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Are There Enigmas Concerning The Pathophysiology Of Lymphedema After Breast Cancer Treatment?

Prof. MED. Michael Földi

Bates, Levick and Mortimer[1] published a paper in 1993 about "the swollen arm after breast cancer treatment," expressing the view that "there are several quite fundamental uncertainties about this condition."

Most of the "uncertainties" are only of theoretical interest. However, the authors raised a question on one of the "uncertainties" on which I wish to focus: "...why does swelling usually not commence until months or years after the treatment?"

This question has important practical implications because the answer is linked to the advice that the physician must give a woman who has undergone breast cancer treatment, i.e. the do's and don'ts.

To appropriately answer the question raised by Bates and his colleagues, I initially will briefly outline the scientific background. There is a fundamental difference between the driving force of the blood in the veins and that of the lymph in lymph vessels. Venous blood is driven in the recumbent position by the heart. The left chamber pumps the blood into the aorta producing a mean pressure of 100 mm Hg; the blood reaches the blood capillaries at a pressure of about 30 mm Hg., while the pressure in the veins in the dorsum of the foot amounts to approximately 8 mm Hg. The pressure from the left chamber then pushes the blood into the veins in the right atrium where the pressure is zero.

The lymph vascular system starts with the initial lymphatics in the tissues and ends at the venous angles, representing only half of a circulation. The heart produces no driving force for the lymph. The necessary force is generated by the lymphangions (segments of lymph vessels bordered by two valves) which act like tiny hearts, or lymph pumps.

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PRESIDENT'S MESSAGE

Saskia R.J. Thiadens, R.N.

What a wonderful experience to have so many colleagues, patients, doctors and therapists from around the world, all involved in some way with lymphedema, together for 3½ days during the Third NLN Conference in September; like a family that is growing rapidly. I agree with the title of this year's conference, Uncovering The Hidden Epidemic; indeed, it has been hidden. But I'm glad to say that lymphedema finally is coming out of hiding and getting the medical attention it deserves. Together, WE have planted lymphedema on the U.S. medical map.

During the conference opening ceremony, a number of wonderful video spots were shown: Fran Visco, President of the National Breast Cancer Coalition, addressed the urgent need for education, prevention and getting the message out to our policy makers on the Hill about lymphedema after breast cancer surgery; Dr. David Rosenthal, President of ACS, expressed great concern and interest in working with the NLN to address this long-ignored condition; and we were honored to have Sam Donaldson, our ABC Prime Time white house correspondent, share about his own lower extremity lymphedema post-melanoma surgery – he expressed his support of the NLN, our mission, and creating awareness about lymphedema. One could feel the wave of new energy and enthusiasm in the halls and rooms, making it a very special ten-year anniversary for the NLN. Already, we have initiated the development of our Year 2000 NLN Conference which, tentatively, will take place in New York City. More information to follow.

In this issue you will find detailed overviews of the Third NLN Conference written by Gwen Forbes-Kirby, PT, and Joe Guppy, a lymphedema patient. And, since October is Breast Cancer Awareness Month, we are featuring an article by Prof. med. Michael Földi about breast cancer-related lymphedema and "uncertainties." Thank you for your excellent contributions.

This was a very productive 10th Anniversary year for the NLN, and my staff and I would like to take this opportunity to thank our NLN members for your wonderful words of encouragement; we support each other. And, thank you all who have graciously contributed funds, time and energy to keep the NLN up and running. We are in desperate need of an office of our own with more space, as well as additional staff and volunteers; it is our goal that, this next year, our needs will be met. Together, we make things happen.

Best wishes to you all in the New Year and have a Happy Holiday Season.

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The lymphangions' function is governed by the same mechanism as the heart with analogous consequences in similar situations. If someone suffers from a heart attack triggered, for example, by coronary sclerosis and she/he survives, the following may occur:

(1) Congestive heart failure with cardiac edema and breathlessness at rest appears, if the damage is so severe that the heart is unable to cope with the needs of the resting body;

(2) The functional reserve of the heart decreases, however, under normal circumstances, it is still able to supply the body with blood. There are no signs or symptoms while the body is at rest, but a doctor can detect the condition by administering an exercise test;

(3) The functional reserve remains unchanged.

With reference to (2), the functional reserve has a tendency to decrease further due to the progression of coronary sclerosis and aging and, depending on several factors, sooner or later congestive heart failure will occur. Obesity, high blood pressure and diabetes will cause the heart to fail sooner, while absence of these risk factors plus living and eating healthfully can postpone or even prevent congestive heart failure.

Regarding the lymph pump in an equivalent situation, when the axillary lymph nodes are removed, the following consequences can arise:

(1) Congestive lymphatic failure (lymphedema) can appear if, during surgery, so many lymph vessels were destroyed to transport the normal lymphatic fluid load;

(2) The functional reserve decreases, but the transport capacity still remains higher than the normal lymphatic fluid load. In this circumstance, no swelling of the arm would occur. This condition is detectable through lymphoscintigraphy.

(3) Functional reserve of the lymph vascular system remains unchanged.

The second outcome is relevant to the "uncertainty" in lymphedema of the arm after breast cancer treatment, since it is clear that aging decreases the force of the lymph pumps. And, lymphatics that were spared during surgery compensate by taking on the work load of the missing lymph pumps. Fatigue and structural changes are inevitable, as is lymphedema. At what time the lymphedema becomes apparent depends on several factors: Lymphedema will manifest itself sooner if healing of the surgical wound is disturbed, or if postoperative radiation therapy is applied, because X-rays hinder the regeneration of lymph vessels; if lymphatics are destroyed through the onset of lymphangitis and/or erysipelas, this will precipitate the appearance of lymphedema; and, if the patient disregards the do's and don'ts of everyday activity, lymphedema will appear. Summarizing, to postpone lymphedema indefinitely, ***avoid activities that can trigger a further decrease of the transport capacity of the lymph vessels and/or unnecessarily increase the lymphatic fluid and protein load of the axillary lymphatic system.***

Last February, I took part in a conference organized by the American Cancer Society, where a participant gave a paper about post-cancer treatment patient education in which he said that arm and hand precautions should be listed in terms of evidence-based importance. He further stated that 28 factors were analyzed, but that only two of them were found to be statistically significant: (1) arm infection/injury/surgery, and (2) weight gain after cancer treatment. This means that all the other do's and don'ts are only "anecdotal" (of which are disapproved) and that only "evidence-based medicine" is acceptable.

I must declare that I regard medicine as a natural science and that I agree with this principle. Nevertheless, there are cases in which "anecdotal observations" are in harmony with scientific facts and established knowledge, are looking for evidence by prospective, random clinical studies, but are prohibited by ethical considerations. For example, some of the *don'ts*, which fall into the category of "anecdotal observations" are:

(1) ***One should not administer intravenous injections and infusions into the endangered arm.*** There are several cases in which lymphedema has arisen within hours of such injection/infusion. Although observance of these cases is "anecdotal," and, therefore, disregarded by "evidence-based medicine" advocates, this *don't* is in harmony with established knowledge, i.e., by piercing a cannula into a vein, perivenous lymph vessels can be severed, possibly causing phlebitis, periphlebitis, perilymphangitis, lymphangitis and lymphangiothrombosis. And what concerns a study: should one collect a homogenous group of women who, after breast cancer treatment and free of lymphedema necessitate some kind of operation – say an orthopedic intervention – which has to be performed under general anesthesia which is then administered in a random manner to 50% of the women into the cubital vein of the endangered arm and to the other 50% into that of the contra-lateral arm?

(2) ***Avoid sunbathing and sunburns.*** It has been shown that soon after excessive exposure, inflammatory edema (a symptom of erysipelas) often appears, turning into lymphedema. Despite the "anecdotal" character of this observation, clinical lymphologists accept this *don't*, because it is text-book knowledge that healthy elastic fibers are a pre-requisite for lymph formation and that sunshine can destroy those elastic fibers, leading to lymphedema. To try to achieve an evidence-based study would be unethical.

(3) ***Never carry heavy handbags or bags with over-the-shoulder straps.*** From time-to-time, patients who have disregarded this advice appear with a swollen arm. Again, although "anecdotal," the advice is sound, based on established knowledge. It has been shown that when a woman who has undergone breast cancer surgery (but is free of lymphedema) carries a bag weighing 4 kg, her axillary vein becomes markedly constricted, causing the blood capillary pressure in the arm to increase which, subsequently, increases the lymphatic fluid load. Performing a random study on this "don't" would be absurd.

By pointing out these facts, I could be misunderstood. Therefore, I would like to declare that I reject the so-called "alternative medicine" with its anecdotal observations. The methods of "alternative medicine" lack any scientific evidence. It would be possible to carry out prospective random studies in order to examine these methods, however, physicians who practice "alternative medicine" object to the performance of such studies.

"Coping With Lymphedema," is a very useful book

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about lymphedema written by Swirsky and Sackett Nannery[2]. However, I object to their inclusion of the "alternative medicine" with its obscure methods. We must not give the impression that lymphedema is a disease that can be managed easily by these methods. The consequences, especially with regards to health insurance companies, could be disastrous.

I also want to discuss and give explanation to a statement in Rockson's article, "Secondary Lymphedema of the Lower Extremities," published in the July-September 1998 *NLN Newsletter*. Rockson wrote, "Curiously. . . some patients with otherwise clear-cut primary lymphedema report injury as an initiating event."

This fact can be explained easily: Before the injury, due to a malformation of the lymphatics, the patients are living free of symptoms in the "Stage '0' of latency." A minor trauma is enough to reduce the transport capacity of the lymphatics to below the level of the normal lymphatic fluid load, causing the patient to exhibit signs of the early stage of lymphedema.

My goal in this writing primarily has been to explain some specific questions concerning lymphedema. However, I do want to intrude briefly into the topic of my dear friend, Dr. Marlys Witte, namely "medical ignorance."

An example of such, in my opinion, is found in the book, "Lymphedema: Diagnosis and Therapy," written by Weissleder and Schuchhardt[3]. It contains a table in which the authors propose that "an increase of the interstitial protein concentration causes fibrosarcomas, liposarcomas, basal cell carnomas and, perhaps, melanomas." I would like to reassure the patients suffering from the high-protein edema lymphedema that this is absolutely not true. The only malignant tumor that can arise (rarely) as a complication of lymphedema is "angiosarcoma" (Stewart-Treves Syndrome).

Weissleder and Schuchhardt also state that lymphangiosarcoma arises from lymph cysts and fistulae; These authors have misunderstood the following fact: Immune deficiency exists in the lymphedematous area. If a patient, who suffers from lymphedema in the arm after breast cancer treatment, later on contracts a carcinoma of the uterus, which starts to disseminate, the lymphedematous arm will be a preferential site for metastasis. For the patient who suffers from lymphedema, this does not mean an additional risk, because, in such cases, metastases will appear in other parts of the body, also. Only angiosarcoma constitutes a real risk in lymphedema, but I can set the mind of lymphedema patients at ease: in all probability, a good Complex Decongestive Physiotherapy will prevent angiosarcoma to recur.

[1] BATES, DO; LEVICK, JR.; MORTIMER, PS.: *Change In Macromolecular Composition Of Interstitial Fluid From Swollen Arms After Breast Cancer Treatment, And Its Implications*. Clin. Sci., 86, 737-746, 1993.

[2] SWIRSKY, J.; SACKETT-NANNERY, D.: *Coping With Lymphedema*. Avery Publishing Group, Garden City Park, NY, 1998.

[3] WEISSLEDER, H.; SCHUCHHARDT, CH.: *Lymphedema: Diagnosis and Therapy*. Second Edition. Kagerer Kommunikation, Bonn, 1997.

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IN DEFENSE OF THE 18 STEPS TO PREVENTION

Wm. J. Schuch

During the recent 1998 NLN Conference, Prof. med. Michael Földi addressed the issue of the insistence of some U.S. physicians on "evidence-based" validation of the do's and don'ts contained in the "18 Steps." As he pointed out, "there are cases in which 'anecdotal observations' are in harmony with scientific facts, with established knowledge and looking for evidence by prospective, randomized clinical studies is prohibited by ethical considerations."

Cancer survivors who have undergone the excision of lymph nodes and/or radiation therapy are at risk for lymphedema. Yet, the majority of these individuals are unaware of this risk and what can be done to avoid or, at least, delay the onset of lymphedema.

The National Lymphedema Network's *18 Steps to Prevention* for both upper and lower limbs has been widely disseminated in an attempt to inform those at risk and their health care providers as to the activities or events which have been identified by experienced MD lymphologists as potential triggers for the onset or exacerbation of lymphedema.

As the American medical profession is slowly beginning to be brought up to speed on lymphedema, its prevention and treatment, some physicians are inclined to dismiss many of the precautions advised in the *18 Steps* because they lack scientific substantiation, i.e. there have been no controlled studies to evaluate which of these events or activities are capable of precipitating the onset of lymphedema in those at risk. This attitude is most unfortunate since patients who might otherwise observe these precautions are, instead, often advised essentially to resume their normal activities. As a consequence, many are blindsided by the onset of lymphedema.

While it is true that many of the activities listed in the *18 Steps* as potential triggers are based on anecdotal reports rather than structured studies, this is not a problem for experienced MD lymphologists who understand the pathophysiology of lymphedema.

In simplest terms, a regional lymphatic network that has been subjected to nodal basin excision and/or radiation has had its capacity to transport and filter the necessary lymphatic load – protein, water, metabolic wastes, viruses and bacteria – curtailed to a greater or lesser degree. This reduced transport capacity is frequently not enough to result immediately in the swelling which is characteristic of lymphedema.

From that point forward, however, any activity or event which directly or indirectly further impairs the transport capacity of the affected lymphatic network or increases the lymphatic load (the amount of hi-protein interstitial fluid that is to be returned to the circulatory system via the regional lymphatic networks) has the potential to trigger the onset of chronic lymphedema, viz. swelling that is visible, measurable and palpable.

With a thorough understanding of the anatomy, physiology and pathophysiology of the lymphatic system, it is possible to identify certain events or activities which either reduce the transport capacity or increase the lymphatic load, or both. Therefore, it is not a quantum leap in defensible reasoning to conclude that those certain events or activities ought to be avoided to minimize, as far as possible, the risk for lymphedema.

Clearly, the following can have the effect of further reducing transport capacity of superficial impaired regional lymphatics: the high-end pressures involved in the taking of blood pressure on the afflicted limb, carrying heavy handbags with over-the-shoulder straps, wearing tight jewelry or elastic bands around afflicted fingers or limbs, wearing heavy breast prostheses, narrow bra straps, tight bras, underwire bras, tight socks, stockings, shoes and underpants.

The amount of lymphatic load is directly related to the level of blood flow to the affected areas. Approximately 10% by volume of the fluid delivered to the cells through ultra-filtration ultimately is returned to the systemic circulation via the superficial and deep lymphatic networks. Therefore, heavy lifting with the affected limb, extreme climatic heat and cold, extreme water temperatures when bathing or washing dishes, hot tubs, saunas, sunburn and vigorous repetitive movements against resistance, all of which increase blood flow, should be avoided.

Airplane travel involves pressure changes which allow interstitial fluid to pool in the dependent extremities while the vasomotor activity of the lymphangia (the valved vessels which pump the lymph towards the regional lymph nodes) is at a low level because the individual is essentially at rest during flight. Hence, the need to wear compression bandages, sleeves or stockings and to move around as much as possible to prevent the pooling which increases the lymphatic load.

Infections have the potential for not only curtailing transport capacity, but also increasing the lymphatic load. Cellulitis and lymphangitis, which can become episodic, inflame the superficial lymphatic vessels, rendering them progressively dysfunctional and, thereby, adversely affecting the transport capacity.

A second effect, the so-called "inflammatory response," increases the permeability of the walls of the arterial capillaries to allow for the ultra-filtration of additional plasma protein into the interstitial spaces already laden with the troublesome hi-protein fluid. This increases the lymphatic load and promotes the proliferation of fibrotic tissue which, in turn, further impedes transport capacity.

Even a needle puncture, for whatever purpose, through a perfectly antiseptic topical environment can evoke the inflammatory response in the absence of an infection. Therefore, it is important to avoid needle sticks of every kind into the affected limb (cuts, insect bites, animal scratches, cuticle trimming, shaving underarms and legs with a razor blade) and necessary to keep the affected limb, hand or foot scrupulously clean and supple, and as free of topical bacteria and fungi as possible.

All of the above precautions make preeminent sense. However, whether or not one or more of these events or activities will be the immediate or ultimate precipitating trigger is dependent upon a number of factors. They include, but may not be limited to, the initial degree of surgical impairment(number of lymph nodes excised or the extent of other surgical disruption, or collateral →

damage of nearby lymphatic networks and the amount of lymphatic scarring from radiation therapy) , or the degree of impairment from other causes, i.e. burns, infections, or severe physical trauma; the degree of obesity, if any; the individual's specific lymphatic anatomy and the level of anastomoses (connections) between neighboring lymphatic networks and regions; the lymphangion fatigue factor resulting from long-term dynamic compensation for the impaired networks; and the cumulative or progressive effect of the previously cited events and activities subsequent to the initial impairment.

Because cancer survivors and others with secondary lymphatic impairment frequently are not afflicted with lymphedema immediately and appear able to carry on their normal activities without modification does not mean that these activities and events will not trigger the onset of lymphedema eventually. Upwards of five percent of breast cancer survivors are afflicted with lymphedema in their first year of survival, but the lifelong affliction rate is reported to be between thirty and forty percent – secondary to en bloc excision of lymph nodes and radiation therapy.

There is an abundance of reinforcing anecdotal reports that experienced MD lymphologists and lymphedema therapists, both here and abroad, have heard from their patients concerning one or more events cautioned against in the *18 Steps* which immediately preceded the onset of their lymphedema. I would conclude, therefore, that those who choose to ignore these cautions place themselves at risk for lymphedema.

The *18 Steps* are prudent advice, notwithstanding the lack of scientific research studies which some physicians insist on having before endorsing these precautions.

In view of our understanding of the factors in the lymphedema trigger equation – transport capacity vs. lymphatic load – and the substantial anecdotal history that points to the cited activities and events as lymphedema precipitators, one wonders whether controlled studies in which some of those at risk for lymphedema would be encouraged to resume normal activities would be medically advisable.

The construct of such controlled studies also would be complex because of the number of alleged triggers, their cumulative or reinforcing effects, the variations in the lymphatic anatomy of individuals, the degree of lymphatic impairment and the fact that the risk for lymphedema is over a lifetime. Clearly, there are significant technical and logistical obstacles to the scientific evaluation of the individual alleged triggers in the short and intermediate term.

Observance of the *18 Steps* is a matter for the at-risk patient to weigh seriously and to decide. Tragically, lymphedema is a serious quality-of-life issue for many thousands of people who were uninformed as to its prevention and treatment.

The *18 Steps* are positive steps for improvement in the life-styles of those afflicted with this disease.

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