A Practice Approach for Identifying Previously Unsuspected Environmental Contributors to Systemic Lupus Erythematosus and Other Complex Diseases

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Existing medical records and health surveys provide insights into potential environmental contributors to complex chronic diseases. Those recognizable risks (e.g., workplace exposures and behaviors including smoking) do not, however, exhaust the domain of potential environmental contributors. Qualitative ethnographic investigation can be used to generate statistically testable hypotheses about environmental contributors to complex disease that otherwise would not be recognized as such. Consequently, we can empirically specify lifestyle beliefs and behaviors usually summarized by proxy identities such as race, ethnicity, gender, class, and culture. The investigation of potential environmental contributors to complex diseases may be particularly useful in confirming or disconfirming suggestive or established linkages and for indicating the kind of gene–environment interaction that may be involved. *Key words:* **complex disease, gene–environment interaction, research design.** *Environ Health Perspect* **111:593–597 (2003). doi:10.1289/ehp.5665 Available via** *http://dx.doi.org/* **[Online 30 October 2002]**

Sequencing of the human genome and development of powerful analytic techniques such as neural networks have greatly improved our ability to identify genetic contributors to disease susceptibility, particularly for complex diseases in which those contributors are non-Mendelian. However, the additional role of other nongenetic environmental factors can confuse both those environmental effects (which may manifest only in genetically susceptible individuals) and genetic effects (which may manifest only when there is a history of exposure to environmental contributors) (Ottman 1996). Consequently, the investigation of environmental factors may be especially useful in identifying and confirming a specific gene, haplotype, or polygenic combination responsible for disease susceptibility and in understanding the functional mechanism by which that susceptibility is expressed as a disease. Thus, although the analysis of gene–environmental interaction is less problematic after a specific genetic contributor to a complex disease has been identified, the study of environmental contributors can be a valuable aid in making that identification, particularly when linkages are established based on genome scans and marker data are available for families (Ottman 1996). The last 2 years have seen rapid development of methods to analyze such gene–environmental interactions in a variety of study designs [e.g., Blangero et al. 2001 (pedigrees); Gauderman and Siegmund 2001 (sib pairs); Eaves and Sullivan 2001 (parent-child triads); Andrieu and Goldstein 1998 (for a review of earlier methods)].

Getting Beyond the Usual Suspects

These new, powerful analytic techniques for including gene–environment interaction are pointless, however, if the environmental measures being used are ill conceived or imprecise. Unlike genomic data, however, environmental data are not discretely segmented into linear sequences of base pairs that can be read using a standardized technology. Although one can determine "the" genetic factor by moving along this linear genome using an increasing gradient of evidence for association, there is no clear "next" environmental factor to consider if the current candidate is suggestive but not convincing. Instead, identification of candidate environmental factors for quantitative analysis often depends on qualitative observation and surmise.

Before we can count manifestations of an environmental factor and put that number in a 2 × 2 table, we first must recognize it as significant enough to enumerate and correlate. To a great extent, that recognition is both structured and limited by our preexisting cultural and linguistic categories for identifying behaviors and exposures as discrete phenomena. Linguistic anthropologists long have observed that those categories vary from one language community to another, serving to limit speakers' intuitive awareness of the world around them (Duranti 1997). No single language or culture provides a comprehensive or objective categorization of all possible human behaviors and exposures that may contribute to susceptibility to, or higher risks for, a complex disease.

Most efforts to identify environmental contributors have focused on the "usual suspects"—behaviors and exposures that have been recognized as discrete categories that may affect health (Cooper et al. 1999). Researchers often decontextualize these usual suspects from the social and cultural settings in which they occur, analyzing them as discrete, isolated events rather than as components of patterned lifestyles. Arguably, there is a need to develop a more explicit method for identifying candidate environmental contributors to complex diseases beyond those factors already categorized discretely in medical and other records (e.g., medications, viral exposures, birth order, occupations, geographic residences, environmental toxins). Such an approach would be complementary to ongoing genetic linkage studies for which candidate genes or haplotypes have been suggested or established but not confirmed. For example, linkage studies of systemic lupus erythematosus (SLE) pedigrees have identified more than 50 established or suggestive linkages, although none of these has yet been confirmed by the molecular characterization of an SLE disease gene (Kelly et al. 2002). At the same time, environmental associations with such existing categories as smoking, birth order, and Epstein-Barr virus have been suggested for SLE. These linkages usually dominate in one ethnicity or another and often are found in some sample collections but not in all, suggesting that the responsible polymorphisms may vary both by the frequency of genetic variation within a given human population (variation by ethnic or other social identity) and by the frequency of genetic variation among the affected participants (often members of multiplex families from the same geographic region) who happen to donate samples (variation by family and locality).

A further possibility, however, is that some of this observed variation is the result of common environmental contributors that are present only in particular human populations or in particular sample collections. Environmental contributors specific to

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members of some ethnic populations or to members of some families and localities could be an additional reason that linkage studies using different populations and sample collections have found different candidate loci for SLE. Thus, population- and collection-specific environmental contributors could help explain why different polymorphisms appear to be associated with SLE in each linkage study, either because SLE is environmentally triggered in more than one way and each environmental trigger involves a different genetic loci, or because the various environmental contributors to SLE are somewhat stronger than currently expected and result in spurious genetic associations that are artifacts of unrelated linkage disequilibrium within specific populations and among donors to particular sample collections. In either case, investigation of environmental contributors possibly specific to populations, and collection donors can be crucial to confirming genetic associations as SLE polymorphisms.

Indeed, many complex diseases occur at differing rates and severities depending on the population in question. For example, it has been known for some time that SLE is a complex disease 10 times more likely to affect women than men and is expressed at different rates in different ethnic populations (Fessel 1988). Those gender- and population-specific differentials clearly have both genetic and environmental contributors, with different combinations of these contributors resulting in specific affected individuals (Maddison 1999). Summary terms such as gender, race, ethnicity, class, and culture often are used as proxies for perceived differences in lifestyle. These categories, however, both conceal specific beliefs and actions that may directly contribute to disease susceptibility and obscure significant variation among persons within each category.

Practice Theory

Alternatives to the use of proxy terms such as race and ethnicity in describing behavior are available in social science. Practice theory is a prominent approach in sociology and anthropology (Bourdieu 1977, 1990; Certeau 1984) that uses qualitative ethnographic observations and interviews to discover the *habitus* that integrates the details of everyday routine as a holistic lived experience (Brown and Szeman 2000). Habitus is composed of internalized schemas based on a lifetime of socialization and experience that individuals use to perceive, interpret, and take action as they encounter new experiences. As such, habitus is largely unavailable to conscious awareness or manipulation, much like the internalized grammatical and other structures of human language.

As Bourdieu (1984) describes the schemas of habitus,

> . . . they embed what some would mistakenly call *values* in the most automatic gestures or the apparently most insignificant techniques of the body—ways of walking or blowing one's nose, ways of eating or talking—and engage the most fundamental principles of construction and evaluation of the social world, those most likely to express the division of labor (between the classes, age groups, and the sexes) or the division of the work of domination . . . . (p. 466)

Thus, specific forms of habitus are shared by individuals who have had similar experiences and social "conditioning," that is, those who comprise analytically distinct social classes or categories. Those categories may be labeled cultural, ethnic, economic, religious, gender specific, geographic, or whatever (and often are), but their functional existence is primarily due to a shared set of practices derived from their common habitus.

That functional relation between habitus and the specific lifestyles that are its products facilitates the empirical investigation of beliefs and behaviors that may contribute to the expression of a complex disease such as SLE. Unlike more general covering terms such as "culture" or "society," the concept of habitus directly implicates observable collective practices evidenced by individual human action and interaction rather than by intangible abstract collective entities reified by symbolic labels or identities. Moreover, because of the largely unconscious nature of habitus, the practices, lifestyles, and social conditions that it integrates are not subject to the conscious manipulation or "politics" to which more explicit ethnic, economic, and other cultural and social identities are subjected both in academic discourse and in public health debates. Although a relationship exists between those publicly salient identities (e.g., race) and the social conditions that form a common habitus among individuals (the idea of race being one of the conditions that continues to shape social experience in the United States as well as reflect it), the practices and lifestyles that manifest in an individual life are not reducible to any one such label (Certeau 1984). Practice theory is an ethnographic approach that identifies specific everyday routines that structure the social life of communities and analyzes the ways in which these routines are linked as distinctive lifestyles. Indeed, practice theory contrasts significantly with the traditional reliance of social scientists and epidemiologists on abstract cultural, ethnic, economic, and other labels as imperfect proxies for the integration of everyday practices that add up to distinctive lifestyles that may differentially contribute to such complex diseases as SLE (Lindbladh et al. 1996).

Habitus and Health

Although somewhat novel in health research, a practice approach has been applied previously to studies of disease. Virtanen et al. (2000) and Cockerham (2000), for example, have used practice theory to identify specific practices that are integrated into lifestyles that contribute to employee sickness absence in Finland and alcoholism in Russia, respectively. Both find that social conditions (life chances) that shape a common habitus are more functionally central to the illness in question than is individual agency (life choices). Crossley and Crossley (2001), in a study of how people with mental illnesses talk about their diseases over a 40-year period, use practice theory to show that changes in patients' representations of their illnesses are primarily a function of their common experiential relationship to broader transformations in social conditions during that historical period. Gordon (2000) uses practice theory to specify the common schemas used by members of the Fulani community in sub-Saharan Africa to identify particular symptoms as manifestations of specific named illnesses and then take culturally appropriate action to treat each, in the process reaffirming their identities as "Fulani," in contrast to those of other surrounding communities as well as Euro-American biomedicine.

In each of these examples, practice theory uses the empirical evidence of specific patterns of situated behavior to investigate the ways in which a variety of social conditions (including cultural tradition, differential relations of economic and political power, and family and other local social structures) are combined in the choices that individuals (each of whom has a specific personal history that informs those choices) make about how to construct their social lives. Arguably, this is a more functional, naturalistic approach to identifying environmental contributors to complex disease than is isolating particular social conditions (e.g., socioeconomic status or ethnicity) and then categorizing individuals under those abstract rubrics.

It is important to note that similarities in habitus (i.e., schemas for perceiving, interpreting, and initiating behaviors) and the lifestyles of patterned behaviors it motivates are units of analysis too complex for quantitative epidemiologic analysis, composed as they are of multiple beliefs and practices. The advantage in isolating such common patterns, however, is that this considerably narrows the range of human action and interaction within which potential contributing environmental factors are to be inferred. Those more specific inferences then can be tested using established quantitative epidemiologic methods because it assumes that lifestyles are integrated combinations of behaviors rather than treating behaviors as isolated (although repeated) actions.

At the same time, it is likely that more than one environmental factor may contribute to the occurrence of a complex disease, that different combinations of those factors may have similar phenotypic effects in persons with genetic predispositions for the disease, and that different genetic predispositions for the disease may be triggered by different environmental contributors. In the case of sporadic complex diseases in which environmental factors have the primary causative role, such as in most types of cancers, a constellation of those factors that are summarized as "long-lasting family habits" may be implicated (Lichtenstein et al. 2000). A practice approach will identify only some of the environmental factors that may contribute to a complex disease (others are outside the realm of everyday routine that practice theory explores), but arguably will prove to be a powerful method for identifying that subset of linked factors (usually subsumed as lifestyle or culture) that is most resistant to more traditional quantitative epidemiologic investigation. In particular, a practice approach will be more sensitive to weaker, incremental environmental contributors that are localized in relatively small populations.

In addition to identifying novel environmental factors, a practice approach also can help us differentiate alternate forms of previously identified factors. Smoking, for example, is not necessarily a singular behavior but may be modified by different practices associated with it. In many Euro-American contexts, for example, smoking often is associated with stress such that smoking may be a proxy for other stress-related behaviors and physiologic states. In contrast, in many Native American contexts, smoking often is associated with more meditative ritual or religious activities, whereas at the same time chain-smoking tends necessarily to be limited by the less affluent economic circumstances of many Native people. Indeed, tobacco use is constructed differently in each cultural context in which it has become pervasive (Hilton 2000), suggesting that local practices may function to modify its carcinogenic and other physiologic effects. Thus, even such a recognizable environmental factor as smoking may be modified significantly by practices derived from a distinctive habitus, as may be other factors such as alcohol and caffeine consumption that are deeply engrained in everyday lifestyles.

Similarly, the as-yet-unexplained phenomenon of birth order in SLE incidence, for example, also may result from a combination of physiologic and social contributors. Certainly, we know that the experiences of first-borns are somewhat different from those of subsequent children—and that the experiences of singleton children are somewhat different from those with siblings. By relating those experiential differences (which are constructed in large part both by parents and by the social conditions in which children are raised) to an underlying habitus (Miller and Goodnow 1995), we may better understand the relationship between biologic and environmental factors in the occurrence of SLE.

This effort, however, requires more than just traditional epidemiologic methods. As Bourdieu (1984) has observed,

> Social subjects comprehend the social world which comprehends them. This means that they cannot be characterized simply in terms of material properties, starting with the body, which can be counted and measured like any other object in the physical world. (p. 482)

Thus, before we can quantify environmental contributors, we must first recognize them as such and also understand how they manifest in practice, which necessarily requires a research design that combines both qualitative and quantitative analyses.

As Kaufman and Cooper (2001) recently noted in evaluating strategies for analyzing the effects of race and ethnicity on health,

> If common epidemiologic methods are limited in their utility for some hypotheses about race and health, might there exist alternative methods that would be preferable? If one wished to explore an etiologic hypothesis about, for example, a coping strategy that is culturally specific to African Americans, it seems likely that the tools of history, anthropology, and political economy are more appropriate than epidemiologic tools that were developed for assignable exposures. . . . Epidemiologists ought not to be troubled by this proposition that some questions are best answered by resorting to other disciplinary sources of knowledge. Rather, this simply is an acknowledgement of the rather incontrovertible notion that, when encountering a nail, one should put intellectual provincialism aside and pick up a hammer. (pp. 291–292)

This perspective suggests that investigation of environmental contributors to complex diseases requires a hybrid design that includes both qualitative and quantitative approaches.

Qualitative and Quantitative Hybrid Design

When using qualitative techniques to generate environmental hypotheses, participants should be selected on the basis of similarities and contrasts that should assist us in identifying differing practices resulting from differences in participants' habitus. For a qualitative design, this is a question of establishing criteria that create similarities and contrasts likely to allow ethnographers to recognize distinct practices among the people we study, not to validate those as statistically significant (which is the task of a subsequent quantitative survey and analysis of a larger sample of affected and control individuals).

Genetic linkage studies already recruit participants for biologic analysis who also have social and cultural contrasts useful for ethnographic analysis. Linkages based on sibling or family studies often comprise pedigrees that cluster in specific geographic localities and that reflect either common or contrasting constructions of gender, class, ethnicity, and culture. Pedigrees on the basis of which linkages are suggested or established can be selected for qualitative, ethnographic investigation to emphasize those similarities and contrasts. There may be reason to select affected participants whose everyday lives are not yet significantly limited by SLE so that we can record as much information as possible about routines that may have preceded their initial diagnoses. Nonetheless, Bourdieu's theory of practice suggests that, even in the case of severe disease, traces of prior practices will remain in the everyday lives of those whose lives are physically limited by SLE symptoms.

Unaffected family members and matched, unrelated controls also can be recruited to augment those comparisons. This aspect of study design will amplify the habitus of a relatively small number of those affected by studying their relatives and neighbors who have lived under similar social conditions and so developed similar experiences and expectations to guide their everyday actions. We believe this is a better procedure than the alternative (i.e., ethnographically studying a larger number of affected individuals from more pedigrees distributed across more localities) because it will allow us to focus in finer detail on the practices derived from the habitus of each locality as a whole rather than only the individual domains of those affected. Although in this article we have focused on locally defined populations, populations in transition (migration or Westernization) also could be studied using this approach, identifying the habitus associated with the geographically situated transition process.

Finally, contrasts in the ethnicities of study participants would serve as an initial proxy for specific differences in cultural practices that may contribute to the different rates of disease incidence in those populations. We anticipate that differences between family membership, ethnic membership, and geographic residence will underlie most cultural differences in behavior and environmental exposure, although we also anticipate some potentially important differences among persons of the same family, ethnicity, and locality.

Ethnographic methods for collecting and analyzing fine-grained qualitative data provide a means for identifying these similarities and contrasts. The participant-observation method of collecting qualitative data entails spending extended periods of time interacting in the community being studied, learning through that interaction how to act appropriately as a community member. Thus,

participant-observation ethnography is well suited for learning the schemas or experiential guidelines that constitute habitus and prefigure everyday practices that may contribute to disease susceptibility. Ethnographers spend extensive periods of time with study participants, observing and recording information on everyday routines as well as collecting detailed life histories. In addition, life histories elicited from participants can serve both to identify prior and continuing practices and to document the ways in which participants perceive their lives (Goodson 2001). The latter could be important evidence of the ways in which people explicitly construct beliefs, rationales, and explanations for their lifestyles (although, following Bourdieu, we know that these will be only partial reflections of the full extent of everyday practice in a given community).

The combination of ethnographic observation and life histories would give the approach both prospective and retrospective dimensions. Multiple related and unrelated controls for each of the individuals affected, who vary in age but are matched for other characteristics (e.g., locality, socioeconomic status, ethnicity, gender, culture), could assist investigators in detailing generational variations within a particular habitus or lifestyle, allowing investigators to extrapolate retrospectively the time perspective of the study beyond its prospective ethnographic duration. Indeed, recruiting larger numbers of unaffected controls may be a particularly useful surrogate for identifying environmental contributors among relatively small numbers of affected individuals in the case of complex diseases in which the absence of genetic susceptibility eliminates or greatly lowers disease risk.

Hypothesis Generation and Testing

The environmental hypotheses themselves will be based on extrapolations of the implications of situated practices. The implications of a practice (e.g., smoking in a particular manner in a specific sociocultural context) may not be fully understood if decontextualized or analyzed without considering how the practice is integrated into the habitus that structures the lifestyles of members of a given community. It also is possible that the same practice may have different implications for environmental contributors in differing contexts and, equally, that differing practices may have similar implications because of how they are modified by context.

Clearly, if a practice is present in all affected individuals and in none of the controls, then analysis is moot, although this is unlikely to occur if only because a practice is seldom totally present or absent in an individual's life—rather, it is a matter degree. The intent here is perhaps to distinguish between a real tendency and wishful thinking and not to prove or disprove anything. The caveat is that the samples, at this stage, are very small. Rigorous analysis will follow in a broader survey of a larger number of affected individuals and unaffected related and unrelated controls. The criteria for selecting suitable variables for that survey are, first, that there is an apparent difference in the variable, either *a*) between affected and unaffected individuals; *b*) between, on one side, pedigree members (both affected and unaffected) and, on the other side, their matched but unrelated, unaffected controls in a specific locality; *c*) between, on one side, pedigree members (both affected and unaffected) and their unrelated, unaffected controls and, on the other side, members of other pedigrees and their matched controls; or *d*) between members of pedigrees (both affected and unaffected) in a particular linkage and members of pedigrees in other linkages; and second, that in all cases the variable can be measured easily and unambiguously using a mailed survey or telephone interview format.

As Ottman (1996) has noted, environmental contributors that depend on genetic predispositions will not produce straightforward evidence. Thus, the results of our survey will not necessarily implicate a specific environmental factor in SLE. Instead, our results will suggest various possible relationships between the environmental factors and SLE and between the environmental factors and genetic factors. Some of those will be as follows:

a) Where an environmental factor is present only in affected individuals (regardless of linkage) but absent in unaffected individuals (including first-degree relatives), this may be taken as an independent contributor to disease. The factor may be present only in affected individuals in particular pedigrees (and not in others) because of differences in local conditions rather than differences in gene–environment interaction. Demonstrating that an environmental contributor is independent also may mean that some presumed linkages may be artifacts of the manner in which it is found among pedigrees that happen to share a non–disease-related genetic similarity.

b) Where an environmental factor is present in affected individuals in one pedigree and unaffected first-degree relatives but absent in controls for that pedigree, this may be taken as a family-specific factor that may contribute to disease. If it is present in both affected and unaffected individuals for more than one pedigree or for more than one linkage or for both linked and unlinked pedigrees, this is incrementally stronger evidence for its contribution to disease. If it is present in multiple pedigrees for only one linkage, however, this constitutes supporting evidence both for its contribution to disease in a gene-interaction model and for the validity of that linkage as having a disease gene(s).

c) Where an environmental factor is present in affected individuals in one pedigree, unaffected first-degree relatives, and unaffected, unrelated controls for that pedigree, it may be taken as a community- or locality-specific factor that may be a contributor to disease. If it is present in both affected and unaffected individuals for more than one pedigree or for more than one linkage or for both linked and unlinked pedigrees, this is incrementally stronger evidence for its contribution to disease. If it is present in multiple pedigrees for only one linkage, however, this constitutes supporting evidence both for its contribution to disease in a gene-interaction model and for the validity of that linkage as having a disease gene(s).

d) The absence of an environmental factor from some pedigree or linkage affected individuals but its presence in other affected individuals in that same pedigree or linkage may not be definitive evidence that it is not a contributor to disease, where more than one environmental contributor may have similar disease susceptibility interactions with the same disease-predisposing genes. Differences in disease symptoms, progression, or severity associated with the presence of specific environmental factors may be helpful in demonstrating their contribution to disease.

These different possibilities recognize that environmental contributors to complex diseases can interact with genetic contributors in different ways such that it is not simply or only a question of whether an environmental contributor is present or absent.

Indeed, it may be most persuasive to show that an environmental factor is present only or predominately among linked affected and unaffected individuals (including unrelated controls) because that will constitute more likely evidence that the factor interacts with a specific genotype across a number of different pedigree-specific localities than it would be to show that it is present among a number of linked and unlinked affected individuals.

Conclusion

The large numbers of unconfirmed linkages already suggested or established for complex diseases such as SLE suggest either that the genetic bases for a single disease are multiple or that current methods of genomic analysis produce a large number of false-positive artifacts. In either case, the fact that the genetic bases alone are not sufficient to express a disease means that we must look beyond genetics itself to confirm or disconfirm most candidate linkages, particularly when those linkages appear to be associated with geographically, ethnically, or culturally defined populations.

Hypotheses about specific environmental factors, however, are themselves linguistically and culturally defined and, perhaps more important, are necessarily limited by those conceptual origins.

For all these reasons, it is important to develop new ways to generate previously unanticipated environmental hypotheses and to do so in concert with ongoing genomic analyses of linkages and the particular pedigrees or sib-pairs on which those are based. That kind of environmental investigation may be facilitated by the use of a qualitative/quantitative research design and by approaches that empirically specify quantitatively testable practices rather than proxy identities or categories such as culture, ethnicity, gender, and class.

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