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EDITORIAL

THE PLACEBO "ARM"

In this issue of the Journal, Burgos et al (1) in a well-executed clinical trial compare the efficacy of two different dosages of benzopyrone (coumarin) in alleviating arm lymphedema in women that developed as an aftermath of treatment for breast cancer. After 12 months, there was no difference in the outcome between the low dose (90 mg/day) and the high dose (135 mg/day) and accordingly they concluded that the lower dose is equally effective and therefore preferable. Unfortunately, there was no placebo "arm" (pun not intended) in the trial, which turns out to be a serious omission. The authors maintain, perhaps not unreasonably, that a placebo control group was both unnecessary and unethical citing several publications reaffirming the effectiveness of coumarin in the care of peripheral lymphedema. Despite these citations, however, considerable skepticism has persisted worldwide regarding the accuracy of these previous clinical trials as well as the putative pathomechanism by which benzopyrones ostensibly decrease edema. Although it is often claimed that in lymphedema coumarin hydrolyzes and converts plasma proteins trapped in the interstitium into amino acids that are then absorbed directly into the venous system thereby circumventing the need for lymphatic macromolecular transport and dissipating tissue protein osmotic pressure, this conclusion is largely based on deductive reasoning. No actual quantification of such proteolysis and direct bloodstream absorption has been provided nor has urinary excretion or catabolism of these so-called amino acid byproducts been documented. Equally important, most of the clinical trials claiming efficacy of coumarin have been either small cohorts of patients or carried out in underdeveloped areas (e.g., China, India) where epidemiologic monitoring is limited and the underlying diagnosis of lymphedema is either unconfirmed or the condition is compounded by comorbid conditions such as phlebitis and cellulitis that make final interpretation of the effects on edema problematic. Whereas Burgos et al failed to find any notable adverse effects of coumarin, warnings of hepatotoxicity have circulated in Europe regarding benzopyrones distributed under the trade name Venalot, and the Australian Drug Regulatory Agency two years ago removed oral coumarin from the approved formulary because of concerns over liver damage, quality control in manufacture, and unconvincing evidence of efficacy (2).

Nonetheless, oral coumarin has enjoyed considerable enthusiasm as an effective drug for treatment of lymphedema. This attitude may change, however, with the most recent publication in the *New England Journal of Medicine* (2/4/99) from the Mayo Clinic in Rochester, Minnesota (3). In this placebo-controlled trial of coumarin (400 mg/day), the investigators found no benefit of this agent in reducing arm lymphedema that developed as a consequence of treatment of breast cancer. They also observed a disturbingly high incidence (6%) of hepatotoxicity. In brief, coumarin was neither effective nor harmless.

By accepting that coumarin's efficacy has previously been irrefutably documented and thus considering it unethical to have a placebo-treated patient group, Burgos et al

may have missed a golden opportunity to demonstrate that a lack of difference between coumarin dosages was not because the lower dose was equally effective (and thus preferable) but rather because neither dose was effective in alleviating edema to begin with (assuming that if a placebo "arm" was included as in the recent Mayo clinic trial, the outcome would have been similar to the coumarin-treated patient groups). Indeed, whereas Burgos et al claim a 13-15% reduction in edema volume over the 12-month period of study, in point of fact, this volume reduction did not reach an acceptable level of statistical significance (p value=0.122). In this regard, the arm volume stability is consistent with the findings of Loprinz et al (3), who demonstrated over a period of 12 months that with or without coumarin treatment arm lymphedema volume was remarkably stable and unchanging for the vast majority of patients.

The study of Burgos et al once again demonstrates that scientific inquiry, no matter how seemingly logical and ethical the assumptions, the most important ingredient for obtaining reliable information is still a valid control group.

REFERENCES

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3. Loprinz, CL, JW Kugler, JA Sloan, et al: Lack of effect of coumarin in comen with lymphedema after treatment for breast cancer. New Eng. J. Med. 340 (1999), 346-350.

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