GUEST EDITORIAL

Etiology of Periodontitis: The Heterogeneity Paradigm

Increasingly, the literature is providing evidence that periodontitis, similar to many complex familial diseases in medicine, is a heterogeneous group of disorders that share a clinical characteristic; i.e., periodontal destruction, in common.[1,2] Heterogeneity means that the characteristic or phenotype seen clinically as periodontal destruction is attributable to different genetic and/or environmental etiologies and, therefore, has important implications for both clinician and researcher. These different disorders, grouped together on the basis of some common clinically diagnosed characteristics, may have distinct histories, genetic backgrounds, and pathogenesis and may also respond differentially to various preventive and therapeutic strategies. The first step, before any analytic (including genetic) study of etiologies can become fruitful, should, therefore, be designed to uncover unrecognized heterogeneities and to clarify homogeneous subforms of the disease.[3]

In this issue of the *Journal* there is an article concerned with characterizing the clinical and laboratory phenotypes of early–onset periodontitis.[1] This paper represents a much needed attempt to separate out laboratory subforms and to correlate laboratory and clinical phenotypes. The major contribution is the additional evidence the report has provided to confirm heterogeneity among the phenotypes broadly classified as localized and generalized periodontitis. The authors have further emphasized etiologic heterogeneity for future research.

Complex familial diseases with heterogeneous etiologies usually display marked variability in age of onset as well as in clinical severity, so that a diagnosis of unaffected may not be at all possible at the time of examination. Also, various definitions of affected and unaffected by different investigators delimit diagnosis. Most problems have resulted, however, from using arbitrary cut–off points for continuous and metric traits as clinical diagnostic criteria when such criteria may not have sufficient specificity to warrant diagnosis. The sensitivity of a criterion measure for disease is the probability that an affected individual will be correctly classified as affected, while the specificity of the measure is the probability that an unaffected individual will be correctly classified as unaffected. The cut–off point in the metric scale determines the sensitivity and specificity of the criterion in differentiating the affected from the unaffected in the sample. A quantitative basis for disease classification in early–onset periodontitis (e.g., according to age, mm loss of attachment, number of teeth involved) has evolved historically and at present comprises categories that are defined arbitrarily, have blurred borders, and overlap. Most clinical studies so far have adhered to rigid constraints imposed by historical definitions so that possible false negatives and misclassifications conceivably may affect the conclusions drawn.

Following tradition, Astemborski et al.[1] used *a priori* definitions for early–onset periodontitis based on age (12 to 35 years), for the affected and the unaffected based on mm loss of attachment (5 mm), and for localized and generalized types based on number of teeth affected (14 teeth). From their results, considerable heterogeneity is evident for age, gender, race, and for laboratory and clinical parameters among and within the phenotypes broadly classified as localized and generalized periodontitis. The authors have appropriately pointed out in their Discussion section that current technology does not permit discernment of all types of locomotor defects and individuals with normal chemotaxis response may have different abnormalities. This implies that, as technology advances, more heterogeneous subforms may emerge. However, the inferences that "chemotaxis and/or specific bacteria may be contributory but not always necessary factors in these

disorders" (in Abstract and Summary sections) and that "the absence of chemotactic defects in a large proportion of our patients clearly shows that the defect in and of itself is not required for the development of early onset periodontitis" (in Discussion section) are not consistent with their hypothesis of etiologic heterogeneity. An alternative explanation is that their results on chemotaxis and/or specific bacteria are clear indications that localized and generalized periodontitis *as defined* are not distinct disorders but may encompass heterogeneous subforms overlapping the two defined groups, and that the subforms may be uncovered by laboratory techniques such as by their analyses on chemotaxis and/or antibodies to specific bacteria. This paper should, however, lead to future studies specifically designed to uncover as yet unrecognized heterogeneities. For example, a reversal of the study design using laboratory phenotypes to search for subforms of clinical phenotypes that have not been arbitrarily pre-classified may result in better insights into the etiologic heterogeneity of early-onset periodontitis.

A major clinical feature that complicates the study of familial diseases is the continuous nature of measured phenotypes that define health and disease, so that the separation of individuals into unaffected and affected necessarily becomes arbitrary. The use of a cut-off point to define disease as a fixed classification cannot reflect the many preclinical conditions of the disease nor the multiple etiologies that ultimately result in clinical disease. It is therefore conceivable that, if the cut-off points (e.g., age 12 to 35, 5 mm loss of attachment, 14 involved teeth) were changed, different results and conclusions may emerge. Constraints from traditional clinical definitions and classifications may have to be relaxed in favor of new and increasing resolutions provided by the molecular delineation of the disease,[2] so that the intervening gene actions that make individuals disease-prone can begin to clarify. Perhaps the time is now here for this periodontitis variant to be defined in terms of a number of biologic variables identified in smaller homogeneous and more distinct groups, rather than in terms of gross clinical classifications. It is entirely possible that studies of subclinical biologic phenotypes that link genotype to ultimate disease manifestation may lead to a change in the definition and classification of clinical disease.

A large portion of human disorders is determined by genetic variation. In order to appreciate the implications of the above cited problems, a review of the basic underlying links between genes, environments, and clinical disease phenotypes will be helpful.

Genetics in medicine and dentistry has made the greatest progress by clarifying the unifactorial etiology of the relatively rare Mendelian and chromosomal disorders: A single gene defect underlies Mendelian diseases (in dominant, recessive, X-linked inheritance) and a cytogenetic error results in severe developmental defects. However, the influence of genetics on medicine and dentistry is much more profound. Many chronic diseases occur more commonly than the rare Mendelian diseases and exhibit familial aggregation, but few are directly inherited according to simple Mendelian principles and most, if not all, have complex and multifactorial etiologies that are both genetic and environmental. These common disorders have a greater impact on the general health of the population than the Mendelian disorders. Periodontal disease and its variant, the early-onset periodontitis, appear to belong to this group, similar to its medical counterparts such as diabetes, coronary heart disease (and its risk factors such as hypertension and hypercholesterolemia, etc.), cancer, peptic ulcer, arthritis, epilepsy, and schizophrenia, among others. A new and burgeoning field of genetics, known as Genetic Epidemiology, has targeted the genetic study of these complex diseases and has accounted for recent successes in elucidating the etiologic heterogeneities of (at least) diabetes and coronary heart disease.[4-6] Current thinking about these diseases postulates a multifactorial model where a number of genes (i.e., polygenes) that may include one or a few major genes are involved to produce a predispositon or susceptibility that then interacts with environmental factors to produce the clinical disease phenotype.