

Issues in Modern Histomorphometry: 50 Years Later

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This session was occasioned by recent developments in human bone histomorphometry associated with drug interventions that cause marked reduction in bone remodeling. We titled it, “Issues in Modern Histomorphometry: 50 Years Later”, to honor the milestone publication by Dr. Harold Frost in 1960. In the Henry Ford bulletin, he published a single case of a 57 year old male in which he examined a lower extremity surgical specimen that had tetracycline labels in it from pre-surgical tetracycline administration for infection. This was the first attempt at calculating dynamic remodeling from a fluorochrome tissue-time marker, tetracycline. Subsequently, in the 60s and early 70s, it became apparent that the only practical sampling location for living human bone histomorphometry was the transiliac bone biopsy described by Bordier in 1964. In the ensuing decade or so, the stereological theories, the histological measurements, and the calculations were worked out in order to provide information on variables such as activation frequency, mineral apposition rates and bone formation rates. In the process, we learned much about bone remodeling, and bone biology in general, in humans and vertebrate animals.

With the advent of remodeling suppression therapy in humans with osteoporosis, we began to see biopsies that had little or no tetracycline label. This created difficulties in interpretation. These have resulted in planning for the current session which will try to establish reasonable consensus for a number of questions. These include; how to express and interpret bone forming surface in the absence of label in standard sections areas, what is the value of extended label searches in specimens, how to calculate mineral apposition rate, and activation frequency. Other questions include what is sufficient section area sampling, and cortical bone sampling. All of these, and more, have become very important in the past two decades. This session will have an overview plus three presentations, all directed at answering a list of questions provided for the audience. In addition, there will be nearly two hours for open discussion with the panelists with audience participation. The object is to come to consensus regarding the questions posed by animal and human biopsies obtained in the presence of treatment with agents that suppress remodeling, and to refine our understanding of the strengths and limitations of human and animal bone histomorphometry. The following is a list of questions that will be discussed:

1. How should we express and interpret forming surface (MS/BS) in the absence of label in the standard section area?
2. Is an “extended label search” worth doing in the absence of label in the standard section area? If label is found, how should it be expressed?
3. How should mineral apposition rate (MAR) be expressed in the absence of double label in the standard section area?
4. Should MAR ever be imputed?
5. Should MAR be measured and reported if found only on extended label search?
6. What is an adequate sample of double label width measurements for a reliable estimate of MAR?
7. How should we interpret the calculation of activation frequency? Is there a problem with the assumptions required? Is it a valid expression of remodeling rate?
8. What is an adequate section area sample? 40mm^2 ?
9. Should we examine cortical bone in human biopsies? What variables?

10. What is the confidence in extrapolations from a transiliac biopsy (1/14,000 of the skeleton) to the entire skeleton?
11. Can we define “anabolic” in histomorphometric terms?
12. What is the histomorphometric definition of “over-suppression” of remodeling (or “excessive remodeling)?
13. Can we measure “erosion depth” reliably in human biopsies, and is it valuable to do so?
14. Is the “obliquity correction” required for width measurements?