LETTERS TO THE EDITOR

MEASURING PERIPHERAL OEDEMA AND BIOIMPEDANCE

We read with interest the article by Dr. Casley-Smith, entitled "Measuring and representing peripheral oedema and its alterations," published recently in *Lymphology* (1994, 10:56-70). This article addresses the important questions of how best to minimize the errors inherent in measuring changes in peripheral oedema and the most informative way in which to present the results. The paper discusses, in particular, the errors associated with the estimation of limb volume by geometric methods and the author concludes that the *best* equation to use in bilateral oedema is *"Difference in Volume/Initial Volume"* whereas in unilateral oedema the best equation is *"Difference in Oedema/Normal Volume."* (Implicit here is the assumption that a change in volume is reflective of a change in the amount of oedema only, a moot point as discussed below). While accepting the correctness of these conclusions, based on the analysis as presented by the author, we would like to draw the attention of readers to the following issues.

In discussing the precision of various mathematical relations Casley-Smith correctly states that *"the important consideration is the relative error"* (p59); however he apparently interchanges absolute and relative errors in the discussion. This interchange can lead to incorrect deductions from the analysis of the precision associated with various relations. A valid comparison of the precision of different measurements can be obtained from the corresponding standard errors of the estimate, or from the corresponding relative precisions (relative errors, or percentage errors), but not

necessarily from the absolute precision. To demonstrate how incorrect deductions can be drawn from interchanging absolute and relative errors the following examples use the example discussed by Casley-Smith, assuming a precision of ± 5%

Initial volume U=11 (L)   ± 5% (±0.55)
Normal volume N=5 (L)   ± 5% (±0.25)
Final volume F=9 (L)   ± 5% (±0.45)

(eqn 2)

$$\text{Diff / Init Vol} = \frac{F}{I} - 1$$

$$= \frac{9 \pm 5\%}{11 \pm 5\%} - 1$$

$$= \frac{(0.818 \pm 10\%)}{-0.182 \pm 10\%} - 1$$

yielding an absolute error = ± 0.018 L

Similarly:
(eqn 3)

$$\text{Diff / Final Vol} = 1 - \frac{I}{F}$$

$$= 1 - \frac{11 \pm 5\%}{9 \pm 5\%}$$

$$= 1 - (1.22 \pm 10\%)$$
$$= 0.22 \pm 10\%$$

yielding an absolute error = ± 0.022 L

Hence equation 2 does not have a greater precision, as stated by Casley-Smith, than equation 3; theoretically they have identical precision (i.e., identical relative errors). This confusion between absolute and relative errors in the article continues: e.g., equations 6 and 7.

(eqn 6)

Diff in Oedema $O_d = \dfrac{F - I}{N}$

$$= \frac{(9 \pm 0.45) - (11 \pm 0.55)}{(5 \pm 0.25)}$$

$$= \frac{(9 - 11) \pm 50\%}{5 \pm 5\%}$$

$$= -0.4 \pm 55\%$$

yielding an absolute error $= \pm 0.22$ L

(eqn 7)

Change in Oedema $O_c = \dfrac{F - I}{I - N}$

$$= \frac{(9 \pm 0.45) - (11 \pm 0.55)}{(11 \pm 0.55) - (5 \pm 0.25)}$$

$$= \frac{(9 - 11) \pm 50\%}{(11 - 5) \pm 13.3\%}$$

$$= -0.33 \pm 63\%$$

yielding an absolute error $= \pm 0.208$ L

Similarly, Casley-Smith states that the errors associated with equation 7 are less than that of equation 6. Numerical analysis reveals that equation 6 has a lower relative error and hence a greater associated precision.

However, *Figs. 2, 3 and 4* of the article suggest that the author, when quoting "an error of 5%" is referring to an error in the assumptions of the measured quantity as opposed to imperfections in the precision of the measurements. If this is the case *Figs. 2, 3 and 4* are demonstrating the degree of susceptibility or conditioning of the various equations towards the various parameters. A true comparison of the various equations described by the author would be an analysis of the relative errors of each when a reasonable estimate is placed on each and every measurement simultaneously.

In Part 1 of the article, Casley-Smith summarizes data from a number of studies which compare volume measurement based upon water displacement with that based upon calculation assuming a truncated cone (frustum sign) geometry. It is concluded, apparently on the basis of correlation analysis between the two methods, that each *produces results which are nearly identical for statistical purposes of comparing one treatment with the other"* (p58). However, as elegantly pointed out by Bland and Altman (1) a high correlation coefficient can be misleading and does not necessarily mean a close agreement between methods. Indeed, a recent study (2) found a correlation of 0.93 between the frustum sign method and water displacement volumetry of the leg, yet the limits of agreement analysis (1) indicated that the water displacement method tended to have a bias of a larger volume by 521 ml with a 95% confidence limit of 483 to 559 ml.

When the geometric analysis was refined to estimate volume as the sum of the volumes of adjacent 30 mm discs (3) along the length of the limb, the correlation coefficient improved to 0.99, but the bias decreased to -45 ml (i.e., the disc model estimating a larger volume) with confidence limits of -57.5 to -32.5 ml. It would have been informative to have seen such an analysis applied to the data presented by Casley-Smith. Furthermore, although the data presented by Kaulesar Sukul and colleagues (2) was from a study of non-oedematous limbs, they do highlight the improvement in volume estimation achieved using the disc model rather than the frustum cone procedure. It would appear, therefore, to be prudent to adopt the disc model when calculating the volume of limbs in clinical practice. It is noteworthy, that such an approach would also minimize errors associated with inclusion of non-oedematous regions in a frustum cone procedure spanning a greater limb length.

In Part 2 of the article, Casley-Smith addresses the issue of representing the degree of oedema and its diminution upon treatment. In the case of bilateral oedema it is suggested that difference in volume should be indexed to initial volume whereas for unilateral oedema indexing should occur against the contra-lateral normal limb volume. In either case, as pointed out by the author, what is of chief concern to the patient and to the therapist is alteration in the amount of oedema, i.e., the

change in extracellular fluid accumulation in the limb at the start of treatment to that at the end. Notwithstanding any errors associated with measurement of limb (or limb segment) volume, simple external geometric measures may not be reflective of change in extracellular fluid volume. It is possible to envisage a patient in whom a decrease in extracellular fluid (oedema) is matched by a complementary increase in muscle or fat mass such that overall limb volume is not appreciably altered. In such instances a causally-related measure of oedema is required. Recently we (4), and others (5), have investigated the potential of multiple frequency bioelectrical impedance analysis (MFBIA) for the estimation of total tissue and extracellular fluid content of limbs. MFBIA is clearly capable of distinguishing, with accuracy at least equivalent to that of geometric methods, limb oedema and monitoring its regression upon treatment. Its advantage is that impedance changes at appropriate frequencies (6) are causally related to changes in either total fluid or extracellular fluid content alone. In addition, when comparing groups of individuals, impedance data need to be indexed to normal limb impedance (i.e., the contralateral limb) thereby rendering the method unsuitable for bilateral oedema. For any individual, however, the serial change in absolute impedance with time of therapy is indicative of change in fluid volume. Thus, the problem of abnormal "normal" limbs addressed by Casley-Smith, is obviated.

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Reply:

Most of Ward and Cornish's criticisms of my paper (1) are merely errors and misconceptions. An important component of their correspondence comes near the end, i.e., their espousal of bioimpedance. Whereas bioimpedance may become a viable technique for measuring edema, it has not as yet been shown to be useful and I examine its shortcomings later.

Relative vs. Absolute Errors

Ward and Cornish claim that I "apparently interchanged absolute and relative errors". This distinction is vital; however, I did not interchange them. I consistently discussed relative errors (1; p59-60). Equations 1_p and 2_p are examples of how such errors in all the equations were treated.

Effects of Errors on the Various Equations

Ward and Cornish try to substantiate their contention using my equations 2 and 3

(1). However, they have several errors in their calculations (quite apart from their omission of a minus sign before "0.22" in their equation 3). When comparing my equation 2 and 3, they treat the "±5%" as if these were actual values rather than ±5% *of some other figure* and, when simplifying, they simply add the two ±5%'s together. This is algebraically incorrect; it should be:

Eqn. 2: Difference/Initial Volume =
F/I-1 = (9±5%)/(11±5%)-1 =
(9.45 or 8.55)/(11.55 or 10.45)-1=-0.182,
-0.096, -0.260, -0.182

(using, respectively, the first and third, first and fourth, second and third, and second and fourth terms in the brackets). Since the true value is -0.182, the relative errors are, respectively: 0%, 47%, 43%, 0% (neglecting sign differences). Similarly:

Eqn. 3: Difference/Final Volume = 1-
I/F=1-(11±5%)/(9±5%)=
1-(11.55 or 10.45)/(9.45 or 8.55)=-0.222,
-0.106, -0.351, -0.222

(using, respectively, the first and third, second and third, first and fourth, and second and fourth terms in the brackets—the order was varied to accord with that used for equation 2). The true value, -0.222, gives relative errors of: 0%, 52%, 58%, and 0%. These values are all greater than, or equal to, the errors from equation 2. Hence equation 2 gives lesser relative errors—as was demonstrated algebraically and shown in *Figs. 2 and 3* (1).

Incorrect calculations are also used by Ward and Cornish for my equations 6 and 7 (1), leading to similarly erroneous results and conclusions. When one divides a Mean by another, it is essential to take account of the Standard Errors as described (1; p. 69). Otherwise, gross errors occur in the Standard Error of the resulting Dividend. Ward and Cornish's incorrect calculations would lead to mistaken results.

Ward and Cornish attempt to separate "the assumptions of the measured quantity as opposed to imperfections in the precision of the measurements". This separation is quite unnecessary. The outcome is the same whether an error is caused by poor measuring technique, imprecise apparatus, or a so-called "normal" limb being different from the true normal for an oedematous limb.

Water-displacement Versus Circumference Measurements

Ward and Cornish criticize me for supposedly saying that water displacement and volume calculations from circumferences are identical. My thrust, however, was to point out that the two methods although closely correlated, *may yield quite different results,* as was indeed demonstrated (1; p 57-58). Nonetheless, the good correlations between the two signifies that either can be used safely to compare *changes* in oedema.

Cone versus Cylinder (Disc) Approximations for Limb Volume

Ward and Cornish next discuss differences between the truncated cone approximation (2) and that using cylinders ("disc") (3) believing the latter more accurate. Others have also confused the (negligible) effects of different geometrical approximations with the benefits of using closer measuring positions, e.g. 40mm as used by Kuhnke (4) when describing the cylinder approximation (not 30mm as cited by Ward and Cornish). Those I utilized were at 100mm intervals; had they been 40mm, the results may have been slightly more accurate. In practice, however, 100mm intervals are usually sufficient to evaluate results of treatment (4). Indeed, these intervals were used in a recent article co-authored by Ward (5). Except in unusual circumstances, closer measurements do not give enough increased accuracy to justify their time and trouble.

To clarify this issue, the cone calculations (1) were repeated using the cylinder ("disc")

method (3). Oedema was estimated, (volume of oedematous limb/normal limb -1), for 1,300 measurements of filariatic lymphoedemas, 200 of leg lymphoedemas from various causes and 150 of postmastectomy lymphoedemas (all as in the previous paper) (1). Correlation coefficients between the two methods were: 0.96, 0.98, and 0.97, respectively, with no significant differences between them. The three linear regression lines of cone versus cylinder also did not differ significantly. The combined line was 1.013 + 0.0052 (Standard Errors: 0.012 and 0.002, respectively). Either method is equally valid. If they differ from water displacement results, it is to the same extent and for the same reasons.

Ward and Cornish are also mistaken when they claim that the cylinder ("disc") approach would "minimize errors associated with inclusion of non-oedematous regions," since the cone and the disc use the same longitudinal intervals.

Bioimpedance

Finally, Ward and Cornish recommend use of bioimpedance spectroscopy (which they term "MFBIA") to measure oedema. Whereas this technique may someday prove useful for measuring the volume of extracellular fluid in peripheral oedema, this is not the case at present, nor is extracellular fluid necessarily the only parameter to monitor.

Oedema is not precisely defined (6; p. 43-44). It is often used loosely and incorrectly just for the surplus fluid rather than for fluid plus other excess tissue elements (i.e., total swelling). In lymphoedema, as in other chronic high protein oedemas, there are other alterations in the tissues such as increased fibrosis, other cellular and non-cellular components of the interstitium, and proliferation of blood and lymph vessels (6,7). Together they contribute to the increased bulk of a limb and hence patient discomfort. Most also aggravate the disease process.

The non-fluid increases are relatively great. This has been shown in the skin and subcutaneous tissues of congenital lymphedematous dogs (8) and chronic inflammation caused in rats by stagnation of plasma proteins in the interstitium (9). Whereas the increase in interstitial fluid is not negligible, it is considerably less than for the solid elements.

Increased limb volume is an important measurement when gauging the seriousness of a condition and the effect of treatment. Although not the sole feature (e.g., patient symptoms and limb tonometry are also noteworthy), total volume is more important than assessment of extracellular fluid alone. Ward and Cornish and others (11) mistakenly consider that measuring excess fluid alone is sufficient to assess the "swollen limb".

Thus far, most bioimpedance studies have concentrated on the whole body; few have examined the whole limb. Physical treatment of lymphedema requires assessment of how a limb is altered at many measuring positions (4). Unless bioimpedance can be refined to measure cross-sections of a limb just 20-40mm wide, it will be of limited practical usefulness. Whereas accurate measurement of extracellular fluid volume is desirable, bioimpedance has limitations in this regard as well.

Bioimpedance spectroscopy uses alternating currents to traverse the skin and to measure the conductance of the extra-and intracellular fluid (11-14). Many frequencies are used to exploit the frequency dependency of the cell membranes (high frequencies traverse the cells, low ones do not). Results are extrapolated to zero and infinite frequencies to calculate the volumes of these fluids. Some workers have attempted to measure extracellular fluid using needles with direct (10) or alternating currents (15). In 40 standard experimental acute lymphoedemas (16), these methods yielded poor correlations between conductance and oedema. Several possible reasons may be invoked for this discrepancy including variations in morbid tissue architecture and variations in composition of the fluid, which in longstanding high protein oedema are great from one site to another and between subjects (8,9).

Whereas measurements using direct current may be unlike those using alternating current, the basic principle is nonetheless similar; that is, measuring the conductivity of the oedema fluid. Despite good correlation between impedance results and other estimates of extracellular fluid (11-14,17-19), one wonders about the accuracy of bioimpedance when applied to a variety of localized oedemas. Although there are good correlations with experimental low-protein oedemas of the peritoneal cavity (20) and of the rat leg (21), these oedematous states are not synonymous with high protein (lymph)oedema.

Some studies have been performed in human lymphoedema. In one (22), the correlation coefficient was only -0.614 between the resistance of the oedema fluid and the cross-sectional area of the legs (13 patients). In another study on postmastectomy lymphoedema (15 patients and 15 controls) co-authored by Ward and Cornish (23), the correlation between limb size and the conductivity was 0.7. These data, although promising, are probably too diverse when applied to individual patients. Thus, to quote Ward et al (23), *"The ranges for the impedance plots ... overlapped to a greater extent and failed to discriminate between lymphoedematous and control limbs"*, and further *"limitation of the technique at present is the lack of algorithms which relate body segment impedance ... to fluid volume as exist for whole body measurements"*. Their previous results and comments tend to negate their assertion in the letter that *"MFBIA is clearly capable of distinguishing, with accuracy at least equivalent to that of geometric methods, limb oedema and monitoring its regression upon treatment"*. Moreover, although there were no sequential measurements during treatment in the studies they cite (22,23), Ward et al (23) nonetheless claim that *"sequential MFBIA could be an invaluable tool in the routine diagnosis and management of lymphoedema"*.

Ward and Cornish also maintain that bioimpedance can circumvent the problem of comparison to a normal limb as with patients with bilateral limb oedema. Yet they agree that a contralateral limb is indispensable for comparison if the amount of extracellular fluid is to be related to normal. Many techniques may show that a limb has lost volume during treatment, but unless one can estimate the true normal these losses cannot be related to alterations in the amount of oedema. In this regard, bioimpedance as a technique is no different from any other.

Bioimpedance measurements appear to be excellent for estimating both intra- and extracellular water under certain conditions (11-14,17-21). Yet differences exist as to how to evaluate the results. One group favors using the Z at the "characteristic frequency" (Fc) for total water and extrapolating to zero frequency for determining extracellular water content (18). Others maintain that a single frequency is far too prone to error and insist that a much wider range be used to determine both zero and infinite frequencies for accurate determination of extra- and intracellular water (11,17). They also consider certain techniques such as the use of L^2/Z as overly simplified because of the complex nature of tissues and oedema fluid, and that the use of Z at Fc is misleading. Some criticism has also been directed at the performance of bioimpedance at high frequencies (13,19), but this shortcoming has been shown to be unfounded (18).

In summary, Ward and Cornish's enthusiasm for bioimpedance must be tempered by its extant limitations.

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ON MICROWAVES

I have read the Editorial by Prof. Földi (1) with great care and wish to draw attention to an erroneous impression about "cancerogenic microwaves" that appeared in the section under Combined Physiotherapy.

Lymphedema is a complicated issue in medical practice; there are many questions that still remain to be resolved including its etiopathology and optimal treatment. It is still debatable that one treatment program is better than another because of the lack of well-controlled clinical trials. During the last three decades, we have successfully evolved a heat and bandage program for treating peripheral lymphedema from the primary electrical heating device to a modified microwave oven used nowadays and have obtained excellent therapeutic results in more than 2500 patients with lymphedema (2-4). We designed a microwave oven with 2450 MHz frequency and generator power output of 100-300 watts because this microwave has the ability to penetrate to a tissue depth of 1.7 cm (5); after 5 min of treatment, the deep tissue temperature is 41°C to 43°C, which is sufficient for therapeutic requirements. This innovation has greatly improved the therapeutic effects for lymphedema, with the outcomes excellent or good in 90% of patients. The patients are comfortable during treatment. Each course of treatment lasts 20 days for 60 min each day. This heat and bandage program has the advantage of simplicity. Since introduction of the microwave for heating treatment of lymphedema, no overt complications have occurred either early or late and no microwave-related cancers have developed.

Microwaves have found wide use in medical and other fields just like ultrasound and x-rays. The effects of high energy radiation (e.g., x-rays, gamma rays) have been studied extensively. In spite of the vast amount of information available about ionizing radiation, the public, including many physicians, are ignorant of its quantitative and qualitative effects. The term "radiation" still evokes emotional responses both from lay persons and professionals. Most people are still unfamiliar with radiation biology or the quantitative nature of the risk and the physical characteristics of microwave radiation. Commonly, microwave, ultrasound and ionizing radiation risks are confused. Actually these three forms of energy are quite different. Microwaves have much longer electromagnetic waves than x-rays or gamma rays, a variable ability to penetrate and unlike x-rays and gamma rays do not produce ionization. The primary biologic effect of microwaves is hyperthermia, although the existence of non-thermal effects of these electromagnetic waves is still being investigated. Cataract development is perhaps the most widely known complication of prolonged microwave or radar exposure (6).

Microwave, radar, shortwave, diathermy, FM broadcast radio waves are various forms of long-wave length electromagnetic radiation that have little in common with x-rays and gamma rays, at least from a biologic standpoint. Maximum permissible levels for occupational and medical exposure have been suggested for these forms of energy. Persons working near FM radio stations, radar, and microwave ovens are not exposed to the maximum permissible level. A microwave oven generates 2450 MHz microwaves, which can produce hyperthermia above the 24 mW level with penetration of several centimeters. There is no way to receive exposure from a microwave oven without bypassing several safety interlocks. Moreover, it is easy to shield microwaves; a proper screen or thin metal foil is 100% effective in shielding all microwave radiation.

Theoretically, if a microwave oven had a door leak, one could be exposed if a part of the body is placed in direct contact with the wave-

emitting area. In this way, it is conceivable that after several hours, one might receive measurable exposure. On the other hand, because electromagnetic waves dissipate at a rate related to the square root of distance, it is apparent that a leaking microwave oven would have no major consequences several meters away unless it interferes with an electronic device that is sensitive to that wavelength of electromagnetic radiation.

Radar, microwave, radio waves, FM, and diathermy all involve electromagnetic waves ranging in frequency from 27.5 MHz (diathermy) to 10^4 to 10^5 MHz (microwave). Diathermy electromagnetic waves have great penetration and can readily heat a human torso; microwaves of 2450 MHz with 915 MHz has less penetration but can also produce significant hyperthermia. Microwaves with frequencies above 10,000 MHz have minimal penetration but could produce significant hyperthermia at the skin level if the energy were high enough.

The non-thermal effects of microwaves are still being studied. The organs most vulnerable to the thermal effects of microwave radiation are the eye and developing embryo as these structures have the least capacity to dissipate heat. There is, however, no data that these forms of electromagnetic energy have the capacity to produce mutations or malignancies (6). Large epidemiologic studies of the potential role of microwaves in carcinogenesis has demonstrated negative results (7). Cellular radio waves are also not ionizing. Indeed, there are currently over 11 million cellular telephone users in the United States and to date, there has not been evidence of potential toxicity (8). In conclusion, exposure to microwave radiation below the maximal permissible level presents no measurable risk to human health; therefore, the clinician can reassure patients that a microwave oven properly handled is safe and that patients are not being exposed to "cancerogenic microwaves."

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Editor Comment:

We have published this letter for its informative ideas. Actually, Dr. Chang misinterprets Prof. Földi's point in his overview regarding treatment of lymphedema. Rather than suggesting that microwaves cause cancer, Földi was drawing attention to the difficulties of formulating blinded control clinical trials in treatment of lymphedema. He not only alluded to the impossibility of maintaining confidentiality of those who received or did not receive hyperthermia in the clinical setting but also noted that an "overzealous" physiotherapist suggested to patients that they were test subjects exposed to cancerogenic microwaves! The clear implication was that a physiotherapist in ignorance may go beyond the bounds of his or her professional expertise and inappropriately frighten the patient, thereby compounding the practical limitations of carrying out a carefully controlled trial as to the value of microwave treatment. Professor Földi certainly did not mean to convey that microwaves are cancerogenic.

As for Dr. Chang's assertion regarding the therapeutic effectiveness of hyperthermia in treatment of peripheral lymphedema, the readers are advised to review his article in Lymphology *[(1989), 22:20-24] and the accompanying Editorial [(1989), 22:2-3] by T. Ryan.*