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Integrating Social and Biologic Factors in Health Research: A Systems View

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An important focus of recent calls for interdisciplinary approaches in health research has been the integration of social and biomedical sciences in understanding the causes of ill-health. Typical models for the incorporation of social factors into biomedical research include social factors as distal antecedents of more proximate biologic factors and gene-environment interaction. Under both models the distinction between social and biologic factors remains clear-cut, and consideration of social factors is not indispensable for understanding the biologic processes leading to disease. However, recent evidence suggests that social and biologic processes are inextricably linked in systems. This paper reviews models for the incorporation of social factors into the study of health, discusses the potentialities of systems approaches, and highlights implications for population health and epidemiology.
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INTRODUCTION

Recent years have witnessed an explosion of calls for interdisciplinary research in the health field. An important focus has been the integration of social and biomedical sciences. It is assumed that the integration of social and biologic approaches will lead to a more comprehensive scientific understanding of the causes of ill-health and to the development of more effective disease prevention strategies. But the way in which social factors should be incorporated into health research (and indeed the extent to which they can and should be incorporated) remains a contentious issue. It is unclear whether renewed calls for these approaches imply a true transformation of the dominant paradigm or simply restate earlier and (unfortunately) often sterile calls for more "social" approaches to medicine and public health. In this paper I review models for the incorporation of social factors into the study of health, discuss the potentialities of systems approaches to transcend the false dichotomy of social and biologic factors, and highlight implications for future work in this area.

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MODELS FOR THE INCORPORATION OF SOCIAL FACTORS INTO BIOMEDICAL RESEARCH

Social Factors as Antecedents to Biologic Processes

The simplest and most common model incorporating social factors into biomedical research views social processes as distal antecedents of the proximate biologic causes of disease. Thus, for example, the social patterning of coronary heart disease in industrialized countries, by which coronary heart disease rates increase as education decreases, results from the fact that persons of low education are more likely to smoke, be sedentary, or have unhealthy diets, which in turn have biologic consequences that contribute to the development of atherosclerosis (1). A variant of this model is that low education is associated with more stressful living conditions or with psychological processes such as anxiety and depression, and that these in turn have biologic consequences which participate in the processes leading to heart disease. More elaborate versions incorporate the idea that factors operating over the life course are relevant (2) or that the biologic consequences of social disadvantage accumulate over time and across biologic systems (3).

The "social factors as antecedent" model implies that distal social factors may be related to multiple diseases through either common or clustered pathways. Low education may be related to diet and through diet to both coronary heart disease and cancer and may also be related to sexual behaviors and drug use, and through these to AIDS. These pathways may also change over time or geographic contexts,

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as, for example, the social distribution of smoking appears to have changed over time. Thus low education may "cause" coronary heart disease in one historical period but may protect against coronary heart disease in another, depending on the social distribution of the mediating factors. Some view these distal social factors as "fundamental" causes in the sense that they endure over time and place, regardless of changes in the most common causes of disease and death (4).

Although the social antecedent model has implications for disease prevention, under this model the incorporation of social factors is not really necessary when the main objective of research is to elucidate the biologic processes leading to disease. Once the biologic pathways are completely understood, it may be possible to eliminate social gradients by intervening at the level of these proximate determinants, ignoring the social antecedents altogether. This may explain why, despite repeated calls to incorporate distal social causes into health research, the social antecedents model has had little impact on how biomedical research is conducted or on how scientists formulate or answer biologic questions.

Social Factors as Modifiers of Genetic Effects

A second model for incorporating social factors into biomedical research views social factors as contexts which interact with biologic processes leading to disease. The exemplar of this model is gene-environment interaction, with environment broadly understood to encompass social factors as antecedents to behaviors, physical exposures, or psychosocial processes which interact with genes. In one example, Caspi et al. (5) reported that a functional polymorphism in the promoter region of the serotonin transporter gene (*5-HTT*) moderated the relationship between stressful life events and depression, such that stressful circumstances were only related to depression in the presence of the genotype. Interactions between genes and early life experience have also been demonstrated in animal studies (6). Other examples involve interactions between socially patterned behaviors (such as smoking or alcohol intake) and genotype (7, 8).

By definition, the gene-environment interaction model implies that the role of a particular genotype in causing disease (or more specifically in explaining variation in disease) differs based on the context. Analogously, the role of a particular environmental or social exposure in causing disease differs based on an individual's genetic makeup. Thus causes are not absolute but context dependent. Under this scenario partitioning out contributions of "social" and "biologic" components becomes a futile exercise. This is because "the environmental variation depends on the genotypic distribution, and the genotypic variance depends on the environmental variance" (9).[p 1166] Although it is often argued that gene-environment interactions are likely to play a role in many, if not all, diseases, replicable empirical documentations of these interactions remain rare(10).

Calls for the investigation of gene-environment interactions are common, and the study of these interactions is the primary goal of large studies (11, 12). The predominant focus, however, is often on understanding the genetic causes of disease. Context is important insofar as it contributes to the ability to identify these genetic "causes." This imbalance is reflected in the contrast between the sophistication of the genetic measurement and the limitations of the measurement of environmental or social exposures (13). In the classic gene-environment interaction model the distinction between social and biologic factors remains clear-cut. If social context can be held constant, the biologic process itself can be studied and understood in isolation.

Social Factors as an Integral Part of Biologic Systems

A third model for the integration of social and biologic factors views social and biologic factors as tightly entwined in systems. Under this model social factors are capable of actually modifying both functional and structural aspects of biology. Thus social processes are not only antecedents or modifiers of biologic processes but actually become embodied in them (14). Effects of social context on biologic parameters are well established in several species. In a simple yet striking example of social effects on biology, Yeh, Fricke, and Edwards (15) showed that social experience modifies neuronal response to serotonin in crayfish. The effect of serotonin on the response of a neural circuit involved in a specific escape behavior was found to be exactly the opposite in dominant and subordinate animals. These differential responses to serotonin were reversible when the social context changed. Studies of social insects have long demonstrated striking effects of social organization on biology. For example, interactions between individuals within colonies regulate biologic development and behavioral maturation in bees (16). These environmentally modulated changes in behavior are associated with changes in brain structure, brain neurochemistry, and gene expression (17). Polyphenism, a process common in some species by which different phenotypes evolve as a result of environmental cues, is another example of the often profound effect of environmental context on biology (18).

The responsiveness of biology to social context is also illustrated by the plasticity of the brain and its responsiveness to the environment. In animal models, stress hormones have been shown to generate dendritic atrophy or inhibit adult neurogenesis in sections of the brain (19). These structural changes may have consequences for brain functioning, including aspects of learning and cognition (20). Thus the social environment affects biology, and these structural

changes in biology affect other biologic processes which in turn have social consequences later in life. The biologic response to stress is itself modified by earlier social experiences. In a series of animal experiments Meaney (21) and others have demonstrated that early childhood environments can "program" neuroendocrine responses to stress in adulthood. These effects are associated with enduring changes in gene expression in the regions of the brain that participate in the stress response (22). This enhanced responsivity to stress could result in greater exposure to mediators of the stress response over the life course, with potential consequences for a variety of systems. In addition, these acquired differences in biologic responses may be transmitted across generations, as responsivity to stress may have consequences for maternal behavior, which subsequently affects the early childhood environment of the next generation (21, 23).

Under this model of social-biologic interrelations, social experience has the capacity to directly alter both the structure and functioning of biologic systems. These factors are not viewed as distinct and susceptible to separation but rather as integral parts of a complex system, which encompasses factors ranging from DNA to social organization. The social environment is not an adjunct, but rather a key piece in understanding the functioning of the system itself.

A COMPLEX SYSTEMS VIEW OF SOCIAL-BIOLOGIC INTERRELATIONS

The functioning of genes is intricately linked and constantly modified by the cellular environment in which genes exist; similarly, the functioning of biologic systems in intricately linked to the broader environment in which these systems exist. Just as it is not possible to predict phenotype from genomic and proteomic databases alone (in the absence of information on dynamic interactions between genes and genes, and genes and proteins) (24), it may not be possible to predict health outcomes at the individual or the population level without understanding the dynamic relationships between biologic substrate and social context. Although different models for the integration of social and biologic factors may be useful in specific circumstances, the most general (and probably the most "realistic") views social and biologic factors as tightly entwined in complex systems. The social antecedents model and the gene-environment interaction model are in fact reduced cases of this more general model.

Key Features of Complex Systems

Very simply stated, a complex system is "made up of a large number of parts that have many interactions" (25).[p 183] The behavior of the system is dependent on the behavior and interrelations of all its parts (26). For example, an individual organism is a complex system because its functioning results from the interrelations of its lower level components (e.g., organ systems and cells). Two key properties of complex systems are that they are composed of heterogeneous interdependent units and that they exhibit emergent properties (26, 27). Interdependent units are parts that directly influence each other; for example, in an organism the functioning of one cell in a tissue affects other cells around it and the functioning of one gene within a cell affects the functioning of other genes in the cell. Emergent properties are properties of the system that arise from the functioning of its interdependent components but are not simple aggregates of component-level properties (26, 28). For example, the presence of disease can be viewed as an emergent property of the individual organism that arises from the functioning of the component parts of the organism.

Another characteristic of complex systems is the presence of nonlinear relationships and feedback loops. Causal processes involve more than linear chains of events; every element in a sequence has the possibility of affecting everything else in the sequence before and after it. Thus the effect of an initial change can be magnified as the change reverberates through the system. Another consequence of these nonlinear dynamics is that a force applied to the system at a particular location and time can have effects distant in both space and time (29). In complex systems, very small uncertainties in initial conditions can blow up and become large uncertainties in future predictions (28, 30). This is referred to as sensitivity to initial conditions or dynamical instability. It is because of these uncertainties that even a small change in an initial condition can potentially lead to a large number of different possible results. Although all these results are logical consequences of the same initial change, it may be difficult to predict exactly which result will actually occur, although the probability of occurrence of each outcome can sometimes be determined.

Population Health as an Emergent Property of a Complex System

It is not difficult to see that biologic organisms are complex systems. But how is this relevant to the integration of social and biologic factors in population health and epidemiology? Infectious disease epidemiologists have long viewed disease epidemics as the manifestations of the functioning of systems (31). It is obvious that the rate of an infectious disease is affected by interactions between individuals due to the transmission of infectious diseases (31). However, other aspects of population health, including chronic diseases, also result from the functioning of populations as complex systems. This is because the disease rate in a population results from the characteristics of individuals that compose the

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population, the interactions and interdependencies between these individuals, the effects of population-level emergent properties on individual-level health outcomes, and the dynamic interplay between individuals and population-level properties. Consider the example of obesity. Although in the naïve sense, the population prevalence of obesity is simply the aggregate of the properties of individuals (because it is calculated by summing the individuals with obesity), the outcome for each individual is the result of the functioning not only of the individual organism but also of the interdependencies between individuals (e.g., transmission of social norms), emergent properties of the population as a whole (e.g., mass marketing of foods, social organization of transportation), and the dynamic and reciprocal relationships between the behavior of individuals (e.g., their diet) and the environment (e.g., the advertising and availability of unhealthy foods). Hence the population-level manifestation of obesity (the obesity rate) is the result of the functioning of the system as a whole.

Another example of how predicting health at the population level requires understanding the functioning of the system as a whole (as opposed to simply aggregating what we know from individual-level studies) is provided by recent work on macroeconomic fluctuations and health. There has long been evidence that for an individual, being unemployed is associated with increased mortality, due to health selection as well to the health effects of unemployment itself (32, 33). However, at the population level, a higher unemployment rate is associated with lower rather than higher mortality (34–36). This is because low unemployment is a marker for acceleration of the economy, and acceleration of the economy may be associated with system-wide changes in work pace, social connections, and behaviors that may lead to worse rather than better health in the majority of the population, despite potential negative effects on the minority of the population that is unemployed. This paradox is resolved if one thinks of the population as a system, and population health as the manifestation of the working of the system as opposed to the aggregation of individual-level effects.

IMPLICATIONS FOR RESEARCH AND ANALYTICAL APPROACHES

As defined by Ideker, Galitski, and Hood (37) with reference to biology, a systems approach "…does not investigate individual genes or proteins one at a time, as has been the highly successful mode of biology for the past 30 years. Rather, it investigates the behavior and relationships of all the elements in a particular biologic system while it is functioning." Analogously, a "systems" approach to the study of population health would not investigate individual risk factors (or individuals) one at a time, rather it would investigate the behavior and relationships of multiple elements in a particular population system while it is functioning. Calls for systems approaches to epidemiology are by no means new (38–41), but practically speaking, what would such an approach look like?

The common epidemiologic approach is a bottom-up approach that focuses on isolating "effects" of individual-level predictors of health outcomes in models with individuals as the units of analysis. In contrast, a systems approach begins with the system as a whole, moves to the parts, and then synthesizes both types of information in a comprehensive model. The first step in a systems approach is to define the components of the system and compile information on them. Existing information on these components and a priori theory are then used to develop a model of the system with two objectives: to adequately describe the key components and their interactions and to be able to predict properties or outcomes of the system given specific perturbations (37). The model can be refined through experimentation or by contrasting its predictions with observational data.

The resulting model allows one to simulate outcomes of the system under different scenarios. This allows the researcher to see how changing a given variable reverberates through the system as a whole. In epidemiologic terms, one can observe how a given perturbation to the system (e.g., an individual-level or system-level change) affects an individual's probability of disease or affects the overall outcome or emergent properties of the system itself (e.g., the disease rate). This is fundamental for a science such as epidemiology whose ultimate objective is not just to describe the state of reality but to identify the interventions that would effect a desirable change.

In contrast to traditional epidemiologic approaches which essentially manipulate observational data to attempt to approximate isolation of a causal effect under (often artificial) experimental conditions, a systems approach focuses on understanding the system functioning so that changes in response to an intervention can be predicted. This approach has two important advantages. One advantage is that it allows evaluation of the effects of an intervention under conditions which are more likely to approximate real life (with dynamic relationships, feedback loops, complex interactions, and dependencies), as opposed to controlled experimental situations in which other conditions are held constant in order to isolate an indisputably identifiable but possibly "ungeneralizable" effect. This is especially important for public health interventions where systems-wide contagion effects of individual-level interventions as well as interventions on the system as a whole (e.g., through policy) are likely to be common. A second advantage is that the interventions evaluated can be thought-experiments, things we would like to change but have never been changed, and

TABLE 1. Selected characteristics of traditional individual-based and systems approaches to epidemiology

	Individual-based epidemiologic approaches	Systems approaches
Main objective	Identify individual-level causal effects	Understand system functioning in order to quantitatively predict changes resulting from interventions on the system or its components
Systems-level properties	Aggregates of individual components	Emergent properties connected to but not reducible to individual components
Analytical approach	Bottom-up (from components to system)	Top down followed by bottom-up and synthesis
Role of data	Used to isolate associations indicative of causal effects	Used to develop and test models of system functioning
Role of description	Generate hypotheses for testing	First step in model development
Role of mathematical models	Manipulate observational data in order to approximate isolation of causal effect under experimental conditions	Describe system functioning under real-life conditions so that effect of perturbations can be assessed using simulations
Types of relationships assumed	Linear relationships Recursive	Nonlinear dynamics Nonrecursive
Generalizability and forecasting	Inferences based on observed "treatments" and only strictly generalizable to similar conditions	Allows forecasting effects of perturbations (or "treatments") not necessarily observed, or of observed "treatments" under new conditions

therefore are not able to be evaluated through observation (and sophisticated analytical manipulation) of existing data. Selected differences between traditional individual-based approaches and systems approaches are summarized in Table 1.

The study of the obesity epidemic provides an illustrative example. The traditional epidemiologic approach begins with a study of the risk factors for obesity in individuals. The genetic, behavioral, and social characteristics of individuals are examined in relation to obesity. The "independent" effects of these variables are isolated in regression models. The assumption is that once we understand these individual-level causes of obesity, we can add them up to understand the causes of the obesity epidemic. In contrast, a system approach would begin by describing the component parts of the system in which the obesity epidemic is embedded. These components would include not only the biologic, behavioral, and social characteristics of individuals but also systems-wide features such as the mass production and marketing of foods, the organization of transportation, and the presence of social norms regarding behaviors and body size. A model would be developed that describes the interrelationship between these components. The model would have to be simple at first but would gain in complexity as the functioning of the system is understood. The model could then be used to predict system changes in response to an intervention. By definition, such an approach necessarily integrates social and biologic factors into the functioning of the system.

Epidemiology has benefited from its ability to draw on complementary methodologies. It may be time to add systems approaches to the arsenal of methods we use. For this we need exemplars of this approach and studies that contrast different approaches. It has long been clear that the notion that biology is somehow prior to the environment in understanding system functioning makes no sense in biologic research; we need to recognize that the same is true of biomedical and epidemiologic research. Systems approaches may enhance our ability to integrate social and biologic factors in health research, not only at the level of biologic organisms but also at the level of populations.

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