

LETTER TO THE EDITOR

**ON THE PATHOPHYSIOLOGY OF ARM LYMPHEDEMA
AFTER TREATMENT FOR BREAST CANCER**

In two recent international congresses and two papers (1-4), Bates et al reexamine the pathophysiology of arm lymphedema that occurs after operation and/or irradiation for treatment of breast cancer. Classical theory has long accepted that edema after axillary dissection or radiotherapy destroys lymphatic continuity and edema arises as a consequence of "low output failure" of the lymph circulation. Moreover, the protein concentration of such edema fluid is high in comparison to edemas that arise as a result of venous disease or increased hydrostatic pressure in semipermeable peripheral blood capillaries. According to Bates et al, however, after examining the Starling forces as reflected in the arm edema fluid in these patients conclude that capillary filtration and hence lymph flow are actually increased in this condition.

According to the Landis-Pappenheimer formulation, in the steady state net capillary filtrate or lymph load (F) = lymph flow (LF) or

$$LF = C[P_c - P_i] - \sigma(COP_p - COP_i) \dots \text{eqn. 1}$$

where C=capillary filtration coefficient, P_c =blood capillary pressure, P_i =pericapillary interstitial fluid pressure, σ =protein reflection coefficient, COP_p =protein osmotic pressure in blood capillaries, and COP_i =protein osmotic pressure in pericapillary tissue fluid.

The basis of Bates et al's hypothesis rests on the concept that in a steady state the protein concentration of free interstitial fluid (C_i) or lymph equals the rate of net transcapillary flux of protein (FPR) divided by the

net capillary filtration rate (F) or lymph flow (LF) (5), or in effect:

$$C_i = \frac{FPR}{LF} = \frac{FPR}{C[P_c - P_i] - \sigma(COP_p - COP_i)} \dots \text{eqn. 2}$$

Bates et al conducted two series of measurements in patients with arm edema after breast cancer therapy.

- 1) They compared C_i and COP_i , respectively in tissue fluid in the swollen arm of these patients and compared the findings to that of tissue fluid in the non-edematous contralateral arm. Edema fluid was obtained either by the "Wick" method (6) or by direct puncture of the skin. Tissue fluid from the non-edematous arm was obtained solely by the "Wick" method. Their data which is summarized in *Table 1* show that both C_i and COP_i were significantly lower in the "Wick fluid" obtained from the lymphedematous arm than the non-edematous arm. According to equation 2, this observation is compatible with an increased capillary filtration rate and hence increased lymph flow (LF) in the steady state of these patients (4).
- 2) They estimated arm volume from sequential measurement of the limb circumference at 4 cm intervals between the wrist and the shoulder. By assuming that the limb segments were near perfect truncated cones, the volume of the arm (V_A) was estimated from the formula:

TABLE 1*
Comparison of Protein Content in the Interstitial Fluid (C_i)
and Tissue Colloid Osmotic Pressure (COP_i) of the Lymphedematous
Arm with the Non-Edematous Contralateral Arm

INTERSTITIAL FLUID			
	Lymphedema	No edema	p value
C _i (g/dl)	Aspirate: 3.24±0.75 "Wick": 3.58±0.73	- "Wick": 4.14±0.67	<0.01
COP _i (cm H ₂ O)	Aspirate: 16.3±4.4 "Wick": 19.2±4.1	- "Wick": 21.4±3.8	<0.01

*Taken from Bates et al (2)

$$V_A = \frac{\pi}{3} \sum (X^2 + Y^2 + XY) \dots \text{eqn. 3}$$

Where X is the circumference measurement at a single point and Y is the circumference of the arm 4 cm proximal to X. Change in limb volume is expressed as the percentage increase in volume of the swollen arm relative to the non-edematous normal arm (7,8). Both C_i and COP_i in arm edema fluid showed a weak but statistically significant negative correlation with the percentage increase in arm volume (r=-0.47; P<0.005, and r=-0.35; P<0.05, respectively).

Based on equations 2 and 3, Bates et al conclude that the worse the lymphedema, the higher the capillary filtration rate and hence the greater the lymph flow.

Closer examination, however, suggest certain fallacies in this reasoning.

Equations 1 and 2 are only valid in a strictly steady state and even then only in a statistical sense. It assumes that the interstitium is like a barrel or a container into which liquid is poured and protein molecules

are added at a constant rate, while a bulky spoon continuously stirs the fluid mixture. If there is a "hole" in the bottom of the barrel through which the volume of liquid flows out equal to that coming in, the composition of the barrel fluid should correspond to that of the barrel content. But, the "interstitium" is much more complex. As Arturson suggests (9) "[the interstitium] *previously thought to be only a well-mixed storage chamber for fluid and solutes, is today recognized to have important physiochemical characteristics, such as self-regulation due to oncotic buffering and protein wash-down and mechanisms that govern the rate of transport of minerals ... The most widely accepted model of the heterogeneous, complex interstitium is a) free fluid channels that may or may not contain mobile hydrophilic molecules; b) a gel space with high electrical charge densities due to the presence of hyaluronate and/or proteoglycans in a meshwork of collagenous fibers, and c) cells. The interstitium behaves as a gel-exclusion chromatography column with respect to its effect in blood-to-lymph transport of macromolecules.*"

Moreover, in lymphedema, the edema fluid is often sequestered or trapped by fibrous tissue. Accordingly, it is more than probable that the composition of edema fluid obtained by piercing a needle through the skin may not be representative of the entire lymphedematous area.

In physics, Heisenberg's uncertainty principle is a generally accepted doctrine which expresses that measurement of both the position and the momentum of a particle at the same time is inherently inaccurate because the process of measuring alters either the momentum or its position. Yet those who insert a needle with a wick into the tissue environment fail to recognize that per force the local steady state and the capillary filtration rate of protein are altered.

C or the capillary filtration coefficient is the product of the capillary hydraulic permeability and the available surface area for fluid and protein microvascular exchange. Are these variables truly refractory to introduction of a wick? Insertion of a wick provokes not only an inflammatory reaction but also microscopic bleeding. Indeed, Bates et al acknowledged that the "*ends, and any parts of the wicks visibly stained pink were cut out.*" This observation signifies that the portion not removed was not visibly pink but nonetheless still likely contaminated with red blood cells and therefore blood plasma. Of related interest, the introduction of hemoglobin or erythrocytes into the interstitium and adjacent lymphatics impairs a pivotal mechanism of the lymph pump namely its intrinsic contractile function (10). In other words, by simply introducing a wick, lymphatic capillary plexuses, precollectors and collectors are microscopically damaged and arm lymph oozes into the wound. "Wick fluid," therefore, contains a mixture of blood serum, inflammatory exudate, tissue fluid, and lymph. The protein concentration of "wick fluid" is accordingly higher than the intact tissue fluid. Moreover, local P_i and local interstitial fluid volume (IFV) increase and σ decreases. Under these circumstances, the following equation

expressing the local micro-vascular forces should be properly formulated as:

$$\int_{t_1}^{t_2} LF \cdot dt = C \int_{t_1}^{t_2} [(P_c - P_i) - \sigma(COP_p - (COP_i))] \cdot \Delta IFV \dots \text{eqn. 4}$$

Where t_1 =where the observation starts and t_2 is where the observation ends (removal of the wick).

In other words, LF is properly determined by at least 9 variables!

In addition, compliance of the pericapillary interstitial space should be considered:

$$\text{Compliance} = \frac{\Delta IFV}{\Delta P_i} \dots \text{eqn. 5}$$

or, $\Delta P_i = (1/\text{compliance}) \cdot \Delta IFV \dots \text{eqn. 6 (11)}$.

Thus, if compliance increases and IFV is unchanged, P_i decreases; conversely if compliance decreases and IFV remains unchanged, P_i rises.

Because lymphedema alters compliance of the interstitium, a comparison with a non-edematous contralateral arm is probably not valid.

Equation 2 is based on the assumption that under physiological conditions no plasma protein catabolism takes place in the interstitium. Whereas no data pro or con exists on this point in normal tissue, there is little doubt that interstitial protein catabolism takes place in lymphedema. If macromolecules stagnate in the tissues, they undergo biochemical alteration which in turn stimulates an inflammatory reaction (11). Macrophages are certainly capable of engulfing and digesting "denatured" or foreign proteins and ample evidence exists that lymphedematous tissues are rich in macrophages with proteolytic activity (12). Moreover, experimental lymphedema worsens when these macrophages are poisoned or inactivated (12).

When these facts are taken into consideration, equation 2 should be rewritten as

Fig. 1. Right Above — Untreated lymphedema of the arm; Right Below— After completion of phase I of combined physical therapy (manual manipulation and bandage-compression wrapping) with reduction in edema.

Note the distorted shape of the arm as opposed to a theoretical cone with a perfect circle as the base.



$$C_i = \frac{FPR - CAT}{F} \dots \text{eqn. 5}$$

where CAT represents catabolized protein.

Although C_i and F (protein filtration) are inversely proportional, $(FPR - CAT)$ and F are directly proportional. In other words, a lower C_i does not necessarily mean a higher capillary filtration rate; it can also signify a decrease of $(FPR - CAT)$ or, in effect, the higher the CAT the lower is the C_i .

Bates et al point out that a reduced transcapillary permeation of protein can theoretically explain a fall in COP_i , although the converse, increased protein permeability is

usually the case in pathophysiological states. Whereas this statement is valid, it is also possible that in lymphedema, blood may flow through microscopic arteriovenous shunts (13) which theoretically could lower the transcapillary permeation of plasma protein.

Another consideration needs to be examined. The investigation of Bates et al were "carried out mostly in the early afternoon ... Patients who are being treated with an elastic sleeve, which is normally removed at night and worn during the day, were asked to refrain from replacing the sleeve on the day of the study." As a consequence, the volume of the arm increased. But even if patients did not

wear an elastic garment, the physical activities performed between arising in the morning and the early afternoon are inconsistent with the assumption of an absolutely steady state in the lymphedematous arm.

Blister fluid is easily obtained by using a suction device. Yet the protein concentration in such fluid is lower than that of so-called "wick fluid." Blister fluid yields values of approximately 2.0g/dl (14). But as "suction" may also exert a traumatizing effect, even 2.0g/dl may be misleadingly high. But in Table 1, in the non-edematous contralateral arm the average protein value in C_i was 4.14g/dl, an amount more than twice as much as even blister fluid. It is therefore improper to assert that lymphedema fluid protein concentration is lower than the protein concentration of normal interstitial fluid. One can only maintain that the protein concentration of a drop of wick fluid obtained from a lymphedematous arm is lower than the protein concentration of wick fluid from a non-edematous arm. Whether we can extrapolate this finding to mean that protein flux = lymph flow and the latter is higher in the lymphedematous arm than in the non-edematous arm is highly dubious for the reasons enumerated.

Neither wick fluid nor prenodal lymph should be construed as identical to pericapillary fluid. The fact that many investigators accept this caveat by simply dismissing data which contradict it (15) is unconvincing. The statement of St. Thomas Aquinas (16) *Quod ... ab omnibus communiter dicitur, impossibile est totaliter falsum*" (what all people say can't be totally false) may be appropriate in "Apologetics" but not in matters of science.

I turn now to the significance of a negative correlation between the percentage increase in arm volume in patients with arm lymphedema and C_i and the negative correlation between the percentage increase in arm volume in COP_i ($r=0.37$ and 0.45 , respectively). The "truncated cone" method is based on the assumption that the arm segments correspond to cones each having a perfect circle at its base. But this assumption is

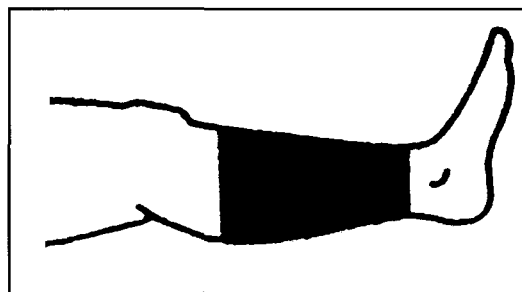


Fig. 2. Segment of the lower leg as measured by Stranden (ref. 17). Compare with Fig. 1.

valid only in an otherwise healthy arm. In patients with arm lymphedema particularly if edema fluid has been mobilized, the cross-section of the arm corresponds not to a circle but to an ellipse (Fig. 1). Accordingly, the calculated volume by assuming that each segment is a truncated cone is 0.6 to 33.9% higher than the actual volume (17). This calculation is in contrast to that of Stranden (18), whereby the truncated cone method measurement fitted with a correlation coefficient of 0.98 to a line with the formulation $Y=1.128X-1.4$, where Y is the leg volume calculated from a measurement of circumference and X is the volume measured based on water displacement.

Stranden performed his measurements on a segment of the lower leg in patients with leg edema after femoropopliteal bypass grafting (Fig. 2). But, acute postoperative edema has little in common with chronic lymphedema involving the entire arm. Stranden acknowledged that above an 11% increase in leg volume there is a slight overestimation by the indirect method, but the method was found satisfactory for clinical use. This conclusion does not, however, mean that the method is necessarily valid for statistical scientific calculation.

Taking all these issues into consideration, it becomes highly questionable whether the low correlation ($r=0.47$; 0.35) as found by Bates et al between C_i and COP_i and the % increase of arm volume is truly meaningful. But even if this protein discrepancy truly exists, a more

prudent conclusion is that the more severe the arm lymphedema and the lower the C_i and COP_i the greater is tissue proteolysis by macrophages.

In conclusion, one should continue to maintain that arm lymphedema after treatment of breast cancer is the result of decreased lymph flow from obliterated or obstructed lymph drainage in the axilla. The attempt by Bates et al to suggest that net capillary filtration and hence lymph flow is increased in this condition should be viewed with healthy skepticism in light of this discussion.

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**Prof. Prof. h.c. Michael Földi, M.D.
Földi Klinik
D-7824 Hinterzarten
GERMANY**

Reply

We thank you for the opportunity of replying to Prof. Földi's letter which questions on methodological grounds the validity of our recent findings on the pathophysiology of lymphedema after treatment for breast cancer.

We, too, were surprised by the finding of a lower interstitial protein concentration (C_i) and colloid osmotic pressure (COP) in the swollen arm when compared with the contralateral non-swollen arm, and equally importantly the significant negative correlation between C_i and arm volume. We

cannot, however, accept that the results are an artifact. This possibility was in fact assessed in considerable detail in our papers (1,2) and is summarized below. Regarding the implications of the finding, Prof. Földi overstates our position repeatedly with assertions such as that we... "conclude that capillary filtration and hence lymph flow are actually increased". In our articles, we have stated very clearly that three, not one, *possible* explanations exist for the fall in C_1 and COP: i) increased capillary filtration, ii) increased tissue proteolysis, and iii) reduced capillary protein permeability.

With regard to the invalidity of the wick method for extracting tissue fluid, we make two points:

1. We draw readers' attention to the authoritative and extremely careful experimental evaluation of this method over more than a decade by Aukland and

coworkers (3) who was recently honored for this contribution by the International Society of Lymphology, and who kindly taught the method to the principal investigator (D. Bates). Certainly the wick method is not without error but Aukland's demonstration of its basic validity cannot, we suggest, be lightly dismissed. It is not possible here to catalogue the wealth of evidence on this point (see reference 3 plus supporting material in our own Discussion sections).

2. Overwhelming support for the wick results (fall in protein concentration with increasing arm volume) came from experiments where the *performed* edema fluid was sampled in minutes by *direct aspiration* and *exactly the same negative relation existed*.

Prof. Földi appears to recognize the validity of the direct aspiration procedure but then dismisses the negative relation between

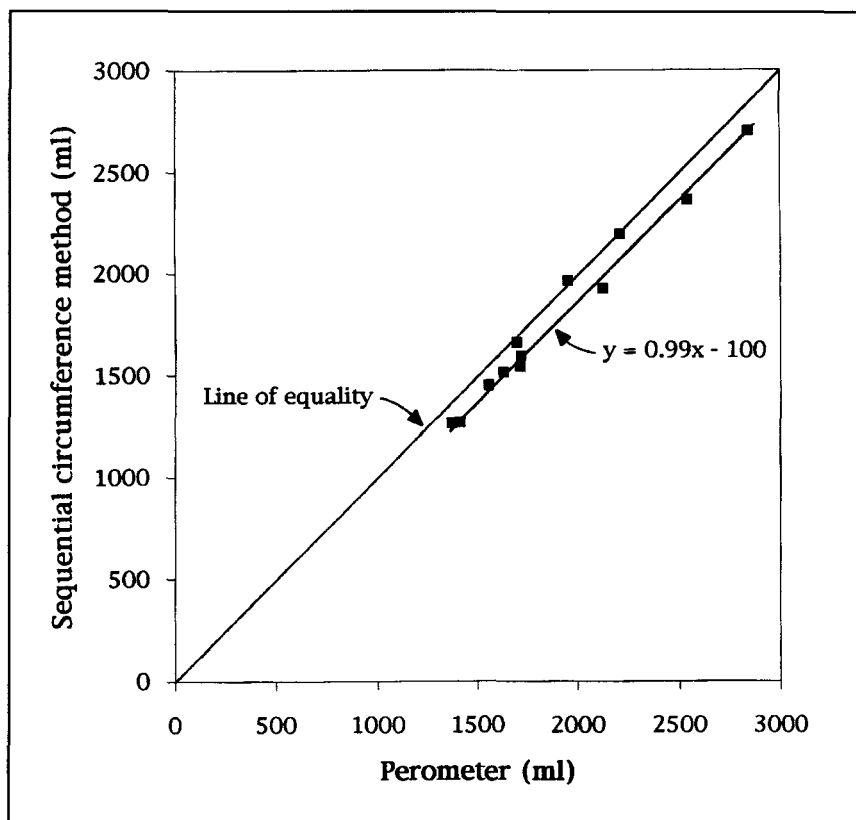


Fig. 1. Arm volume measured by sequential circumference compared with an optoelectronic volumeter (Perometer).

aspirate C_i (or COP) and arm volume, on the grounds that the measurements of limb volume based on surface circumference measurements were erroneous. Collins et al (4) have used computed tomography to study cross-sectional profiles of arms of women treated for breast cancer, and demonstrated that the lymphedema limb was no more or less of an ellipse than the contralateral non-swollen arm. Moreover, correlation between arm volume determined by surface measurements and an optoelectronic volumeter (Perometer[®]) is excellent, with a correlation coefficient of 0.988 ($p < 0.001$) for 12 swollen arms measured by the two methods. *Figure 1* illustrates this close relationship. A similar high correlation exists when normal arms ($r = 0.985$, $p < 0.001$, $n = 12$) and mannequin arms ($r = 0.999$, $p < 0.001$, $n = 6$) are measured (personal observations). Pani et al (5) have also found good correlation between surface measurements and another method, water displacement. We, therefore, reject the possibility that the observed correlation was an artifact of inaccurate volume measurement.

The influence of hosiery removal on C_1 and COP, concerning which Prof. Földi advances a qualitative argument, has in fact already been assessed *quantitatively* in the cited papers (1,2). It was clear that the overnight volume increases were far too small (and did not correlate with arm volume) to be a reasonable explanation quantitatively for the results.

Prof. Földi cites suction blister fluid composition as evidence of wick fluid invalidity. He fails to point out, however, that suction blister fluid has an *abnormally low* protein concentration because it is acutely generated *de novo* by massive suction, which deliberately raises filtration rate and lowers C_i . The use of blister fluid for comparison is thus totally invalid.

In summary, we accept that our results are surprising but stand by them and the

carefully considered discussions relating to their interpretation. Debate based on a sound scientific reasoning is healthy but what is needed is further experimentation to exclude or support the various (three) pathophysiological mechanisms that could explain these results. We would welcome good quality experimental contributions from other laboratories. The traditionalist's view that axillary dissection or radiotherapy destroys lymphatic continuity thereby giving rise to a "low output failure" and a relatively "high protein edema" is far too simplistic and does not explain many of the failures observed with arm lymphedema after breast cancer treatment.

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P.S. Mortimer, MD, FRCP
J.R. Levick*, DSc BM BCh DPhil
A.W.B. Stanton, MB BCh PhD
St. George's Hospital Medical School
Departments of Physiological Medicine
and *Physiology
London SW17 ORE, United Kingdom