subject taking daily dosages of more than 50 mEq potassium, and more than 50 mg of captopril, should have it proven that a potentially dangerous degree of potassium retention has not occurred. Because peak potassium retention may not occur until 1-2 hours after the alkalinizing agent has been taken, the serum potassium should be checked then, rather than a fasting state preceeding medication administration. (4) Rarely, when a patient taking very high dosages of potassium is also taking very high dosages of a beta blocker (E.g., Inderal, Lopressor, etc.) since beta blockers may retard the rate at which potassium enters systemic cells.

POTENTIAL ADVERSE EFFECTS FROM ACETAZOLAMIDE: Although acetazolamide sounds like an ideal agent, it has major drawbacks in that in chronic use, at high dosage, it causes too much accumulation of acid in the body (metabolic acidosis), markedly lowers (stone-protective) urinary citrate and elevates urinary calcium (from skeletal leaching.) This combination, in the face of urine at pH 8.0, grossly favors the formation of calcium encrustations and calcium stones in the urinary tract. For these reasons, acetazolamide is frequently used only intermittently, during phases of sodium intolerance. In selected individuals, however, it can be excellently tolerated and may prevent a cystinuric patient from requiring penicillamine or Thiola. In our experience, it also greatly aids nocturnal alkalinization and can be a vital force in cystine stone dissolution (when losses of potassium and bicarbonate are judiciously replaced.)

CONCLUSIONS AND SUMMARY: For the treatment and prevention of cystine calculi, a regimen of urinary dilution and urinary alkalinization provides the best combination of efficacy and safety. Since the components of this regimen are complementary in their actions (decreasing urinary cystine concentration and increasing urinary cystine solubility), they should always be used together. Penicillamine and Thiola lower urinary cystine excretion but they possess a much greater risk of toxicity. Since forced hydration and urinary alkalinization are also complementary in purpose to penicillamine and Thiola, they should always be added to a regimen of the latter. Forced hydration and urinary alkalinization may reduce the requirements of penicillamine and Thiola and, in milder cases, even substitute for them. Significant urinary cystine solubility begins at urine pH 7.5 and peaks at 8.0. Therefore, sufficient alkalinizing agent should be given to always reach this target pH range. Intensity of treatment with alkalinizing agents and hydration, should be determined empirically: intermittent and/or low-intensity regimens are likely sufficient for mild cystinurics whereas high intensity, around-the-clock, long-term regimens will likely be required for severe cystinurics. Penicillamine or Thiola should be initiated only after an optimal regimen of forced hydration and urinary alkalinization has proved insufficient. The intensity of Cystinuria can be defined on the basis of 24-hour-urine cystine excretions, with some exceptions. Potassium-based alkalinizing agents are probably superior to sodium-based ones because they do not elevate urinary cystine or urinary calcium, nor at high urine pH as strongly favor the formation of calcium stones and calcium encrustations in the urinary tract. Acetazolamide is a very useful drug for urinary alkalinization, especially for nocturnal use, sodium retainers and rapid stone dissolution. However, because of its unique adverse effects profile it should be reserved for special situations. Focused and vigorous application of forced hydration and urinary alkalinization are a major modality for the treatment and prevention of cystine calculi.

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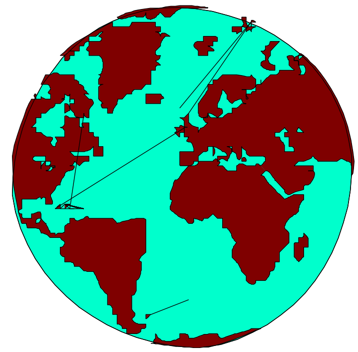
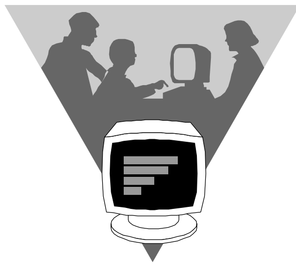


Cystinuria to be Studied as Part of a New Collaborative International Effort

Written by Ellis D. Avner, M.D.
Director, Division of Pediatric Nephrology
Children's Hospital and Medical Center
Seattle, Washington

The International Study of Genetic Renal Diseases (ISGRD) is a newly formed international study group which plans to establish patient registries and facilitate genetic studies of certain diseases which effect the kidney. Pediatric Nephrologists and Geneticists from the United States, Great Britain, Italy, France, The Netherlands, and Germany have united in this important effort. Cystinuria is one of the 11 renal genetic diseases to be studied by this group. An on-line electronic genetic registry will be developed so that researchers around the world can readily identify groups of patients with Cystinuria, and contact their physicians regarding ongoing genetic studies to isolate the gene which may cause the kidney transport defect which is the cause of this disorder. Isolation of the gene which is mutated in Cystinuria should lead to new methods of diagnosis, and eventual treatment. Patients can find out more about this study by contacting their local Pediatric Nephrologists or addressing an inquiry to:

Dr. Gianfranco Rizzoni
Pediatric Hospital of The Infant Jesus
Piazza S. Onofrio
4 Rome Italy, 00165.
Telephone 39-6-6859-2126. Fax 39-6-6859-2602.



Cystinuria Support Network ON-LINE

Written by Ben Lokos
CSN Participant

Jann Ledbetter should be commended for the excellent job she is doing with this support group. I personally have learned a lot more about Cystinuria through the Support Network.

With Jann's help I am trying to bring the Cystinuria Support Network "OnLine". There are a multitude of benefits for an on-line group. Imagine coming home and checking your "email" (electronic mail) on America OnLine, and discovering that "gene replacement" will eventually lead to a cure for Cystinurics. Or having the ability to go on-line and talk to 20 members of the Cystinuria Support Network simultaneously in an on-line "chat room". Maybe even talk to experts in the field of nephrology or urology on-line and "email" them at their internet address for an opinion. This is all possible through computer bulletin boards.

I have discovered the hard way that America OnLine (AOL) is the least expensive of all the bulletin boards and the simplest to get around in. If you would like a copy of AOL software please call me and I will have them send you the latest version. You will need at least a 386 IBM compatible computer with 4 megabytes of RAM for the windows version (or the Mac equivalent) and a modem. If you have a 286 machine or just want a DOS version, AOL has this also. (Windows version is much better than DOS version.)

After loading and setting up your software, you will need to select an "on screen" name that is unique. (Mine is BEN SCUBA, Jann's is JANNMOO, Michael Jordan's is STARSTRK.) You will also need to select a password which you will type whenever you go "on-line". Then you are ready to go!!!

Once on line you will want to go right to a special area where we can list messages for the group in a folder. In order to get there you should first choose "Go To" from the Menu at the top of your screen. Select "Keyword" and type in "Health". This will take you to the Better Health Forum. Click on the "Health Message Center" (?), then click on "List Categories". Once in the discussion area, click on "Self-Help and Support Groups" and look for the Cystinuria folder in the "Rare Disorders" category.

We are also trying to get a special on-line room just for us, where we can communicate with each other at the same time. To find such a room, Go To, Keyword, "Chat". This will take you to People Connection. Click on the icon "Rooms". That will take you to "Active Public Rooms". Click on "Available Rooms" and that will take you to "Member Rooms". That is the window where you should find us. Scroll through the "Room Names" until you find "Cystinuria". If you don't see us in the list, *don't panic*, simply hit the "more" button at the bottom of the Window. Hopefully, you will find us in the Cystinuria Room.

We can leave personal email messages for each other using the email features of AOL. To send a private message, choose "Mail" from the top menu, then choose "Compose Mail". You will need to know the screen name of the person you are sending mail to. We can also leave messages to each other through the Internet by just adding the correct extension of the Internet address. So, for example, my extension would be

Ben Scuba@AOL.COM.

Jann can be reached on AOL at
JANNMOO@AOL.COM or on CompuServe at
75512.3161@Compuserv.Com.

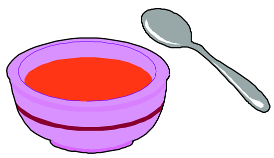
For more extensive information about how to access AOL or how to access any other bulletin board, please do not hesitate to contact me at:

(212) 564-0500 9:00-6:00 EST (Work)
(516) 431-0737 After 9 PM EST (Home)

In closing, as the group continues to grow it is impractical to contact all participants by phone or mail. On-line communication is inexpensive, fast and fun. It also offers the ability to communicate with several people at one time, which eliminates repeating information.

Stone Soup

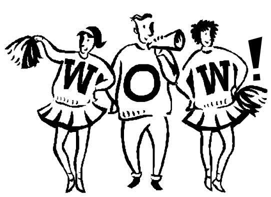
A column containing bits and pieces of information, questions, anecdotes and ideas for discussion.



Thank you *to the Jordan family for their contribution which helped to offset the cost of printing and mailing this newsletter.*

Thank you *to Dixie Johnson for her generous contribution and enthusiastic support of the* ***Cystinuria Support Network****.*

Thank you *to all the doctors and other medical professionals who took time out of their busy schedules to write the wonderfully informative articles for this newsletter.*



The ***Cystinuria Support Network*** *continues to grow steadily. If you would like a new, up-to-date, listing of participants, please let me know and I will be glad to send it to you. There are currently close to 70 participants but I hear from new people most every week and I expect the group to include over 100 people before too long.*

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So many people have told me that they would just love to meet someone else with Cystinuria.

If you are going to be traveling to another part of the country, take a look at your list before you go. Maybe you could make a call and arrange to meet another network participant while you are in their area.

For those who have children with Cystinuria (and the young at heart!), I have found a great source for ***fun*** *water bottles. These 16 ounce plastic bottles will be decorated with the design of your choice and personalized for a total cost of $2.95 each. And they are transparent, which we have found to be very helpful for parents and teachers that need to monitor a child's drinking from across the room. The colorful decoration makes them something the children love to have with them at all times. To order contact:*

Dorothy Urban
24 Columbia Key
Bellevue WA 98006
206-641-9897

I received a letter from Dr. Paul Goodyer from The Montreal Children's Hospital telling me that in Quebec they have a <u>routine newborn screening program for Cystinuria</u>. I found this information to be ***fascinating*** *and have written back to him for more information about the program and the results. What a difference it would have made in my daughter's situation if we had known from the start that she had Cystinuria. I hope to have more information about this in the next newsletter.*

This newsletter will be published as often as there is enough information to make it worthwhile.

Send me an article about yourself and your experiences with Cystinuria so that other participants can get to know you.

Send me a concern you are struggling with that someone else may have some insight into for the "Mailbag" column. This could be a question and answer type column with medical opinions if appropriate.

Send me ideas you have for articles for future newsletters and I will try to locate someone who is willing to address the issue.

I would love to see columns in future newsletters such as:

"Lessons Learned"

"Helpful Hints" and

"Speaking our Minds".

But these will require your input. Please send me anything you would like to contribute. Remember, this is <u>your</u> network!

Send your ideas, questions, articles etc. to:

Jann Ledbetter
Cystinuria Support Network
21001 NE 36th Street
Redmond WA 98053
425-868-2996

If you are interested in participating in the Cystinuria Support Network and have not already done so, please fill out the following form and send it to:

CSN c/o Jann Ledbetter
21001 NE 36th Street
Redmond WA 98053

Name___________________________________

Address_________________________________

City,State, Zip___________________________

Phone_________________Best time_________

Additional Patient Information:

Sex____________Date of Birth______________

Number of Years since diagnosed____________

Current Medications_______________________

Surgeries and other procedures you've experienced______________________________

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Other information you would like to share_______

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How did you hear about CSN?_______________