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REPLY: We are pleased to have this forum to respond to the arguments presented by Dr. Mazess. The primary point of our letter may have been missed. We proposed that the clinical uses of BMC measurements should be well defined before comparisons between techniques are conducted. We indicated that monitoring of treatment effectiveness is one important clinical use, and as high precision is an essential requirement, measurement of multiple bone sites by all three techniques (QCT, DPA, and SPA) may have usefulness for this purpose. We also suggested that assessment of future fracture risk was another important clinical application, and that for this purpose the priorities are different. As a screening test, it must be *safe* and *cost effective*, and it must also be predictive of *future fracture risk*.

Therein lies the root of this apparent dispute. How is "fracture risk" to be defined? In his letter, Dr. Mazess has only referenced studies based upon fracture prevalence data (i.e. fractures that occurred at some, often unknown, time in the past). These fractures were then compared to subsequent BMC measurements. By definition, these studies tell us how well the BMC measurements assess *past* fracture risk. It is our contention that there is little need in clinical medicine for a new test that identifies subjects with previous fractures; virtually all such cases can be identified by proper histories and conventional radiographs. We suggest that what is really needed is a test which will identify, at an early age (40–50 yr), which women are at greater risk for fractures in the future, and who would therefore benefit from preventive therapy. In this particular context, attempts to relate BMC at one skeletal site to BMC at another site are not relevant. Rather, it is the relationship of BMC to clinical outcome (i.e., future fractures) that is needed. In order to determine whether any risk factors, including BMC, are indicative of future fracture risk, they must necessarily be compared to prospective fracture *incidence*. There is virtually no such data in the medical literature.

Our data has been inaccurately paraphrased. [The reader is referred to the original manuscript for an unabridged version (*1*).] We agree that it does challenge "conventional wisdom," but contend that prevalence fractures, which consitute much of the existing data, are inappropriate for assessment of future fracture risk. Consideration of this disease as two discrete variables, i.e., "fracture" vs. "nonfracture" is also inappropriate analysis, since BMC is a continuous variable which relates to a continuum of risk.

Dr. Mazess states that research has shown that direct measurements of osteoporotic fracture sites (hip and spine) are needed to define fracture risk." Is that true? Has that *hypothesis* been tested against prospective fracture incidence, using all possible skeletal BMC measurement sites? The answer is no. However, like many hypotheses in medicine, its apparent reasonableness, has transformed it into a fact in some minds. It should also be noted that "osteoporotic fractures" cannot be arbitrarily limited to hip and spine. All nonviolent fractures occur more frequently in osteopenic bone, and therefore cannot be ignored. In addition, fractures at some sites, particularly wrist, may be indicative of increased subsequent risk for fractures of the spine and hip (*2,3*).

We have been testing the above *hypothesis* in a longitudinal, population-based cohort. We are including multiple appendicular and axial BMC measurements precisely because *none* have been appropriately tested, particularly within the same cohort. We now have some preliminary data which challenges this hypothesis (*1*). Although this is certainly preliminary data and will require further followup, it is appropriate to collect and report such data. During the past 5 yr more than 20,000 individual scans have been performed on this cohort of 3,000 individuals. To date there are 150 prevalence fractures and 50 incidence fractures available for analysis of relative risk. We have more recently presented an analysis of incidence fractures which included a substantial proportion (40%) of spine fractures (*4*). Although the data do suggest that future spine fracture risk can be assessed with spine BMC measurements, there is an equally good relationship for os calcis BMC. For appendicular fractures, os calcis and radius BMC were superior to spine BMC as predictors. Thus, at this time, based upon preliminary analyses of our data, we have concluded that prediction of fracture risk at a given skeletal site, such as spine, does not *necessarily* require direct BMC measurement at that site. By way of analogy, prediction of stroke risk with blood pressure measurements, as employed in a physicians

office, does not require direct blood pressure measurement in the cerebral arteries.

Lest the reader conclude that there is no common ground in this debate, we do agree with Dr. Mazess that spinal BMC cannot be sufficiently predicted from measurements at other sites, such as radius and that hip BMC cannot be sufficiently predicted from spine BMC, and vice versa. We do not, however, believe that all of the answers are in; rather we suspect that some important questions have not yet been asked. Will it be necessary to measure every skeletal site at potential fracture risk in order to screen the population and select those individuals who most need preventive therapy? In the case of hypertension and stroke risk, it has not proved necessary to measure cerebral artery blood pressure; peripheral artery measurements are sufficiently predictive for clinical screening. However, it took years of longitudinal stroke *incidence* data to establish this relationship. Therefore, it will also require additional data to confirm the relationship now suspected between BMC and fracture risk.

We continue to test the hypothesis that peripheral BMC measurements can predict future fracture risk, taking care to include all possible risk factors and BMC measurement sites, without presupposing the results. Despite the incomplete data and our imperfect knowledge, both the nihilistic and the "shotgun" approaches to osteoporosis prevention should be abandoned. For the present, rational osteoporosis preventive choices for *individual* patients depend upon objective measurements, and their acceptance into clinical practice are strongly influenced by cost considerations.

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Correction: Three Phase White Blood Cell: Diagnostic Validity in Abdominal Inflammatory Diseases

In an article by Becker et al. in J Nucl Med 27:1109–1115, 1986, please note the following corrections.

Page 1110, left column, lines 1 and 6 *should read* 90 g/7 min.

Page 1110, left column, lines 3 and 33 *should read* 18.5 MBq.