University of Pittsburgh & UPMC Scleroderma Center

COLLAGEN CONNECTION

Winter 2011-12

Raynaud Phenomenon

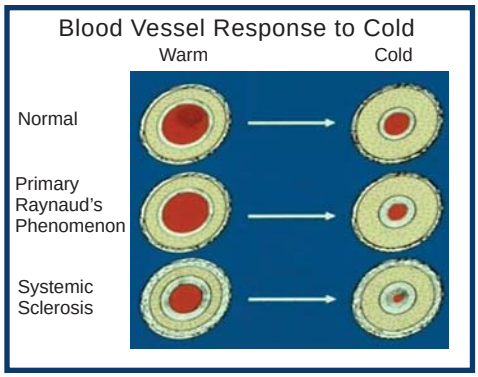
by Robyn T. Domsic, MD, MPH

In 1865, a French medical student, Maurice Raynaud, described this condition, in which an individual experiences repeated episodes of color changes in the fingers (and sometimes the toes) during cold exposure or emotional stress. It is normal for blood vessels supplying the skin or extremities to narrow (constrict) in response to cold temperatures, and this is termed "vasoconstriction". In Raynaud phenomenon, the body's blood vessels constrict in an exaggerated way to cold or stress, resulting in color changes. Typically this may be experienced as "blanching" where the fingers are "dead white", followed by bluish/purplish discoloration and possibly redness when rewarming occurs. Occasionally, patients will experience only 2 of these 3 phases.

What is the difference between primary and secondary Raynaud Phenomenon?

Primary Raynaud, or Raynaud disease, refers to individuals who experience Raynaud phenomenon, but do not have an underlying disease. Primary Raynaud is common, occurring in up to 10% of otherwise normal persons, most often women. Raynaud disease can also occur in more than one person in a family (familial Raynaud disease). There is nothing abnormal about the blood vessels except their excessive response to cold. These patients do not develop fingertip ulcerations, are not disabled by the condition, and respond well to medications.

In secondary Raynaud, the anatomy of the blood vessels is abnormal. There is most often an associated connective tissue disease (CTD), such as scleroderma or Sjogren syndrome. In scleroderma, more than 95% of patients experience Raynaud symptoms, and for many it is the first symptom of the disease. CTD patients develop thickening of the inner lining of the blood vessels that leads to reduced size of the vessels. Then, when vasoconstriction occurs in response to cold, the blood vessel is very narrow and leads to the Raynaud episode. These differences are illustrated in the diagram below.



In patients with scleroderma there may be pits or indentations that develop on the fingertips, which are referred to as "digital pitting" scars. Some patients may develop ulcers of the fingertips and less commonly there is blockage of a larger finger artery resulting in major tissue loss (gangrene).

Robyn T. Domsic, MD, MPH received her bachelor and medical degrees from the University of Iowa. She completed her internship and residency at Duke University Medical Center, and rheumatology fellowship at the University of Pittsburgh. She subsequently finished a Master of Public Health degree at the University of Pittsburgh. She is board certified in Internal Medicine and Rheumatology.

Dr. Domsic's primary clinical and research focus is improving the care of the patient with Scleroderma. She has worked in the Scleroderma Clinic since 2007. She is currently attempting to develop easy tools to assess and score a patient's risk of poor outcome when they develop diffuse scleroderma. She has additional studies investigating early blood vessel changes in patients with diffuse cutaneous scleroderma, and how this relates to later complications. She is actively involved as an investigator in all of the current observational and clinical drug trials at the Scleroderma Center.

IN THIS ISSUE

What can I do to manage Raynaud symptoms?

Patients should take an active part in managing their Raynaud symptoms including:

- Keep the core body (chest, abdomen) and head warm by dressing warmly and wearing a turtleneck, scarf and hat in cold weather.
- Keep fingers and feet warm (mittens are better than gloves, stockings, hand warmers).
- Avoid rapidly changing temperatures (such as the frozen food section of the grocery store).
- Avoid cold breezes.
- Stop cigarette smoking and try to avoid second hand smoke.
- Minimize emotional stress, if at all possible.
- Avoid repeated occupational or recreational injury (trauma) to the fingertips. Some patients may experience vibration-induced Raynaud, and for these patients vibrating tool use should be avoided.
- Practice methods to stop a Raynaud attack after it begins (placing hands under warm water or under the armpits, rubbing hands together, or rotating arms in a windmill pattern).

What are my drug options?

There are several medications which have been shown to help reduce the frequency and severity of Raynaud attacks, promote healing of existing fingertip ulcers or prevent new ulcerations. They are most often blood vessel "openers" or vasodilators. We do not recommend any one of these medications over another, but merely list them because there is medical literature which supports their effectiveness.

1. Calcium channel blockers - *amlodipine (Norvasc), nifedipine (Procardia):* These are the most commonly used vasodilator drugs. They are moderately helpful for some patients. These medications are generally well tolerated. The most common side effects are edema (swelling of the legs/feet), dizziness, headache and rapid heart rate.

2. Angiotensin receptor blockers *– losartan (Cozaar):* These are also vasodilators originally used to treat high blood pressure. They are generally well tolerated, with the most common side effect being headache. Patients should have their blood potassium checked a few weeks after starting this type of medication, as it can raise the blood potassium level.

3. Nitroglycerin: Nitroglycerin is a vasodilator that is available in several forms (patches, creams and gels). It is generally applied directly to the base of the fingers. Headache is the most common side effect.

4. Phosphodiesterase-5inhibitors *- sildenafil (Viagra), (Cialis), tadalafil (Adcirca):* These medications are used for pulmonary hypertension but are also blood vessel dilators in the fingers. These drugs are well tolerated with the most common side effects being dizziness and headache.

5. Endothelin receptor antagonists (*bosentan*): Bosentan is approved for the treatment of pulmonary hypertension and in two studies has been shown to reduce the frequency of new fingertip ulcers. However, no improvement in Raynaud symptoms has been documented. These medications are well tolerated, but can cause edema and abnormal liver tests.

6. Prostacyclins (*epoprostenol, treprostinil*): Prostacyclins are potent vasodilators, initially used in pulmonary hypertension. They are now available in intravenous (IV), oral or inhaled preparations. The IV form is used for severe loss of finger blood flow which threatens to result in gangrene

7. Statins: Small, preliminary studies suggest that atorvastatin, one of the drugs used to reduce cholesterol, may help to minimize scleroderma-associated Raynaud symptoms.

Are there other options?

There are surgical procedures for those patients who have failed medical management. Sympathectomy, or stripping of the nerves which control blood vessel constriction, can be done in the fingers or at the larger arteries in the wrist. Generally, before this is done, an arteriogram (injection of dye into the artery) is done to assess whether improvement with sympathectomy is likely. Surgery in scleroderma patients can sometimes be difficult, as post-operative loss of finger motion occurs more often than in normal persons. A hand surgeon with scleroderma experience should be consulted.

In some scleroderma patients there may be blood vessel narrowing of the larger (radial or ulnar) arteries in the forearm. In these cases, vascular bypass surgery may be useful.

"There is no medicine like hope, no incentive so great and no tonic so powerful as expectations of something better than tomorrow."

-Orioson Swett Marden

Carol Blair Memorial Endowment Fund Created

Longtime patients at the Scleroderma Center Clinic will always remember the support and encouragement provided by nurse Carol Blair. Carol worked closely with scleroderma patients for almost 30 years prior to her retirement in April 2007. Patients immediately remarked how much they missed seeing her at their appointments or hearing her caring voice when they called the office. Carol passed away in 2010 and her husband, Andrew R. Blair, PhD, knew the importance of honoring her memory and dedication to the cause of scleroderma. "I wanted to do something that would be a tangible testament to Carol's memory. She was devoted to the cause of scleroderma patients and to the University's clinical research program that aims to understand the causes of this disease," he explains.

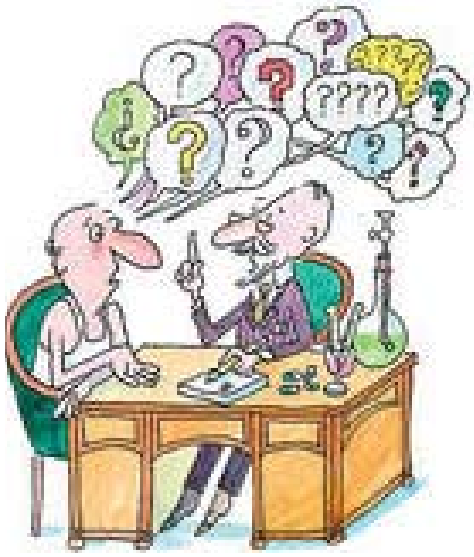
Recently Dr. Blair created an endowment at the Scleroderma Center in honor of his wife. The Carol A. Blair Endowed Fund in Scleroderma will provide support to the Scleroderma Center within the Department of Medicine, Division of Rheumatology and Clinical Immunology at the University of Pittsburgh. "The earnings on this endowment will provide some flexible support for those who are involved in the work of the Center," Dr. Blair, who serves as vice provost for faculty affairs and professor of business administration and of economics at the University of Pittsburgh, explains. "Hopefully, its creation will encourage others who were aware of Carol's dedication to this work to add their own support to the endowment and its future growth. I think that she would be pleased that we are honoring her in this way."

The clinicians, researchers, faculty, staff and patients at the Scleroderma Center thank Dr. Blair for his kindness and generosity. This truly is a remarkable way to remember such an outstanding advocate for scleroderma research and treatment. If you would like to contribute to this endowment in Carol's memory, please contact Gary Dubin at 412-647-9113 or dgary@pmhsf.org.

CONGRATULATIONS
to the winners of our
Summer Newsletter Contest

Kay Cavanaugh
Cindy Grabiak
Barbara Petrick
Dawn Santora

The winners received a gift card to their favorite restaurant.
Thank you to all who entered.



Ask the Expert

Chris C. from Baldwin, PA asks the following:

Question: In the summer issue of the Scleroderma Center newsletter, Dr. Torok wrote about localized scleroderma in children. My daughter was recently diagnosed with LS. Is she more likely to develop systemic sclerosis later in life?

Answer by Dr. Kathryn Torok: This is a question I am frequently asked by parents of my newly diagnosed patients with localized scleroderma. As described in the last newsletter, systemic sclerosis (SSc) and localized scleroderma (LS) are entirely different diseases. Both lead to sclerosis (fibrosis) and both have an autoimmune basis, but beyond that they have no features in common. One does not "evolve" into the other.

These two diseases can occur in the same patient, but it is extremely uncommon. In our Scleroderma Center experience over the past 50 years with nearly 5000 SSc and 1000 LS patients, 10 (1 out of 500 SSc and 1 out of 100 LS) patients have had both diseases. The most frequent pattern among these rare individuals is childhood (age <15) onset of LS followed after many years by adult (age >30) onset SSc.

Walk With Tori

On September 11, 2011, over 500 people came to the first annual "Walk with Tori" scleroderma walk in Doubs Woods Park, Hagerstown, Maryland.

Some people walked in memory of a loved one, in honor of a friend, or in support of a family member, but everyone at the walk is "*Wishin' for a cure*".

Tori said she would dye her hair pink if the walk raised over $15,000. She walked with her family, friends, supporters and other scleroderma patients, Pink and Proud!

Joe Dill prepares the Honor Guard to begin the festivities and lead the way into the park.

Thank you to everyone who dedicated their time and talents to make this walk successful!

Mt. Olivet Presbyterian Church Youth Group members

Walkers enjoyed the beautiful day.

Scizzor Wizzard Salon and friends

Dr. Medsger and Tori are all smiles.

Blair's Bunch

Joe, Dr. Medsger, Tori, Maureen, Mary and Dr. Domsic from the Pittsburgh Scleroderma Center.

Meritus Medical Wound Center

The Pine family and friends

Team Kevelynn

The Bryant family and friends

Hilltop Christian Fellowship

Possom Holler entertains the crowd.

"To accomplish great things, we must not only act, but also dream; not only plan, but also believe."

- Anatole France

Tori said she would shave her head if the walk raised over $30,000....Luckily her husband, Mike, offered to take her place. Debbie Flowers does the honors.

Tori presents a check in the amount of $43,000 to Dr. Medsger to help fund scleroderma research.

Mercedes Shoemaker

Advisory Group Member Profile Mercedes Shoemaker

Philanthropy is vital to finding new and better ways to treat scleroderma. And, thanks to Mercedes Shoemaker, the important research being done each day by Dr. Thomas Medsger and Dr. Carol Feghali-Bostwick at the UPMC and University of Pittsburgh Scleroderma Center will be able to continue well into the future.

"Research really is the key"

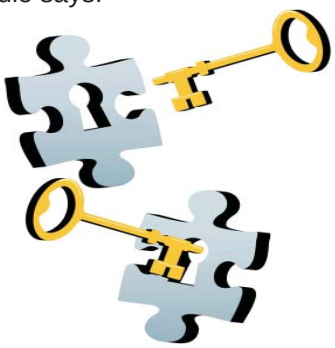
Mercedes, or Merdie, as she is often called, first learned about scleroderma from her late husband, Albert, the former CEO of Consol Coal Co. Albert's first wife, Jean, suffered with scleroderma for 35 years prior to her death. Merdie knew the difficult road that Jean and Albert navigated as they sought ways to alleviate her symptoms. "Al always said that Jeannie had a really positive outlook on life, despite the pain that she was in," she explained. "But this disease really took a toll on her." Between trying to find an accurate diagnosis – many doctors in the 1930s and 1940s weren't well versed in scleroderma – and looking for ways to treat this relatively unknown disease, Merdie knew this was a cause she wanted to champion.

"When my husband and I were discussing things that we wanted to support, I told him that we should do something in honor of Jeannie," Merdie explained. This led to creating an endowment to fund research for scleroderma.

An alum of Purdue University, Merdie has always felt that giving back was crucial – especially toward research and education. "I'm truly hoping that this gift to the Scleroderma Center will be seed money that will accelerate scleroderma research, which is just so important for the future," she explains.

The newly created Scleroderma Research Fund will mainly support Dr. Feghali-Bostwick's work which focuses on finding the cause of this disease by exploring the connective tissue in the skin and lungs. In addition, some of the funds will be used to supplement the research efforts of Dr. Feghali-Bostwick's mentees who are too junior to secure their own grants, allowing these researchers a chance they otherwise may not have had.

Merdie is hopeful that the dedicated scientists at the Scleroderma Center will find new breakthroughs in treating scleroderma. "Carol is one of the most brilliant women I have ever known," she says of Dr. Feghali-Bostwick, "I just love her. She is fabulous!" Merdie's generosity is leading us toward a world where the future is positive for those with scleroderma and no one will ever again have to suffer the way that Jean did. "Research really is the key," Merdie says.



Skin Biopsies in Scleroderma

by Thomas A. Medsger, Jr., MD

Importance

The skin is where the "action" is in scleroderma. The current concept is that cells from the immune system (lymphocytes) migrate out of blood vessels and into the major area of the skin (dermis). There they produce substances (cytokines) which stimulate resting cells in the skin (fibroblasts) to overproduce collagen, which accumulates in excess and results in thickening of the skin.

It is important to examine and compare both affected (thickened) and unaffected skin in the same patient and skin from the same site, for example the forearm, at various stages of disease in the same patient. "Control" skin biopsies from normal healthy persons who are not blood relatives of scleroderma patients (spouses, other unrelated individuals) are also helpful.

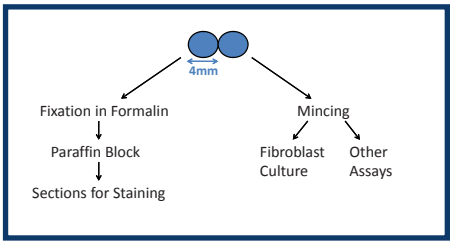
If you are requested to provide a skin biopsy, please give this your serious consideration. Finding substances in affected skin which are present in excess and not found in normal skin may provide important clues for development of new treatments for scleroderma. This has occurred in rheumatoid arthritis (RA), where the cytokine TNF-alpha was very abundant in the joint lining of RA patients. Today the most effective therapy for RA is the group of TNF blocking drugs.

Procedure

After local anesthetic (novocaine), we collect 2 samples using a round punch 3 - 4 millimeters wide, so that the incision looks like a figure 8. The actual size is shown in the diagram below. The incision is closed with a single stitch and covered with a band-aid. The whole process is completed in several minutes.

One sample is fixed in a solution of formalin and then embedded in paraffin wax to make a "block". The block can be sliced into extremely thin sections and these slices can be studied by a variety of staining techniques.

The other sample is "minced" and the tiny pieces placed in a culture dish in an incubator with nutrients, which allows the fibroblasts in the skin to attach to the bottom of the dish and to grow.



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A Special "Thank You" to our Walk with Tori organizers and supporters!

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Logo Contest

The Pittsburgh Scleroderma Center needs a logo! Enter our logo contest for a chance to win dinner on us!

Create and design a logo for the Pittsburgh Scleroderma Center. (Include all three words in logo)
If you are using artwork as part of the logo, it must be non-copyrighted.

Please submit your logo design electronically by February 1, 2012 to laffoonm@pitt.edu.

The winner will be recognized in the next issue of the newsletter and receive a gift certficate to a restaurant of his/her choice.

Good Luck!

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