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Commentary

Periodontal epidemiology: towards social science or molecular biology?

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Abstract – Terms such as 'molecular epidemiology' and 'genetic epidemiology' have been coined to depict the change from 'traditional epidemiology', concerned with disease determinants at the community or society level, over to 'modern epidemiology', which is concerned with determinants operating at the individual level or even below, i.e. at the organ, tissue, cell, or molecular level. In this commentary, we point out to the limitations of this development and suggest that more emphasis is placed on making the presumed causal disease models explicit, when investigating the relationship between putative determinants and disease. Understanding the disease processes at the micro-level is insufficient for understanding disease at the individual level; and disease patterns at the population level cannot be understood unless it is realized that individuals exist in a variety of contexts that cannot be reduced to individual attributes.

Key words: epidemiology; molecular biology; molecular epidemiology; periodontal diseases; trends

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Although a theoretical framework is crucial for the design and conduct of epidemiological studies, attempts to explicate the theories or models underlying such studies are few in dental research (1–3). However, absence of an explicit disease model does not mean absence of a model, and many important aspects of the *implicit* disease models can be perceived from external information. Only a few decades ago epidemiology was very much oriented towards the community and society – or macro-level epidemiology – whereas, nowadays, the orientation is increasingly towards risk factor epidemiology, and increasingly so at the micro-level (4, 5).

As a result, a debate has arisen among epidemiologists centering around claims that the rise of the paradigm of 'modern epidemiology' (Table 1) has been a 'mixed blessing' with major shortcomings (6). The criticism is that 'epidemiology has largely ceased to function as part of a multidisciplinary approach to understanding the causation of disease in populations and has become a set of generic methods for measuring associations of exposure and disease in individuals'. Modern epidemiology is accused of being 'more concerned with intricately modeling complex relationships among risk factors than with understanding their origins and implications for public health' (7). The critics note that although there are huge socioeconomic differences in health – differences that even continue to increase – 'modern epidemiologists rarely consider socioeconomic factors and the population perspective, except perhaps to occasionally adjust for social class in the analysis of the health effects of tobacco smoke, diet, and other lifestyle factors in individuals' (6).

Responses to these criticisms include comments that 'however well motivated, epidemiologists cannot rid the world of poverty'; that public health professionals 'do not have a license to tinker promiscuously with society' (which is seen to be the inevitable result if public health decisions are based on imperfect knowledge); and that 'the more knowledge we acquire of causal pathways at all

Table 1. Epidemiological paradigms: adapted from (6)

	Traditional epidemiology	Modern epidemiology
Motivation	Public health	Science
Level of study	Population	Individual/organ/tissue/cell/molecule
Context of study	Historical/cultural	Context free
Paradigms	Demography/social science	Clinical trial
Epistemological approach	Realist	Positivist
Epistemological strategy	Top down (structural)	Bottom up (reductionist)
Level of intervention	Population (upstream)	Individual (downstream)

points – from the ''most fundamental'' or ''ultimate'' social, political, and economic determinants to the molecular and biochemical determinants most proximal to disease occurrence – the better the foundation we lay for any effective public-health action' (8).

There can be little doubt that epidemiology has made a swing away from the 'upstream' societal perspective towards that of the more 'downstream' and proximal, individual disease causes. Terms such as 'molecular epidemiology' and 'genetic epidemiology' have been coined to depict this development (9). Seen in a historical perspective, the change of focus may be attributed to the replacement of the 'single-agent ''germ theories'' of disease with more complex models of ''host, agent, and environment'' ' (7) resulting from the transition from infectious disease epidemiology to chronic disease epidemiology (6, 7), coupled with political developments over the past few decades that favor individualism; and, not the least, the fact that molecular research is 'privileged as basic science, while population and clinical studies are regarded as the poor intellectual cousins' (10). These changes, which also concern dental epidemiology, are so strong that caveats have been voiced over the increasing tendency for health researchers to have their professional background in the natural sciences rather than in the health sciences (11). However, the hopes attached to the new paradigm may well turn out to be too high: 'now molecular biology offers the same kind of illusion as did the germ theory. It is the illusion that unarguable definitiveness and specificity of this extreme biological micro-level can explain everything…That was never true then and it is not true now, so long as our concern is with the dynamic disease process as it occurs within and across populations' (5).

Clearly, the gradual transition from 'traditional' epidemiology to 'modern' epidemiology also stems from a perception that traditional epidemiology is no longer a tool of choice for the identification of causes of disease (12). This view is, in our opinion, based on three key arguments: (i) that the causes sought are too subtle to be identified by 'crude' and 'insensitive' traditional epidemiology; (ii) that the inferential methods underlying traditional epidemiology are insufficient for the search for the upstream exposures; and (iii) that the response to the identification of an upstream cause is anyway always to go searching further downstream to identify the underlying mechanism.

Concerning the subtle causes, it is increasingly being argued that traditional epidemiology has led to the identification of the more conspicuous noninfectious disease determinants, and that all that is left from now are much 'subtler links between disease and environmental causes or lifestyles' (12). However, the element 'subtle' should not be equated with 'unimportant'. Provided exposure is frequent, small risks may give rise to many more cases than large risks associated with rare exposures (13, 14). The problem lies in the fact that small risks are harder to identify because they are more easily obscured by biases, uncertainties and other methodological weaknesses. A large question remains however, to what extent the 'modern' genetic and molecular epidemiologic methods are better alternatives in this aspect.

The full utilization of the traditional epidemiology approach has also been severely hampered by the limitations of the analytical tools available. Until a decade ago, analytical methods were essentially all based on single-level models, and this has effectively precluded the more realistic multi-level perspective on the design and analyses of epidemiological studies. In many circumstances it is neither possible nor desirable to reduce the exposures to individual attributes, because they operate at different higher aggregate levels. Examples might be the per capita sugar consumption, which could be a national statistic; or the exposure to water fluoride, which may concern a whole geographic area. Conversely, the disease outcomes, and many exposures, are observed at the individ-

ual level while traditional epidemiology strives to reach conclusions at the group level. Unfortunately, attempts to bring together individual-level outcomes and aggregate exposures in a traditional single-level analysis results in the ecological fallacy, which jeopardizes interpretation and inference. Awareness of this problem has made researchers most likely to utilize epidemiological study designs that disregard exposures occurring at more aggregate levels. However, in recent years, analytical tools have become available, which allow for the analysis of even rather complicated multilevel data (15, 16), and this will undoubtedly seriously widen the range of research questions that can be addressed.

The final argument against traditional epidemiology is essentially an argument for 'modern' epidemiology. The argument is that once an upstream cause has been identified, one should start searching for the downstream mechanisms involved. While it may be a matter of fact that this is what often happens, it is important to bear in mind that downstream knowledge is often not even necessary to interfere with the causal pathway. As an example, it may be much more important for the control of caries among school children to issue a policy against soft drink automats in primary schools than to attempt to control caries using individualized measures. Such a policy intervention might even have an additional benefit in combating childhood obesity.

The purpose of this commentary is to show how the paradigm shift has caused the implicit theoretical models for periodontitis to become increasingly focused towards refined exposure assessment and, not the least, individual susceptibility assessment. In light of this, we warn against the illusion that these novel molecular biologic techniques have the capacity to single-handedly elucidate periodontitis causation. One action needed to avoid this unwarranted belief is to bring the issue of causal models from the implicit to the explicit in etiologic periodontal research. Only if causal models or theories are explicated will it be possible to understand the powers and limitations of the research conducted.

Did anyone see the spider – or the cook?

It is not possible to discuss the implications of the turn of the epidemiological paradigm away from the societal perspective in favor of the molecular perspective without reference to a causal theory. As indicated above, explicit 'causal theories' are hard to find in dental epidemiology (1–3); what can be found is more likely a 'causal model'. The distinction between the two is not merely one of semantics. While a theory seeks to explain 'why' phenomena exist and interrelate, a model is less ambitious as it 'just' attempts to depict 'how' the phenomena interrelate. It thus remains a fact that the focus of both the two dominant causal models, the 'web of causation' introduced by MacMahon et al. (17), and the 'component cause model' introduced by Rothman (14) is to precisely to depict the complexity of causal element interrelationships. Both models were introduced for the purpose of accommodating the 'multifactorial' view on chronic disease causation, and, in case of Rothman's component cause model, to allow a distinction between 'component', 'sufficient' and 'necessary' causes, and provide a better means for understanding the concepts of confounding, effect modification, and strength of association. No explanations were provided with the causal web model as to why and how certain components were judged to necessitate inclusion in the model while others should be left out; just as no discussion was offered regarding the origin of the component causes in the component cause model. As eloquently noted by Krieger (7), 'these authors [MacMahon et al.] never invoked – and essentially proscribed – the imagery of the ''spider''. Similarly, in the case of Rothman's ''pies'', the ''cook'' is notably absent'.

However, models are necessarily built on some implicit theoretical considerations as to which elements should be included and how their interrelationships might be. A closer inspection of the causal web model reveals that it 'inevitably focuses attention on those risk factors ''closest'' to the ''outcome'' under investigation, and these typically translate to the direct biological causes of disease in individuals' (7). This matter of fact is frequently argued as being expedient even from a public health point of view as illustrated by a quote from Rothman et al. (8): 'Generally, the further upstream we move from the occurrence of disease towards root causes, the less secure our inferences about the causal path to disease become. Even if our inference is correct, moreover, intervention with respect to upstream causes may be less efficient and therefore less effective than intervention closer to disease occurrence'. Undoubtedly, this viewpoint

is driven by the imagery of the 'spider' web model of disease causation. Visualizing a spider's web, it is relatively easy to accept that the closer to the center of the web (the closer to the disease outcome) the strands of the web are cut (i.e. the causal pathways are blocked), the fewer will be the alternative routes to the center of the web, and the more disease is prevented.

In a political and scientific climate that favors individualism and considers socioeconomic factors 'not easily modifiable' and 'too political' to address (6), it is not surprising to observe that the inability of individual 'life-style' factors to explain disease occurrence at the population level has led to a firm belief that further explanations are found in biological variation between individuals, i.e. in the biochemical, molecular and genetic make-up of individuals. The currently dominant paradigm thus holds that the 'ultimate strand in the causal web' may be identified (and subsequently cut) only by means of dissecting the diseases using molecular and genetic techniques.

Parallels in periodontal epidemiology

The sketched development has close parallels in periodontal epidemiology. In the 1950s and 1960s the 'founding' father of periodontal epidemiology, A.L. Russell, made it his hallmark always to provide an opportunity for comparison of periodontal disease scores across populations (18), just as he was very much aware of the epidemiological group perspective (19). Russell examined hundreds of thousands of persons across a wide range of populations (for review see (20, 21)), and many other researchers used his methodology; e.g. Sheiham (22–24) in an attempt to describe the between-population differences and identify their possible causes among oral hygiene parameters as well as dietary and nutritional factors. Based on these studies Russell concluded that '90 per cent or more of the variance in the P.I. is accounted for by the combined effect of age and oral hygiene, no matter which combination of populations is studied' (25), thus leaving very little variation in periodontal disease levels to be accounted for by factors other than age and poor oral hygiene. Russell's conclusion was based on analyses of the relationship between group mean scores for the Periodontal Index and group mean scores for oral hygiene. This methodology turned out to be a vulnerable point, which effectively resulted in the fall of the population perspective on periodontal epidemiology. One of the major criticisms of Russell's methodology was the use of an index, which amalgamated signs of gingivitis and signs of periodontal destruction (26) as these could be demonstrated to be 'two distinct factors, namely periodontitis and gingivitis' (27). Critics of Russell's approach also pointed out that the aggregation of tooth-based scores into mean mouth scores and subsequently into mean group scores resulted in most of the variation in PI scores effectively being eliminated before the analysis (20, 28), and concealed 'the shape of any characteristic distribution that may exist' (28). Although Russell had noted that 'these distributions [of the individual mean PI values] tend to show pronounced right skewness', he nevertheless considered that 'normal constants are ordinarily appropriate' (18). This conclusion became a focus point for much criticism in the early 1980s when epidemiological studies emerged which described apparent differences between individuals in their susceptibility to various forms of periodontal diseases (29–32). Even so, it is very unfortunate that Russell's idea of a population perspective on periodontal disease causation could not withstand the criticisms that followed from the 'faulty' aggregation of the data and the amalgamation of the signs of periodontal diseases.

In the late 1970s, Löe et al. (33–35) described the periodontal epidemiological findings among Sri Lankan tea-estate workers and Norwegian academics. While the study populations had been chosen to 'show geographical, racial, cultural, socio-economic and educational differences and … represent extremes both as to general health care delivery systems and to dental care', the population perspective was never really invoked. Rather, within-group variation among the study groups became an area of focus when three distinct patterns of attachment loss were described among the Sri Lankan study group (36). These observations corroborated other studies noting a considerable inter- and intra-individual variation in the parameters of periodontal destruction (30–32, 37). Moreover, the dominant view of poor oral hygiene being the only main cause of periodontitis was increasingly challenged by observations of unexpectedly low levels of disease among populations in which the oral hygiene conditions were very poor (29, 32, 38).

This development has resulted in a wealth of studies focused on the description and analysis of the possible causes of the inter- and intra-individual variation in the parameters of periodontitis (for

review see (20)). Two main lines of research can be identified: one line concentrates on the study of the 'infectious agent', while the other concentrates on the 'host response'. Remarkably little periodontal research is focused to more 'upstream' causes. Perhaps this is because of the fact that periodontitis is usually defined as 'an infectious disease' (39) which is understood as a disease 'with microbial dental plaque as the initiator' (40). The apparent failure of the concept of 'poor oral hygiene' to explain the epidemiological features of periodontitis has effectively precluded investigation of 'upstream' causes of periodontitis, and has caused inquiries to be devoted to 'downstream' causes of variation, e.g. within the oral hygiene constituents. This research has mainly centered on the identification of single periodontal pathogens, the elucidation of their virulence factors, and, to a lesser extent, the characterization of the microbial plaque composition and ecology (41). The burst hypothesis (42) and technological developments such as the polymerase chain reaction (PCR) (43, 44) and the DNA checkerboard technique (45) have paved the way for a refinement in the search for the microbial causes. This search has resulted in a rapid change in the causal models within just a few decades – from the 'nonspecific plaque hypothesis' over to the 'specific plaque hypothesis' and to the 'ecological plaque hypothesis' (46–48).

The other line of inquiry has been devoted to variations in the host response to the presence of a microbial plaque along the gingival tissues, primarily related to neutrophil biology (49–51), lymphocyte biology (52), humoral responses (53, 54), cytokine biology (55–57) and, more recently, to the genetic variations underlying different host responses (58–63).

Not only has the focus of periodontal research changed from the population perspective to the individual and intra-individual perspective, but also the study designs used have changed accordingly. Rather than focusing on upstream population contrasts, as attempted by Russell (25), periodontal research is almost entirely focused on contrasting individual cases and noncases, or even moving downstream to contrast diseased and nondiseased sites within individuals (64–71). Such analytical approaches necessarily assume that sick populations may be characterized by a summation of sick individuals who, in turn, are made up of sick sites.

However, almost two decades ago, Rose (13, 72) pointed out that disease causation involves two rather distinct questions – one pertaining to the causes of individual cases (sick individuals) and the other pertaining to the causes of incidence rates (sick populations) – and demonstrated that the answers to these questions are not necessarily the same: 'The determinants of incidence are not necessarily the same as the causes of cases' (72). This means that 'sick populations' are not simply a summation of 'sick individuals' (73). Pertaining to the field of periodontology, we might add that 'sick individuals' are not merely a summation of 'sick teeth'. Rose's observation has very important implications for the utilization of the results of epidemiologic research. When the causal question relates to the occurrence of cases, intervention and prevention is focused on identifying 'high-risk susceptible individuals and to offer them some individual protection' (72). In contrast, if the search is for the causes of incidence, the preventive response is to control the determinants of incidence in the population as a whole. Rose (13) provided ample evidence that the intense focus on individual susceptibility factors may not bring about changes in the occurrence of some of the major diseases, as many more cases may be generated when a lot of people are exposed to a small risk than when a few are exposed to a high risk.

Even so, there is now a deep-rooted and all-pervading belief among large sections of the periodontal scientific community that the answers to the periodontitis problem may be found by exploration of the micro-level domain of the host–parasites interaction: 'When we learn what these molecules do and how they do it and when we apply the tools of molecular biology to manipulate and regulate them, we may well be on our way to the control and the ultimate cure of not only periodontal diseases but other chronic degenerative inflammatory diseases that plaque mankind as well' (74). Such statements serve to illustrate how devoted causal thinking in periodontology has become to scientific issues that are better described as related to periodontitis pathogenesis than to periodontitis etiology. Evidently, the periodontal scientific community has also come to pursue the 'ultimate strand in the causal web'.

How far can the golden era of biology take us?

In line with the perception of being in a 'golden era of biology' (75), the terms 'molecular epidemiol-

ogy' and 'genetic epidemiology' have been coined to depict how these techniques should be integrated into classical epidemiology to facilitate and advance the study of disease causation. The rate at which our knowledge of molecular biology and genetic variation has expanded has even 'excited hegemonic bids by some laboratory scientists who foresee … that classical exposure-disease epidemiology will be largely superceded' [and that] 'modern molecular techniques' [will] 'allow us… to redirect our focus from identifying risks in the exogenous environment to identifying high-risk individuals and then making personalized risk assessments' (9).

There are a number of good reasons why such claims may be considered rather presumptuous. First of all, there is a profound belief that the data generated by molecular methods (i.e. laboratory data) may 'increase the validity and the precision of the measurement of the biologically relevant exposure variables' (76), i.e. provide 'harder' data. However, these methods are indeed susceptible to 'the circumstances in which biological samples are taken, processed, stored and analyzed; the technical aspects of the assays, etc.' (76); e.g. it is clear that the design of PCR primers and the detection of PCR products may be subject to considerable systematic as well as unsystematic errors (77, 78). Moreover, 'molecular epidemiology' is no less prone to bias and confounding than is traditional epidemiology (76, 79–86). In fact, systematic errors may be even more deleterious in 'molecular epidemiology' than in traditional epidemiology because of 'the unknown and often unpredictable ways in which biochemical and molecular markers are associated with exposure, on the one side, and disease, on the other' (82). Whatever the reason may be, it remains a remarkable fact that numerous associations between DNA polymorphisms and variation in disease susceptibility have been reported that have subsequently turned out to be irreproducible (87). Secondly, the claim rests on a rather narrow view of disease causation. In the medical field it is widely agreed that molecular and genetic 'bio-markers' may play a role in epidemiology mainly with respect to three distinct issues: the determination of 'internal exposure' (the biologically effective dose), the measurement of 'the early biologic response' (pre-clinical disease), and the measurement of 'effect-modifying host characteristics' (9, 81). As such, they may be helpful in elaborating the measurement of the effective internal exposures, in elucidating the biological processes involved in disease causation and development and in identifying variations in individual susceptibility (endogenous risk markers) to exogenous exposures (88, 89). In broad terms, the molecular and genetic information and the techniques available allow us to view and study the biological processes involved at a much higher resolution. However, they may have little to offer in terms of the identification of the 'exogenous' modifiable causes of disease. Finally, an important drawback relates to the concept of risk in relation to the desire to identify 'high-risk individuals' (or 'high-risk sites'). Inherently, the risk of an individual (or a site) is a dichotomy: either the person (site) will get the disease, in which case his/her risk is 1; or the person (site) will remain disease-free, in which case the risk is 0. The notion of risk as a continuous measure applies only to a group, and the average risk indicates the proportion of subjects (or sites) in whom a sufficient cause has assembled (14). The risk estimates derived from epidemiologic models do not represent measures of individual risks but denote the average risk among a group of subjects (or sites) with similar exposure characteristics (90). The individual risk estimates that may be derived from statistical models tend, moreover, to cluster around 0, and it is not really possible to single out 'high-risk' individuals based on such models, as there is a considerable overlap in the estimated risks between those who develop disease and those who do not (90). Pertaining to genetic epidemiology, it has thus been noted that 'the absence of a ''genetic risk factor'' rarely (if ever) signifies that an individual's probability of developing disease is much below ''average'' (90). Nevertheless, the hopes and aspirations in the periodontal scientific community remain high: they include the possibility of subclassification of 'the multiple forms of chronic periodontitis into discrete microorganism/host genetic polymorphism groups' (91) and the conviction that 'there will ultimately be a revised approach to patient care that will incorporate genetic information on a regular basis' (92).

Example: 'Racialism' in periodontal research

How far astray can the 'molecular' paradigm take us – if care is not exercised – may be illustrated by an example. It is a longstanding observation in periodontal epidemiology that major between-

group contrasts exist with respect to the distribution of periodontitis: African-American individuals have repeatedly been reported to harbor more widespread and severe signs of periodontitis than others, such as Hispanics, Asians or Caucasians (93–103). Recent research has even indicated that the 'disparities in periodontitis between African-Americans and whites are pervasive and have increased over time' (104). These observations have led to a massive research into the possible biological explanations for these 'racial' differences in the occurrence of periodontitis (59, 94, 105–120). Often these investigations have even resulted in speculations on a genetic background for the differences observed (116–120), as it is frequently advocated that 'racial' differences are genetically based (121–123). However, 'race' is neither genetically nor biologically defined (124). There is by far more genetic variation between subjects within a racially defined group than there is between different 'races' (123–129). Moreover, it is remarkable to note that the search for the genetically predisposing factors usually concerns minority groups: 'since we do not know about the genetic variants that predispose persons to common chronic diseases, one might assume that arguments for the existence of genetic predispositions would be made for all population groups equally. The reality is very different. Minority groups, particularly blacks in the United States, are assumed to be genetically predisposed to virtually all common chronic diseases. Genes are regularly proposed as the cause when no genetic data have been obtained, and the social and biologic factors remain hopelessly confounded' (129). 'Race' is best understood as a 'social classification' (130) based mainly on skin color and facial features in a 'race-conscious society that conditions most aspects of our daily life experiences and results in profound differences in life chances' (121), which should not be used as a proxy for genetic or biological variation (123, 130). Instead it should be realized that 'a person's race/ethnicity is fixed prior to his/her measured social, physiologic, and psychological status; all of these measurable factors are downstream of the exposure in a racially stratified society … [and therefore] … virtually all potential covariates in analyses of racial/ethnic disparities are causal intermediates' (131).

While it is extensively documented that classifications based on 'race' capture major variation in disease occurrence it is also amply documented that the causes of this variation should not be sought in biological variation internal to the individuals (123, 131, 132). 'Some traits, such as skin color vary in a strikingly systematic pattern. The inference does not follow, however, that genetic variation among human populations falls into racial categories or that race, as we currently define it, provides an effective system for summarizing that variation.' (129). Rather, a wealth of external factors seems to capture most of the variation according to the different races. In a recent re-analysis of US national data it was suggested that the causes of the observed 'racial' disparities in periodontal health might be sought in differences in socioeconomic position, social factors, cultural factors, behavioral factors, and in discrimination, segregation and racism (104).

When scientists often perceive their activities as being driven by an innocent wish to know the truth, they overlook the fact that both the questions asked and the methods used to obtain answers are highly value-laden. 'There is a tendency for scientists to ignore the messy social implications of what they do. At the extreme, the argument is made that 'we just tell the truth about nature', and its negative consequences are political problems that do not concern us. Whether or not such a position is defensible from an ethical point of view, the debate over race cannot be sidestepped so easily. Race already has a meaning. To invoke the authority of genomic science in the debate over the value of race as a category of nature is to accept the social meaning as well' (129). Therefore, the choice to focus on the downstream causes of disease is as value-laden as the choice to explore the more upstream causes.

Concluding remarks: sick teeth, sick individuals and sick populations

In the previous sections we have illustrated how the 'spider's web' metaphor commonly invoked to accommodate the 'multicausal' nature of diseases, including periodontitis, has contributed to direct health sciences toward the center of the web in search for the ultimate strand to cut in order to block the road to disease. When combined with a reductionist perspective on the health sciences, according to which the 'whole' is best understood by means of studies of its constituent components, it is understandable that the emergence of new and revolutionary molecular and genetic techniques has driven medical as well as dental sciences

'downstream' in search for the center of the spider's web.

However, as the 'race' example hopefully shows, this 'downstream' approach grossly fails in its inability to embrace the existence of between-population differences and over-time changes in the occurrence of periodontitis. Explanations for these extremely important epidemiological observations thus necessitate the involvement of the 'spider' or the 'cook'. Rather than just going 'downstream', we should be more aware of the 'upstream' causes of periodontitis. Krieger (7) suggested the development of an 'eco-social epidemiologic theory – one that embraces population-level thinking and rejects the underlying assumptions of biomedical individualism without discarding biology' to accomplish this. Using a paraphrase of Diez-Roux (73), we should develop models and methods that integrate teeth in individuals and individuals within their groups or social contexts, that examine the interacting effects of both tooth-, individual- and group-level variables (104, 133), and that take into account the role of interactions between individuals in shaping the distribution of periodontitis. 'Sick teeth' are nested in 'sick individuals', and 'sick individuals' are nested within 'sick populations'. Understanding the processes at the tooth level is insufficient for understanding disease at the individual level; and disease patterns at the population level cannot be understood unless it is realized that individuals exist in a variety of circumstances that cannot be reduced to individual attributes (3).

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