

About

SCLERODERMA

in Quebec





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France Joyal, M.D.

Vascular and Internal Medicine
Associate Clinical Professor
University of Montreal Health Center
(CHUM)

for

Scleroderma Quebec

1 844 990-6789 (toll free number)
info@sclerodermafoundation.ca

www.sclerodermafoundation.ca

1st edition: January 2001
Revised editions: 2007, 2015, 2017

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1 Introduction



If you have recently been diagnosed with scleroderma and you are looking for information that will help you better understand the disease, then this booklet is for you.

If you have been diagnosed with scleroderma but are afraid to learn what complications this disease could bring you, rely on your doctor to help you navigate the uncharted and rough seas, for he/she is always your best source for information and advice with regard to discomfort management. Before putting this book down, it is important that you be aware of the current state of scleroderma research and what Scleroderma Quebec is doing for you. To learn more about this, please read Chapter 11.

Please refer to the Appendix at the end of this booklet to find a cumulative table of available data from major US studies as well as our own group of scleroderma patients (309 patients).

Have a good read. ■

2 What is scleroderma?

By definition, scleroderma is the hardening (sclero-) of the skin (-derma).

The first description dates from 1753 by Curzio of Naples. However, it was not until 1847 that Jintrac introduced the current term scleroderma after recognizing it as a skin condition.

Based on our current understanding, scleroderma gradual hardening and tightening of the skin is due to excessive collagen production. Collagen is a protein which is naturally present in the human body and acts as one of its main constituent. Found throughout the body, its role is to provide support to the organs. Injections of artificial collagen are commonly used in cosmetic surgery to hide wrinkles or make lips more voluptuous.

The typical clinical presentation of patients who «naturally» produce an excessive amount of collagen includes collagen buildups in the skin, resulting in its' hardening as well as an alteration of some bodily functions, with or without discomfort. ■

3 What scleroderma is not

Many people are concerned that scleroderma may be related to multiple sclerosis or amyotrophic lateral sclerosis, which affects nerve fibers in the brain or spinal cord. Fortunately, this is not the case and on the contrary, it is safe to say that despite undesirable complications for other organs, scleroderma patients do not experience any alteration in brain function or decline in mental ability.

Scleroderma is not contagious and is not a form of cancer. Patients will often notice small red dots occurring on their face and upper extremities, which are abnormally dilated tiny blood vessels (capillaries). These small dots tend to accumulate over time: they are an indication of the presence of the disease, not of its severity.

The notion of immunity in scleroderma is somewhat peculiar: the patient's body produces too many antibodies which are directed against its own cells, thus causing adverse organ inflammation (for example the joints, liver, and arteries). Scleroderma should not to be confused with the immune condition of an AIDS patient (Acquired Immunodeficiency Syndrome) which is caused by the HIV virus. In these patients the immune system is deficient and cannot adequately "manufacture" antibodies (defense system) to fight off an infection. ■

4 What is the cause?

The cause of scleroderma appears to be related to an imbalance in the immunity system, which is not fully understood. Although, some contributing factors have been identified:

1) A genetic predisposition:

It is very rare to find another case of scleroderma within the same family. However, some family members may develop Raynaud's phenomenon (cf Booklet # 1: Winter at last) or suffer from a collagenosis (or connectivitis, i.e. connective tissue disease). Rheumatoid arthritis, lupus erythematosus, mixed connective tissue disease, Sjögren's syndrome and scleroderma all belong to the collagenosis group. There is for these families a genetic predisposition or susceptibility to the presence of those diseases.

2) An abnormal activation of the immune system:

The activation of a group of cells, called fibroblasts, results in collagen deposition associated with a surrounding inflammatory reaction (our immune response), which in turn evolve into fibrosis. This transformation, which is abnormal because it is directed against our own cells, may vary from organ to organ and person to a person. It is unclear whether this transformation is the result of damage to small vessels that supply blood to the organs of our body or if it is the blood vessels' disease which subsequently induced a fibrosis reaction around the affected organs. These two damage mechanisms are not necessarily at work in the same organ.

Is the activation related to a virus, a chemical substance or a physical attack? Our environment may have contributed to triggering a cascade reaction resulting in scleroderma. So far, however, we still don't know the cause for a majority of scleroderma patients. ■

5 What are the types of scleroderma?

The information in this booklet is intended for adult patients who have “systemic” scleroderma (also called systemic sclerosis), a type of scleroderma which, in addition to the skin, may also affect internal organs (i.e. signs/symptoms of visceral involvement).

Chapter 7 will provide more details on each of the organs mentioned herein. There are two main subtypes of systemic sclerosis (SSc): *limited and diffuse*.

The **limited form** of systemic sclerosis was previously referred to by the acronym **CREST**:

- C** = Calcinosis cutis (calcium deposits under the skin)
- R** = Raynaud (finger discoloration upon exposure to cold)
- E** = Esophageal dysmotility (disorder affecting 2/3 of the lower esophagus)
- S** = Sclerodactyly (skin thickening and tightening over the fingers due to collagen deposition)
- T** = Telangiectasia (tiny dilated blood vessels visible on the face or hands)

5 What are the types of scleroderma?

In the patient population that we have assessed over the past 30 years, the *limited* form represents about 56% of scleroderma patients. The diagnosis at the outset of the *limited* form of the disease is difficult: the cutaneous involvement, which is limited to the fingers, the forearms and/or the face may be absent if not very discrete. Patients are often referred to us because they have developed Raynaud's phenomenon. During the initial assessment process, other clues can be found as well such as:

- upper digestive tract (esophagus) involvement,
- presence of capillary telangiectasia on the fingers: these are small dilated blood vessels visible to the naked eye or under the microscope (i.e. nailfold capillaroscopy, a technique for the analysis of microvascular abnormalities),
- blood test revealing the presence of scleroderma-specific antibodies (anti-centromere and/or anti-topoisomerase),
- after several years of disease progression, calcinosis (calcium deposits) in some patients.

Each case being unique, not all patients will have the same disease progression. Some patients, for instance, will be prompted to seek medical care for digital ulcers or articular pains as part of the initial presentation of SSc, these being usually later complication manifestations. Involvement of the digestive tract can spread to other segments of the intestine. Pulmonary involvement can be of two kinds: pulmonary fibrosis and pulmonary hypertension. Pulmonary involvement significantly worsens the survival prognosis. With new drugs available each year as well as the possibility of lung transplantation, there is now real hope to beat the odds!

5 What are the types of scleroderma?

The *diffuse* form of systemic sclerosis is, in many regards, much more aggressive: skin damage can be quick and extensive (which may include the arms, lower limbs, and trunk) with joint involvement, and more rarely the muscles, thus resulting in some functional loss.

Accumulation of collagen in the lungs, intestines, heart and/or kidneys can alter the function of these organs. Renal crisis characterized by a sudden and rapid deterioration of renal function may require kidney dialysis, which is now hardly ever needed thanks to the development of new drugs that have proven very effective for the treatment of severe hypertension.

The disease can stop and even regress remarkably at all levels including the skin. Since the CHUM (University of Montreal Health Center) is a referral center for complicated cases, the prevalence rate of this form

of the disease is much higher (44%) than the actual prevalence rate observed in the rest of the patient population (about 20%).

“Localized” scleroderma or *morphea* is a rare form, which is distinct from “diffuse” scleroderma that we have previously commented on. Morphea mostly affects the skin, rarely the underlying muscles and/or bones. It affects women more frequently than men in a ratio of 3:1. Age at disease onset is variable with a frequency peak between the ages of 20 and 40. In adults, there are several types: circumscribed, linear, guttate or drop-like, frontal linear scleroderma (en coup de sabre) and generalized. To date, the cause remains unknown. Spontaneous recovery is usually the most likely outcome of this form of localized scleroderma, which does not require aggressive treatment.

Scleroderma is rare in children as it represents only 3% of all reported cases. The localized form is by far the most common. The systemic form remains exceptional. ■

6 Who can develop scleroderma?

Scleroderma is a disease that can be found everywhere around the globe. According to one estimate, in the United States, the number of reported cases ranges anywhere from 50,000 to 300,000, with an annual incidence of 20 new cases per million population. The exact prevalence of this disease in our own country is unknown.

However, applying the known American prevalence rate to our own population we might infer that there are currently about 10,000 scleroderma patients in Quebec, with 150 new cases being added each year. Although considered a “rare” disease, scleroderma has a higher prevalence rate than muscular dystrophy and leukemia.

Scleroderma is far more common in women than in men, among both the limited and diffuse subtypes. The mean age of disease onset is in the early forties; note that this is an average that includes children under 10 years old and patients over 65 years of age, although these cases remain exceptional.

Among our patients, we observed that disease onset typically occurs later in men (42.9 years) than in women (38.9 years) and that the average duration of the disease before the first visit in men is shorter (4.3 years) than in women (9.3 years). In a previous study (1992), we found that, overall, disease severity was greater in men than in women. ■

7 Target organs: symptoms, diagnoses and treatments



In each of the following sections, we will briefly describe the main symptoms which are most commonly presented by patients. Always seek the advice of your physician or another qualified health provider with any questions you may have regarding your own medical condition.

Above all, avoid imagining that you have a large number of the health ailments described therein, getting overly anxious that these are likely to occur, or being alarmed at the slightest discomfort: although these ailments may be present, most often they are absent or affecting only one organ or part of the body.

We will also describe current treatments. Although there is still no “curative” treatment for this disease, a variety of effective treatments are available to address some of the potential complications that might arise.

7.1 The skin

The degree of hardening of the skin varies from one patient to another. It is the extent of system organ involvement that will dictate which group the patient belongs to. As regards to limited SSc: the fingers will be discreetly puffy (edema) often early in the morning, then the skin becomes infiltrated with collagen. The fingers are often compared to sausages in their appearance (sclerodactyly), shoulders and face being more rarely affected.

With *diffuse* SSc, the hardening also progressively affects the lower limbs, from the feet to the trunk in varying degrees. The thickening of the skin and the extent of its involvement are key factors in determining functionality. Joint and tendon involvement may develop around the affected areas causing fingers to curl inward and take on a praying hands position (flexion contractures).

Subsequently, patients go through a regression phase of the hardening process, which surprisingly begins by the last affected area. Only after several months of observation can one establish, in hindsight, whether the patient is in a progression or regression phase of the disease. It is rather exceptional that a patient should regain 100% of his/her flexibility, hence the importance of remaining as active as possible to prevent a decreased in the range of motion of the extremities, making daily tasks very difficult, if not impossible to accomplish.

A patient who feels his/her skin hardening may have a sensation of scratching (pruritus) in the affected areas, which may partly resolve as the skin becomes more supple. The skin might also become pigmented, with some unpigmented areas, especially on friction surfaces. While moderate exposure to the sun is not contraindicated, it may accentuate the difference in skin coloration between hypopigmented areas (less) and hyperpigmented areas (very). In any case, sunscreen should always be used for long exposure to the sun.

7.1 The skin

Skin infiltration may or may not be accompanied by atrophy (decrease in tissue volume). There may be a typical scleroderma facies characterized by hollow eyes, pinched nose, perioral folds, thin pursed lips, and/or tightened mouth with smaller oral aperture. Atrophy of the cheek muscles may make the teeth appear more prominent. The infiltration of the skin in other areas of the face will erase expression wrinkles so that the patient may appear younger than his/her age. Unfortunately, there are no available statistics regarding the prevalence and severity of these changes. Usually, when present, they can be quite subtle and slow to appear.

Some patients may be tempted to turn to collagen treatment (injection) to remove perioral folds: caution is of the essence, however, as the skin of scleroderma patients

does not respond to collagen treatment in the same way as healthy individuals because it no longer has the same constituents as normal skin... and in any case, the folds come back as pronounced and deeper as ever after a few years. It should be pointed out that collagen treatment is not covered by the *Régie de l'assurance-maladie du Québec*. All too often, doctors are not even registered (private practice), which means that the medical consultation is also at the patient's expense even if no actual treatment is provided during the visit.

The skin is a natural protection barrier against the environment, so we must spare no effort to maintain its integrity:

- maintain a proper humidity level in the house, especially in winter, at about 30%
- avoid overheating rooms
- and try to avoid using products containing perfumes (that dry the skin).

7.1 The skin

Several products are available to keep the skin well hydrated and healthy. Be sure to talk to your pharmacist who can recommend products that meet your specific needs, either for a daily application of hand moisturizer or unscented bath oils. Unscented soaps for hands are recommended as well as the use of a mild soap for your laundry so that the fabrics will not irritate the skin.

There is not unanimous approval on the best course of treatment for the tightening/hardening of the skin. A number of clinical trials are underway, and drugs are currently being tested in patients: colchicine, methotrexate and other immunosuppressants. The future is looking promising as new treatments are expected to become available soon. Since

there is no consensus in the medical community or literature, the choice of treatment can vary from one patient to another and from one doctor to another. In such circumstances, physicians should make every reasonable effort to maintain a consistent course of action. A patient who seeks a second or even a third opinion for his/her condition may end up with as many different courses of action to select from, and thus lose complete confidence in what traditional medicine has to offer. Adherence to treatment and actual compliance to follow-up appointments are essential for successful management of patients with scleroderma. Allow yourself to be professionally guided in the choices you make regarding your health, and weigh your options carefully before moving forward with treatment, as prescribed by your doctor. ■

7.2 The blood vessels

Circulatory involvement in scleroderma can be unique as revealed by the presence of Raynaud's phenomenon or multi-faceted by the formation of (clusters of) small dilated blood vessels (capillary telangiectasia) and/or fingertip wounds (digital ulcers) with or without calcium deposits (calcinosis).

In booklet # 1, "Winter at last" you will find all the relevant information on Raynaud's phenomenon, which may often be an early sign of scleroderma. When exposed to cold, the body normally react by decreasing blood flow to the extremities, thus diverting heat to core organs to aid survival.

The body of people with Raynaud's phenomenon, in the absence of any underlying condition, overreacts leading to repeated and transient arterial spasms upon exposure to cold and/or stress, and the extremities will

also change color (white, blue and/or red) with or without pain or numbness.

Scleroderma patients also have a permanent decrease in blood vessel diameter with a corresponding reduction in flow in surrounding tissue, and the cold will further reduce blood-flow to the extremities. The first recommended treatment is to protect oneself from the cold by wearing warm clothing and footwear. Vasodilator medications (e.g. nifedipine, amlodipine) can often be useful during the cold season. Unfortunately, the most effective drugs are sometimes the most poorly tolerated. Adverse effects include: flushing, palpitations and/or headaches. Occasionally, patients will have to try more than one medication to find the one that suits them best. Any source of nicotine is to be avoided. A single cigarette, for instance, decreases blood circulation in the extremities for 4 to 6 hours, in addition to considerably increasing the risk of lung cancer and atherosclerosis.

7.2 The blood vessels

In scleroderma patients, the deposition of collagen with the surrounding inflammatory reaction affects the blood vessels, especially the distal ones, which, in turn, promotes the development of digital sores (ulcers) to the hands and/or feet, under the nails or nearby skin. They are painful, may vary in extent and severity, are often infected, with or without manifestation of poor (decreased) blood circulation to the affected extremity (cyanosis). If the ulcer area does not receive enough blood supply (ischemia), destruction of this area (necrosis) may occur; the ulcer then transformed into a distinctive brownish or blackish crust (necrotic tissue). On a small surface the crust, during the healing process, rises to make room for a new surface of healthy skin, which is sometimes

more sensitive to cold. It can be accompanied by a slight decrease in the finger curvature (loss of substance). On a more extensive surface, the ulcer area might spread to the core of the finger, reaching a tipping point beyond which the blood supply is definitely and finally cut off (gangrene). However, a sustained treatment with a naturally occurring vasodilator, administered intravenously in the form of epoprostenol, will succeed most of the time in avoiding amputation of the affected area.

To prevent such an unpleasant situation from happening, in winter patients at risk of developing ulcers need to protect their whole body against the cold as well as taking vasodilator drugs. Sometimes an infection might also develop: besides the pain that becomes more intense and persistent, swelling (edema), redness, heat and, at times, discharge of pus may occur.

7.2 The blood vessels

When a digital wound appears, it is vital to take action immediately so that it can heal properly without complications: if it is not painful, it must be cleaned once or twice a day with a non-abrasive soaking solution (chlorhexidine gluconate 0.05 solution, diluted 1:2000) or with water that has been boiled and then cooled to no less than 70 degrees centigrade (°C) followed by application of a sterile dressing. When the ulcer occurs in winter, warmer spring temperatures will generally help heal the wounds. Vasodilator medications can also be used after discussion with your doctor.

A wound may be complicated by an infection whose signs are pain, redness, heat and/or edema (swelling). Aggressive treatment of an infection with pain relief is a transition stage

that will enable the human body to first stabilize, subsequently allowing for a natural healing process to take place. Ointments that contain antibiotics are not very effective in treating these infections and may affect the effectiveness of oral or intravenous drug therapy, so they should be avoided as well as Dakin dips (with household bleach), which are often too concentrated and burn the skin, hampering proper healing and sometimes even encouraging infection.

Winter is a difficult time of year for all patients with scleroderma. For some, the fingers swell when the cold weather comes back starting in fall all the way to spring. Protecting hands with gloves or mitts often causes skin dryness and, hence, the presence of fissures near the nails. Some patients will also develop frictional ulcers on the dorsal portion of the fingers in the tendons. These lesions are different from those already described which occur at the tip of the fingers.

7.2 The blood vessels

They can be painful and may be a potential starting point for an infection. In these special cases, vasodilators will do nothing to promote wound healing. When such wounds occur, they should be covered with a sterile dressing at least during the day.

Prevention of Raynaud's phenomenon and ulcers is primarily based on protection against the cold, with particular attention to maintaining adequate skin hydration by applying unscented cream or ointment. Abrasive products should be avoided and rubber gloves should be worn for housework.

Calcium deposition (calcinosis), whose mechanism is poorly understood, can occur at the distal ends of the fingers, tendons, joint capsules, periarticular sites (fingers, elbows) and

less often at the anterior surface of the legs or buttocks. When the accumulation is close to the surface of the skin, a spontaneous flow (draining) can occur, with or without infection, because this opening to the skin is a new gateway for bacteria to enter the body.

Sometimes calcium buildup is harmful and requires drainage. Some patients may be tempted to take matters into their own hands to accelerate drainage. Be careful! Caution is advised. Too often, the tools used are not properly sterilized, and by doing so patients can then introduce harmful bacteria or other pathogens into their skin, and cause an infection that might otherwise have been avoided. Drainage of calcium deposits should only be performed by a qualified surgeon under sterile conditions with antibiotics. Unfortunately, there is no effective treatment for calcinosis.

7.2 The blood vessels

Capillary telangiectasias are small red spots visible on the skin that disappear under pressure and are common in scleroderma. They are not an indication of disease severity, but their number tends to increase with the duration of scleroderma; they are not contagious. Their distribution is peculiar: the hands, wrists, and face. Under the microscope, telangiectasia corresponds to capillary bulges (dilatations): these constitute the component of the circulation which makes the transition between the venule and the arteriole. Hence, the microscope allows us to distinguish capillary telangiectasia that is specific to scleroderma from dilatations of venules (venous telangiectasia), which are found in the face, neck, shoulders, thorax and upper extremities.

Venous telangiectasia may be a familial condition or present during liver diseases. They are not related to scleroderma.

There is no possible prevention for capillary telangiectasia arrival. To hide them, opaque makeup is available in pharmacies. Although laser treatment of telangiectasia often produced good results, it does not stop the development of other telangiectasias in the same treated area and may leave a different pigmentation area than that of the untreated skin. A dermatology consult should then be requested, and treatments are sometimes covered by the Régie de l'assurance-maladie du Québec (RAMQ).

Ruby spots are often found on the forearms: they are small red dots that do not disappear under pressure. They are not related to scleroderma. Over time, they become brownish and do not require any special care. ■

7.3 The muscles and bones

Muscle-and-skeletal (musculoskeletal) involvement is common in scleroderma and may even be the first sign of disease onset.

Patients' most frequent complaint is joint pain (arthralgia), which can be temporary or intermittent; it decreases with a simple treatment of analgesics (pain relievers) such as acetaminophen. Under conditions of joint inflammation (arthritis), patients will note in addition to pain, heat, swelling and sometimes redness in the hands and/or most often wrists with or without inflammation of the joint envelope (synovitis), much like rheumatoid arthritis patients. In which case anti-inflammatories should be prescribed. Cortisone injection or tablets are usually very effective when taken for a short time for more active and severe inflammatory lesions. Immunosuppressive drugs (methotrexate, hydroxychloroquine) are

indicated for some patients only: they are slow-acting, must be taken for several months at a time and require regular blood tests to detect signs of toxicity.

The process of collagen deposition can affect the envelope (sheath) of the tendons of the fingers, wrists, shoulders, knees, and ankles. A tendon friction rub characteristic of scleroderma occurs: a creaking, leathery crepitus can easily be detected on palpation during active or passive motion of affected joints. Some authors (Steen) have found that the presence of these tendon rubs is indicative of visceral involvement.

On the fingers, when the collagen deposition is accompanied by inflammation, fibrosis occurs which affects several structures: it can lead to permanent and irreversible flexion (articular contracture) of the digits with a decrease in the range of motion. Prevention of contractures through regular exercises is essential.

7.3 The muscles and bones

Bone involvement can be twofold: reduction in bone density (osteopenia) is not only common because of aging but also because of a decrease in physical activity. In addition, bone resorption of distal phalanges (acroosteolysis) may develop in SSc (40 to 80% of all patients) with important changes in the appearance of the fingertips, which become pudgy, shorter and sometimes thicker. Bone resorption is likely the result of poor circulation in the fingers which is indicative of peripheral artery disease (PAD).

The weakness and decrease in volume (atrophy) of muscles are common consequences of joint contractures (80% of all patients) and/or the presence of a chronic disease. There is no treatment for this weakness. As a preventive measure to avoid energy exhaustion, patients must manage their ability to perform certain

tasks, breaking up physical activities into a series of shorter periods, thus allowing one to conserve energy and reduce fatigue while also reducing the amount of energy associated with an activity.

Less frequently (20% of all patients), muscle fibers will be replaced by collagen, with a discreet weakness observed by the physician during clinical examination. The blood work reveal little or no elevation in the level of muscle enzymes (CK). This condition does not progress and does not necessarily require treatment.

More rarely (1% in the limited SSc group, 10% in the diffuse SSc one) scleroderma may be accompanied by inflammation of certain muscles (myositis) with significant weakness: patients will have difficulty climbing stairs or getting up from a chair. Muscle enzyme levels will be highly elevated and an electromyogram (EMG) will confirm the clinical diagnosis. Patients with this condition usually respond very well to cortisone treatment. ■

7.4 The digestive tract

Over 90% of scleroderma patients will have digestive involvement, but only half will experience symptoms. All segments of the digestive tract may undergo a change in their structure and function. However, involvement prevalence rate differs widely: esophagus (80-90%), stomach (75%), small intestine (50%), colon (50%), and mouth (30%).

Regarding the **mouth**, the thickening of the periodontal membrane (gingiva) occurs in 30% of all patients and is due to fibrosis. Thinning of the jawbone associated with gum inflammation (gingivitis) leads to dental instability. Together, the presence of all these factors with, for some patients, a decrease in the production of saliva (dryness or Sjögren's syndrome, makes daily oral hygiene all the more essential, especially if there is a reduction in the mouth opening (microstomia).

Only a small minority of patients will develop pharyngo-oesophageal dysphagia (PD), resulting in a tendency to choke on their own saliva, not just at meal times.

Decreased saliva and/or tears production is referred to as dryness syndrome. It is found in up to 30% of scleroderma patients. The immune system of scleroderma patients produces antibodies directed against their exocrine glands, which secrete saliva and tears. In extreme cases, the lack of saliva will result in a burning sensation in the mouth and/or the throat as well as a difficulty to swallow solid foods. More rarely, the exit duct of the saliva can become clogged (parotitis). A lack of tears will lead to irritation of the cornea of the eyes (keratitis) with eyelids sticking together, especially in the morning. To avoid permanent damage to the cornea early ophthalmology consultation is in order;—and it is also important to start treatment with artificial tears as soon as possible. Artificial saliva is a first step in the treatment of dry mouth caused

7.4 The digestive tract

by hyposalivation (decreased saliva production). Thereafter, pilocarpine could be tried: it is a drug that stimulates the secretion of exocrine glands. The most common side effects are sweating, nausea, runny nose (rhinorrhea), chills and flushing (vasodilation).

Capillary telangiectasia (dilation of small blood vessels) is commonly found not only on the face and hands but also on the lips, the mucous membranes of the mouth (oral mucosa) and on the tongue. In extremely rare cases, telangiectasia could become a source of bleeding from the distal part of the esophagus, stomach and/or other digestive tract sites.

Suspicious of involvement of the *esophagus*, the segment of the intestine located between the mouth and the stomach, should be raised when a patient experiences a burning sensa-

tion in the chest or stomach after a meal and/or when leaning forward. Symptoms may occur at night and the patient will usually feel better if he/she uses more pillows to help him/her sleep. The patient may experience a sensation of blockage of food which seems to “stick” about half-way down the chest, or just behind the lower end of the breastbone, especially when eating dry foods.

As for the esophagus, the first changes brought about by scleroderma can be found at the junction of the lower portion of the esophagus and the stomach where a valve (sphincter) is located. This sphincter closes once the food gets in the stomach to prevent it from going back up into the esophagus. If the sphincter does not close properly (hypotonia or atony), acid in the stomach will irritate the esophagus (i.e. gastroesophageal reflux with esophagitis). The esophagus may tighten during a healing process creating a blockage (stenosis) that will require dilation by bouginage. Another mechanism of sclerodermic involvement is one that affects the muscles of the esophagus wall which are no longer working

7.4 The digestive tract

harmoniously by allowing food to pass from the mouth to the stomach, thus blocking the passage of food.

Examinations including high endoscopy will help determine what causes the discomfort so that the proper treatment can be administered.

To help lessen gastroesophageal reflux, one can try a few lifestyle modifications which can greatly reduce discomfort by:

- avoiding fatty foods or food containing caffeine (tea, coffee, soft drinks); alcoholic beverages should be avoided as well;
- taking smaller and more frequent meals;
- standing for a few hours after a meal and waiting at least two hours after breakfast or lunch;
- having a small supper, refraining from taking snacks during the evening

- and, while lying on your bed, staying flat on your back with your head slightly elevated at least three hours after your last meal.

Tobacco is also prohibited: to avoid stimulating the production of acid by the stomach and because of its relationship with lung cancer, a type of cancer that is already more common in scleroderma patients with pulmonary involvement.

Several drugs are effective in blocking stomach acid production (omeprazole, esomeprazole, pantoprazole, lansoprazole); if necessary, other medications might be used to stimulate the contraction of the esophageal and stomach sphincters.

The **stomach** normally acts as a food reservoir and as a grinder. Digestion begins at this stage with the acidic enzymes, as the food then progresses towards the small intestine. Poor stomach function such as delayed gastric emptying (gastroparesis) will result in nausea, vomiting, abdominal bloating, and early satiety, with or without gastroesophageal reflux symptoms. The same

7.4 The digestive tract

treatment guidelines outlined above for the esophagus apply to the stomach.

The *small intestine* follows the stomach and it is between 5-7 meters long. It constitutes the food processing plant of the body with the addition of enzymes and other secretions produced by the liver and pancreas. If the passage of food is being slowed down by contractions of the wall of the small intestine that has become infiltrated with collagen, bacteria then multiply resulting in patients experiencing abdominal pain, distention of the abdomen, diarrhea and/or weight loss.

The complete stoppage of digestive transit offers a clinical picture very similar to that of an obstruction (pseudo-obstruction). A blood test will tell us exactly what is the vitamins and proteins absorption capacity in addition to X-rays (flat plate of the abdomen and small bowel follow-through examination). A proper diet that substitutes fat with triglycerides will

help reduce diarrhea. Low-dose, long-term antibiotics will slow down the growth of bacteria and therefore also reduce diarrhea.

The *colon* is the last segment of the intestine. Its function is to reabsorb liquids and prepare the body to get rid of waste in the form of stool. The slowing of digestive transit results in constipation, or diarrhea if there is bacteria proliferation. The colon wall infiltrated with collagen presents pouches (diverticula) which, when filled with stool, can produce inflammation (diverticulitis). Assessment of this conditions consists of a barium enema and, if necessary, an endoscopy of the lower gastrointestinal tract. A diet rich in fiber to reduce constipation should be introduced gradually; too much fiber can promote diverticula! Gentle laxatives will complete the treatment efficiently. Occasionally, but very rarely, SSc patients may experience anorectal dysfunction, which can be improved through biofeedback. ■

7.5 The lungs

Shortness of breath on exertion, then at rest, associated with dry cough with or without infection is a possible indication of damage to the lungs and/or heart. Scleroderma can cause two main types of lung damage: pulmonary fibrosis (fibrosing alveolitis) or pulmonary vascular disease that later develop into pulmonary hypertension.

In the case of **pulmonary fibrosis**, which can affect up to 70% of patients, it can remain asymptomatic for a long period of time (without shortness of breath) even if the radiograph reveals its presence. Pulmonary function tests, including the diffusing capacity of the lungs for carbon monoxide (DLCO) at rest, and then, if necessary, during exercise, could indicate the presence of pulmonary involvement. This is a result of collagen which is deposited at

the sites of gas exchange affecting blood oxygenation. When collagen deposits become abundant they are then visible on X-ray especially at the base of the lungs. Pulmonary fibrosis affects both patients with limited and diffuse scleroderma. Shortness of breath when it occurs can go on for more than 10 years before becoming severe.

When scleroderma affects blood vessels in the lungs, which become thickened or clogged with collagen deposition, shortness of breath can quickly become severe (less than 12 months). This condition is referred to as **pulmonary hypertension**. This type of involvement appears to be more common in patients with limited scleroderma. Respiratory function tests (PFT), such as the diffusion of carbon dioxide (CO) in the lungs will be severely disrupted, and an echocardiography will reveal a very high blood pressure in the right cavity of the heart. Several medications taken in combination

7.5 The lungs

including immunosuppressors have significantly improved the poor prognosis of patients with this type of involvement. The diagnosis of pulmonary hypertension requires several examinations including a visualization of the coronaries (arteries of the heart) by a cardiologist. If the diagnosis is confirmed, follow-up is subsequently planned by the cardiologist together with the doctor treating the pulmonary involvement.

Although pulmonary involvement, either by pulmonary fibrosis or pulmonary vascular disease, is now the most common cause of death in scleroderma patients, the possibility of a lung transplant can prolong overall survival for several years.

The only reported cancer more common in scleroderma is lung cancer presumably due to the underlying presence of pulmonary fibrosis.

Because of all these potential adverse changes in the lungs, a scleroderma patient just cannot afford to be a smoker. ■

7.6 The kidneys

Renal involvement is common, but it is only detected in 50% of cases in presence of arterial hypertension, protein in the urine (proteinuria) and/or an increase in the level of plasma creatinine (a protein whose concentration rises in the blood when kidney function is impaired).

Very rarely patients with diffuse scleroderma may experience worsening of their condition, i.e. “scleroderma renal crisis”, a severe complication which is characterized by:

- abrupt and acute renal failure,
- sudden and sharp increase in blood pressure (although some patients may still have normal blood pressure),
- urine analysis which reveals the presence of proteins and cell agglomerations specific to the kidneys (cylinders).

In the past, renal crisis was considered the most common cause of death in scleroderma patients. With the availability of new generations of drugs such as captopril and enalapril that better control blood pressure as well as artificial filtration of blood (dialysis), patient survival has now become the most likely outcome.

After a few months, renal function resumes and dialysis can be stopped. At the same time, some patients have seen a significant reduction in cutaneous induration.

High blood pressure is a common condition that responds well to medication and is unrelated to sudden kidney damage caused by scleroderma. Patients with high blood pressure should therefore be closely monitored and treated accordingly. ■

7.7 The heart

Cardiac manifestations are of two kinds: primary, from scleroderma itself and, secondary, from pulmonary involvement or the presence of severe arterial hypertension. Patients will usually seek medical attention when experiencing symptoms such as shortness of breath or unusual tiredness.

Primary cardiac involvement which develops as a direct consequence of scleroderma, although common, often goes unnoticed for many years. Histological analysis of cardiac cells reveals the presence of fibrosis. It can cause:

- pericarditis (inflammation of the heart envelope: 7 to 20% of cases,
- congestive heart failure due to the inefficiency of the “pumping” function of the heart: 5% of cases,
- a cardiac rhythm disorder, of which 30% of cases occur on exertion.

A heart rhythm disorder results in an irregular heart-beat, with symptoms such as loss of consciousness or weakness. If necessary, recording the heart rate over 24 hours (Holter) can confirm this disorder, and will be treated through medications or the implantation of an artificial pacemaker, a device that uses small batteries which are placed under the skin near the heart that send electrical pulses to prompt the heart to beat at a normal rate.

Secondary cardiac involvement is found much more frequently in limited scleroderma owing to the fact that patients with limited scleroderma are at greater risk for developing (vascular) pulmonary hypertension. In rare cases of hypertension with kidney involvement, the heart is also in a state of exhaustion. Fortunately, these situations remain exceptional.

Angina may manifest itself in the form of pain or discomfort in the chest, which is usually indicative of coronary artery involvement. It is unrelated to scleroderma and is strongly suggestive of the presence of atherosclerosis in the coronary arteries (i.e. arteries that supply blood to the heart). ■

7.8 The liver

The bile is a dark green to yellowish brown viscid alkaline fluid secreted by the liver and passed into the duodenum (first part of the small intestine, where most of digestion occurs) where it subsequently aids the process of emulsification and absorption of fats. It also has several other functions including that of transforming cholesterol.

Less than 10% of scleroderma patients will develop a primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, i.e. a chronic liver disease, presumably autoimmune in nature. PBC mostly affects women (90% of cases) because they are more likely to have limited than diffuse scleroderma.

The first indication of PBC is when blood tests reveal the presence of anti-mitochondrial antibodies that react against specific liver cells. A FibroScan®, a non-invasive, quick and simple technique to assess the degree of liver fibrosis is now typically performed as an alternative to liver biopsy. It simplifies and accelerates diagnosis, reducing risk to the patient by eliminating almost completely the need for a biopsy.

Subsequently, a majority of patients will show, after 5 to 10 years of observation, an increased level of a liver-specific enzyme, i.e. alkaline phosphatase.

Oral administration of ursodiol (Urso) from the onset of this enzyme disruption improves overall liver function. Patient survival does not seem to worsen in this particular circumstance. Obeticholic acid (OCA) is available for patients whose response to ursodiol treatment is suboptimal.

Very rarely patients with an elevated level of alkaline phosphatase, as revealed by blood tests, will show symptoms of PBC: pruritus, jaundice, fatigue, weight loss, increased cholesterol and decreased biliary secretion and, incidentally, liquid stools, pruritus, and icterus. This picture is similar to cirrhosis caused by excessive alcohol consumption. In case of extreme deterioration, liver transplant is an option that greatly improves the quality of life and survival.

Research by our team on the coexistence of scleroderma and PBC (2005-2009) has shown that the simultaneous presence of these two diseases does not aggravate either one of these conditions. ■

7.9 Other organs

The **thyroid** is a gland located in the anterior region of the neck. It regulates the basic metabolism of the body. A decrease in function (hypothyroidism) is common, affecting up to 25% of all patients. Symptoms suggestive of this disturbance may go unnoticed for many months: fatigue, memory problems, dry skin, weight gain and thickening of the facial skin and/or swelling (edema) of the legs. In assessing the thyroid function, a blood test for the hormones (TSH, T3, and T4) will allow for a definitive diagnosis. Thyroid hormone replacement with levothyroxine may help restore normal basal metabolism.

Moderate to severe **depression** can be seen in up to 17% of cases. Persistent, pervasive morning fatigue may be indicative of this condition.

The presence of **fatigue** is a characteristic feature of any “chronic” disease. Fatigue will increase for a few days when patient’s energy

expenditure is greater than usual. The best way to deal with this predicament is by managing one’s energy (more) efficiently, by breaking an activity into a series of tasks, carried over short periods of time, to make the activity more manageable, with the help and support of loved ones.

Trigeminal neuralgia is a chronic pain condition that affects the trigeminal nerve, which carries sensation from your face to your brain. It may cause cheek pain and/or numbness, which can occur on one side and/or the other of the face. Patients may find immediate and satisfying relief with one medication, typically carbamazepine. As the months go by, the pain stop increasing and can even decrease.

Some symptoms may be present without being indicative of target organs involvement: weakness, decreased weight and/or appetite, changes in skin pigmentation, swollen fingers (especially in winter). The patient can report his/her discomforts to his/her doctor. The physician will be able, by taking into account the totality of symptoms, to distinguish what is related to scleroderma and what is not. ■

8 Blood work and capillaroscopy



Your medical visit will often include extensive blood work and a capillaroscopic examination. To get a full picture of the workings of the human body, a battery of tests (and several blood samples) will be required.

Standard *blood work* is performed to evaluate:

- hemoglobin: a decrease in hemoglobin levels is indicative of anemia,
- white blood cells: play an important role in the body's defense against infection,
- platelets: they help heal wounds and ensure coagulation,
- sedimentation rate and/or CRP (C-reactive protein) assay: they indicate the presence of an inflammatory process in the body,
- liver enzymes
- muscle enzymes (CK)
- kidney function parameters
- blood glucose (sugar) and cholesterol levels.

8 Blood work and capillaroscopy

In addition, other more specific investigations may also be carried out to look for the presence of certain antibodies:

- antinuclear whose concentration is expressed in the form of titer (1/80, 1/160, 1/320...);
- anti-centromere antibodies (ACA) are specific to limited scleroderma, with a very stable titer despite years of disease progression,
- anti-topo isomerase I (Scl-70), also very specific to diffuse scleroderma,
- anti-mitochondria, present in more than 95% of cases of primary biliary cirrhosis.

However, up to 50% of scleroderma patients do not have any detectable antibodies using current investigation techniques.

Blood work is essential to confirm the diagnosis and reflects the inner workings of internal organs and tissues. It becomes necessary when certain medications are administered. If necessary, a urinalysis will also be required to assess kidney function.

Capillaroscopy is a technique which uses a microscope to observe the capillaries in the finger and/or toe nail folds. Capillaries are the smallest blood vessels in the body that contribute to the oxygenation of tissues and allow the transition between arteries and veins. Some diseases including scleroderma alter the size and distribution of capillaries that are visible using this technique.

Capillaroscopy has been available since 1984 at Notre-Dame Hospital, now the new CHUM. It helps in the diagnosis and follow-up of patients with Raynaud's phenomenon and/or a connective tissue disease including scleroderma. These observations have resulted in several scientific publications. ■

9 Pregnancy



The most extensive study on scleroderma and pregnancy was conducted by Dr. Virginia Steen of the University of Pittsburgh (1999) in a group of 450 women of childbearing age with scleroderma (SSc).

The study did not report an abnormally high prevalence of infertility among women with scleroderma. Spontaneous abortions were more common only in patients with early diffuse scleroderma. There was a higher frequency of small (low birth weight) full-term infants born to women with scleroderma. In scleroderma patients with associated rheumatoid arthritis, the rate of premature infants was higher than in healthy women. However, the infants all survived.

Skin texture changes, even to the abdomen, allow for an uneventful pregnancy. If a cesarean section is performed, wound healing occurs without complications.

9 Pregnancy

Interestingly, some symptoms are improved during pregnancy, including Raynaud's phenomenon. By contrast, others, like esophageal reflux may worsen (acid reflux and heartburn). Anti-acid drugs can be used as well as other drugs that block the production of acid by the stomach. It is best to have a joint follow up with your attending physician/gynecologist, in addition to your rheumatologist, for proper treatment.

The most feared, but fortunately rare serious complication during pregnancy is renal crisis (see chapter 7.6). It is a sustained high blood pressure that only occurs in the early years of disease progression in patients with diffuse scleroderma. Available drugs such as angiotensin-converting-enzyme inhibitors, aka

ACE inhibitors (captopril, enalapril) may save the life of the mother and the baby during a renal crisis. These drugs have only rarely been associated with congenital malformations.

As a general rule, several medications must be stopped during pregnancy. A discussion with your attending physician is essential before pregnancy to ensure that the mother-to-be and her child will not be at increased risk during and after pregnancy, by tailoring medication regimens to better fit their specific needs.

In summary, an uncomplicated pregnancy is possible with a close follow-up. It is recommended for those with diffuse scleroderma to wait until the cutaneous involvement has stabilized (no new areas of skin induration) at least one year before planning a pregnancy. ■

10 Survival

Should you want to buy life insurance, rates will be lower if you are a young, non-smoking and healthy woman. Indeed, studies conducted on large patient populations have shown that longevity or survival is better for these groups of people.

You have Raynaud's phenomenon or dryness syndrome? Your insurance application will be reviewed and a premium may be charged to insure you even if you have no symptoms of scleroderma. Statistically, studies have shown that survival is shorter in presence of either one of these conditions.

You have scleroderma with some degree of target-organ involvement? It is almost certain that an insurance premium will be charged since it is based on actuarial studies dating back several years.

When learning about scleroderma pay attention to the year when the studies were completed. In recent years with the boost in the number of transplant options available and new drugs being developed for the treatment of scleroderma, survival has significantly improved (but this is still currently not known with any certainty).

Prediction of 5-year survival rate (i.e. the percentage of people who live at least 5 years after being diagnosed with scleroderma) is based on 3 factors: proteinuria, high sedimentation rate, and reduced carbon monoxide diffusion capacity (Bryan, 1999). In the absence of these 3 factors, the 5-year survival rate is 93%.

The coming years should give us more definite answers. Although a definitive cure has not yet been found, treatment for many symptoms has improved dramatically over the years. Cytological and genetic studies we believe will provide solutions and help us succeed in our quest to defeat scleroderma. ■

11 Scleroderma research: what the future holds



**The future holds so much hope
for scleroderma patients.**

The large and growing number of scleroderma patients seen by our medical team at Notre-Dame Hospital (and now the CHUM), the research and scientific publications resulting therefrom, and the strong influence of Scleroderma Quebec have led to **recent tremendous expansion in research into scleroderma**, which translates concretely by the establishment of the **Scleroderma Research Group, SRG, a world-class group of scleroderma experts.**

11 Scleroderma research: what the future holds

The mission statement of the SRG is:

“To conduct key research and generate new cutting-edge knowledge about scleroderma, with the aim of developing novel and effective treatment methods for patients suffering from this serious disease.”

First, the initial group of doctors has expanded significantly. Drs. JL Senécal, F Joyal, and A Roussin were joined by other doctors, namely Drs. JR Goulet, E Rich, JP Raynauld, T Grodzicky, and M Koenig. Among SRG’s founders, Mr. Raymond PHD, an expert in cellular biology, is now retired.

Several projects are already underway including:

- **An epidemiological study of scleroderma patients in Quebec** aimed for the first time at collecting data on basic health indicators relating to our province, such as life expectancy, causes of death, frequency of target organ damage (TOD), and prognostic factors of disease progression. These data are critical to better inform patients and their families, and also to better identify populations at greater risk for complications from scleroderma so that they can begin early treatments. In addition, this crucial information will put the SRG in a better position to participate in international research projects, such as, for instance, those where trials of novel treatments are involved. It is worth stressing that **Scleroderma Quebec provides financial support for this study.**
- basic research projects

11 Scleroderma research: what the future holds

- 1) on the cell itself, **aiming to understand the cellular mechanisms causing scleroderma and its manifestations**. Under the supervision of Dr. JL Senécal, the purpose of the research is to **determine whether scleroderma-specific antibodies (anti-centromere and anti-topoisomerase I autoantibodies) can cause lung damage (pulmonary fibrosis and pulmonary arterial hypertension), a potentially life-threatening complication associated with this disease**. The originality of our approach resides in the fact that researchers take purified autoantibodies from the blood of scleroderma patients and expose human lung cells to these autoantibodies to see if this induce scleroderma lesions. If this is the case, they will determine what is the exact pathomechanism by which autoantibodies cause this deleterious effect. Then they will develop a new molecular treatment to block these bad antibodies. It is hoped that we will be able to stop the progression of the disease and even potentially prevent its development in patients carrying these antibodies. Another project aims to identify new autoantibodies not yet described in scleroderma, to improve diagnosis and prognosis.
- 2) on the genetic aspects of scleroderma in Quebec. The goal is to identify susceptibility genes for developing scleroderma. Since the immune diseases that include scleroderma are modulated by hereditary factors, researchers want to recruit families in which at least two people have scleroderma, or in which there is at least one person with scleroderma and another with Raynaud's phenomenon.

11 Scleroderma research: what the future holds

- 3) on apoptosis in scleroderma. Apoptosis or programmed cell death is a normal mechanism of cell replacement. There may be a defect in apoptosis in scleroderma.

The SRG receives exceptional collaboration from dedicated **hepatologists** and **pulmonologists** (lung specialists) of the CHUM specialized in liver and lung damage in patients with connective tissue disease including scleroderma.

The SRG provides continuity in the provision of capillaroscopy for patients with peripheral vascular disease, PVD (acrocyanosis, Raynaud's phenomenon) with or without connective tissue disease.

The role of Scleroderma Quebec in the SRG is one of catalyst and financial supporter, with the understanding that the SRG will have to uphold the highest standards of excellence by obtaining research funding from other sources, notably by applying for grants from funding agencies with peer committees. ■

13 Our publications



Since 1985, physicians' of the SRG have contributed to numerous publications and scientific presentations.

These not only represent the work of many dedicated researchers and its impact on the national and international level, but also your own participation by keeping your medical appointments, providing us with blood samples and agreeing to undergo numerous medical examinations and diagnostic procedures. **Thank you for your invaluable collaboration in our work.**

Here are some of our scientific publications on Quebec's scleroderma patients by the Notre-Dame Hospital Medical Team, which has now become the new CHUM:

13 Our publications

Research publications

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13 Our publications

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Appendix Frequency tables of sclerodermic involvement

Dr TA Medsger (792 patients, 1999) and other American authors: data collected from disease observations made over a 10 year-period compared to those of

**Dr Sénécal and collaborators* (309 patients):
data collected at 1st visit (2001)**

	OVERALL FREQUENCY	LIMITED SSc	DIFFUSE SSc
EPIDEMIOLOGY:			
- distribution		<u>56%</u>	<u>44%</u>
- age at onset (year)		<u>42</u>	<u>33</u>
- disease duration (years)		12.5 / <u>5.4</u>	3.4 / <u>2.8</u>

	OVERALL FREQUENCY	LIMITED SSc	DIFFUSE SSc
SKIN			
- skin thickening (mRSS*)		5.7% / <u>5.5%</u>	38.5% / <u>36.1%</u>
BLOOD VESSELS			
- Raynaud		97% / <u>93%</u>	94% / <u>77%</u>
- calcinose		44% / <u>26%</u>	13% / <u>40%</u>
- telangiectasias		83% / <u>76%</u>	62% / <u>65%</u>
MUSCLES/BONES			
- arthralgia/arthritis		47% / <u>11%</u>	93% / <u>13%</u>
- muscular weakness	80%		
- myositis	20%	1%	10%
- resorption of fingers	40-80%		
- flexion contracture		<u>56%</u>	<u>82%</u>
- tendon friction rubs		<u>6%</u>	<u>11%</u>

*modified Rodnan skin score

	OVERALL FREQUENCY	LIMITED SSc	DIFFUSE SSc
DIGESTIVE TRACT			
- Sjögren's S. (dry mouth & eyes)	30%	25%	46%
- periodontal thickening	30%		
- esophageal dysfunction	80-90%	<u>25%</u>	<u>40%</u>
- gastroesophageal reflux	60-70%		
- sphincteric hypotonia lower eso.	30-50%		
- gastroparesis	75%		
- malabsorption (diarrhea)	50%		
- pancreatic dysfunction	33%		
- colinic diverticula	50%		
LUNGS			
- diffusion abnormality (DLCO)	70%		
- bibasilar fibrosis	75%	<u>3%</u>	<u>15%</u>
- pulmonary hypertension	>10%		

	OVERALL FREQUENCY	LIMITED SSc	DIFFUSE SSc
KIDNEYS			
- detected involvement:	50%		
- involvement at autopsy	60-80%		
- arterial hypertension		7%	
- proteinuria		7%	
- renal crisis	10-15%	<u>0.5%</u>	<u>1.4%</u>
HEART		<u>9%</u>	<u>14%</u>
- detected pericarditis	7-20%		
- pericarditis at autopsy	70-80%		
- myocardic fibrosis (autopsy)	90%	60%	77%
- cardiac arrhythmia under stress	33%		
LIVER	>10%		
- primary biliary cholangitis		3.9%	

	OVERALL FREQUENCY	LIMITED SSc	DIFFUSE SSc
OTHER SYSTEMS			
- hypothyroidism	25%		
- moderate/severe dépression	17%		
SEROLOGY			
- hypergammaglobulinemia	33%		
- ANA +		93% / <u>30%</u>	94% / <u>52%</u>
- ACA+	25% / <u>44%</u>	51% / <u>54%</u>	2% / <u>31%</u>
- Scl (Anti-topo I)	15% / <u>12%</u>	10% / <u>6%</u>	32% / <u>19%</u>
- High rheumatoid factor	33%		

***Dr. Jean-Luc Senécal et al.:**

Drs. Denis Choquette, Lilian Lonzetti, Jean-Richard Goulet, Tamara Grodzicky, France Joyal, Jean-Pierre Raynaud, Eric Rich, André Roussin, Yves Raymond, PhD and Mélanie Arbour, B.Sc.

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