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Natural experimental models: The global search for biomedical paradigms among traditional, modernizing, and modern populations

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ABSTRACT **During the past four decades, biomedical scientists have slowly begun to recognize the unique opportunities for studying biomedical processes, disease etiology, and mechanisms of pathogenesis in populations with unusual genetic structures, physiological characteristics, focal endemic disease, or special circumstances. Such populations greatly extend our research capabilities and provide a natural laboratory for studying relationships among biobehavioral, genetic, and ecological processes that are involved in the development of disease. The models presented illustrate three different types of natural experiments: those occurring in traditionally living, modernizing, and modern populations. The examples are drawn from current research that involves population mechanisms of adaptation among East African Turkana pastoralists; a search for etiology and mechanisms of pathogenesis of an emerging disease among the Yakut people of Siberia; and psychosocial stress, hypertension, and cardiovascular disease in women working outside the home in New York City and among subpopulations in Hawaii. The models in general, and the examples in specific, represent natural laboratories in which relatively small intrapopulation differences and large interpopulation differences can be used to evaluate health and disease outcomes.**

At the midpoint of this century, a few biomedical scientists realized that small, circumscribed non-Western populations with focal, endemic diseases offered new opportunities to study disease etiology and mechanisms of pathogenesis. Among the best known are the investigations of three fatal neurodegenerative disorders in the Western Pacific: kuru among the Fore people of New Guinea, and amyotrophic lateral sclerosis and parkinsonism-dementia among isolated Pacific populations (1–4). Such natural experiments, as they have been termed, provided unique opportunities for solving etiological and epidemiological problems of widespread medical significance. Subsequent studies by Neel and colleagues (5, 6) expanded the disease interest in remote populations to include the genetic structure of populations. Other studies broadened this perspective by including an evolutionary and ecological explanation of biological variability and adaptation to extreme environmental stressors (7–11).

The initial investigations among small, often remote, non-Western communities were viewed as "exotic" by most scientists outside of anthropology, and of only passing relevance to modern biology and medicine. Yet, by studying health and disease in such populations, investigators were able to avoid some of the confounding factors that exist in diverse modern societies. Such small-scale traditional populations, relative to Western populations, have a built-in system of natural controls, often have high rates of disease, and allow smaller sample sizes because of intrapopulation homogeneity. By comparison with large, diverse Western populations, these groups are often inexpensive to study when carrying out research protocols that combine both a field and laboratory approach to problems. Small-scale traditional populations are disappearing. However, the cultural transitions they are experiencing create new natural experimental models relating to the effects of modernization and acculturation (12–17). Natural experimental models are being developed further in modern, technologically advanced societies where subpopulations and microenvironments are investigated (18). Natural experiments then can be conducted in many cultural settings and provide a framework for investigating normative biology, disease etiology, and mechanisms of pathogenesis (19).

Human Populations as Natural Experiments

Anthropological, epidemiological, and evolutionary problems concerning humans often are difficult to solve because experimental research design is limited. Natural experimental models, however, are designed to solve these problems in that they:

1. Take advantage of a population or special circumstance that naturally isolates a particular problem; that is, a population will be identified as particularly appropriate for addressing an existing scientific problem, and/or

2. Use populations that have unique attributes or biomedical phenomena that direct inquiry and relevance at the local, regional and global levels; that is, a population with unique attributes will identify a new scientific problem.

Both cases are opportunistic: in the first case, the problem dictates the population; in the second case, the problem arises from the population.

Natural experiments have been used to study the full range of human biological diversity and variability. However, the question is often not whether variation can occur, but why it occurs. In natural experiments, contrasts are made between populations having a similar genetic structure and a similar culture and lifestyle and/or those that have differences in these variables but a common environmental stressor or peculiar disease pattern (20). Thus, conceptually natural experimental models in human populations are the reverse of biological reductionism models that purport to explain living systems at all levels of organization (21, 22). Natural experimental models, however, do use molecular and genetic information and events as part of larger con-

Abbreviations: VE, Viliuisk encephalomyelitis; CSF, cerebrospinal fluid.

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structs to attempt to answer questions at increasing levels of organization and complexity.

Natural Experimental Models: Traditional Populations

The factors affecting health, adaptability, and disease outcome in small-scale traditional societies include degree of remoteness and contact, demographic characteristics of the population (size, density, age, and gender distribution), group mobility, ecosystem characteristics, availability and type of food resources, physical environment stressors, physical proximity during work and play, housing types, culturally specific hygienic practices, and degree of natural resistance and differential genetic susceptibility, among others. These populations usually are characterized by a geographically or culturally restricted territory and limited travel outside it, a "simplified" ecology and fixed habitat, a close association with the flora and fauna, a relatively high degree of inbreeding (in mating groups), and unique social and behavioral patterns that often are inextricably tied to a culturally specific disease expression, unusual epidemiological pattern, or health outcome (23). Such populations may be socially isolated (e.g., religious, economic, political, linguistic or ethnic barriers) as well as geographically isolated, by choice or by circumstance. They may be large or small, technologically simple or technically advanced, and represent either closed or semiclosed systems of mating behavior. Traditional groups live as hunter-gatherers, as pastoralists, horticulturists, or groups with varying degrees of agricultural intensity; and they have health problems that often are culturally specific or even unique. The study of health and disease in such groups is usually integrative and opportunistic.

Non-Western Human Diversity. Human biobehavioral diversity found in Western societies, where most scientists reside and conduct their work, is substantial, but limited in global perspective. Considerable human diversity also can be found in traditional societies distributed throughout the world. These populations contain both genetic complexes and biobehavioral variation that is generated by the diverse social and physical environments under which people live. Fig. 1 illustrates the close ties that the people have to the physical environment. Extremes in climate (rainfall, temperature) can have profound influences on food availability, other resources, or disease patterns, and although the sociocultural system tends to moderate climatic variations, the effects on biobehavioral adaptability and health can be pronounced. Although non-Western, traditional populations sometimes are relatively isolated from other populations, they often are influenced by other (external) populations, either directly or indirectly. Competition for resources and warfare are common in neighboring populations: migration and modernization are examples of global influences (also see Fig. 3).

There are several examples of multidisciplinary studies of traditional populations in which the natural experiment focused on adaptation of the population to the environment (24). The Andean project (25) and, later, the research of Schull and Rothhammer (26), compared native Amerindian farmer/herder responses to high altitude with low-altitude residents in the context of health and health-related parameters of adaptation to hypoxia and cold. In both studies, Andean populations were chosen specifically to address questions of altitude and cold stress. Adaptation of hunter/gatherer San Bushmen (27), central African Pygmies (28), and Ituri Forest Pygmies (29) also addressed problems of adaptation and whether these populations could be used as models for earlier paleolithic populations. In these cases, hunter/gatherers were studied to explore prehistoric and evolutionary questions based on contemporary traditional populations.

An example of a traditional nomadic pastoral population is given below. Here, the emphasis is on reproductive health in an East African herding society.

Nomadic Turkana Pastoralists. The nomadic Turkana pastoralists of the dry savanna of northwest Kenya exist under environmental conditions with marginal resources (30, 31). These

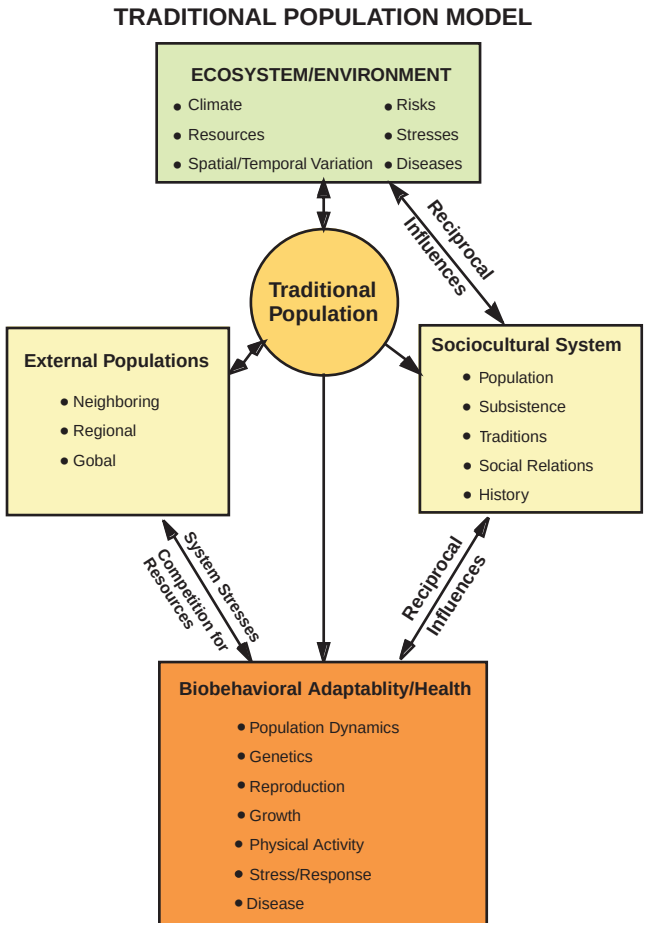

FIG. 1. Schematic representation of a natural experimental model in small remote anthropological populations. The relative genetic, ecological, and cultural homogeneity of the experimental population provides a natural laboratory for the study of health and disease, avoiding some of the confounding factors that exist in larger technologically complex societies.

pastoralists, who have been the focus of the South Turkana Ecosystem Project, are one of a remaining handful of societies that continues to pursue a nomadic pastoral way of life (17). In this hot environment of scrub vegetation and open canopy acacia woodland, rainfall is limited and seasonal, and there is frequent drought. Malaria and other diseases impact the Turkana: livestock diseases affect their animals (camels, cattle, sheep, goats, donkeys), and indirectly, the people. The intensive management and care of livestock is essential for survival of the animals on the limited resources that the dry savanna environment provides. Turkana accomplish this by nomadic movement in search of forage, complex social patterns of reciprocal exchange of labor, animals, and other resources, and a detailed knowledge of the environment and livestock. By careful and judicious application of this knowledge, and a reasonable amount of good fortune, livestock will produce adequate milk, blood, and meat for human subsistence.

One of the goals of the multidisciplinary Turkana research project was to assess the health and biobehavioral adaptability of the Turkana as a reflection of their ability to extract resources from the environment and to maintain their population numbers. There also was interest in how their health and biological status affect their ability to exploit the environment. One component of the several measures of health in Fig. 1 is reproduction and fertility. This is central to our understanding of the maintenance of population numbers and human labor within the family pastoral unit.

Reproduction. Influences on reproduction and its biobehavioral outcome, fertility, are numerous and complex (32–34). Conditions under which the Turkana live serve as a natural laboratory for the exploration of human reproduction in this noncontraceptive, high-fertility population (35, 36).

As members of a polygynous society, Turkana men and their families pay brideprice in the form of livestock to acquire wives. This links a herding family's ability to manage and increase its livestock holdings as an economic endeavor directly to its ability to pay brideprice (livestock) to other families to enhance its reproductive capacity. These exchanges are negotiated carefully, contribute to the redistribution of wealth in the population, and are essential in the production of children who will serve as the labor needed to herd the animals. When imbalances occur within family herding units between human labor for herding and growth in numbers of animals, then there are institutionalized mechanisms for redistributing animals and human labor through loaning/borrowing or giving/asking exchanges (37). Wealth is an ephemeral concept because large herds (wealth) must be balanced with large numbers of dependents (labor) who draw on the resources of the wealth (milk, blood, meat) for food.

The fundamental patterns of fertility of the nomads must be understood within an extremely complex social, economic, and reproductive system (38, 39). Nomadic women have a relatively high lifetime fertility of between 6.6 and 7.1 live births, and by age 65 years, men will have about 2.5 wives and 10 offspring (40). The fertility rate for women shows considerable fluctuation by season and from year to year (35, 39, 41). Short-term and long-term environmental fluctuations, combined with the economic risks of keeping livestock, contribute to patterns of reproduction that show considerable variation through time. These reproductive patterns are tightly linked to child health and growth, maternal health and nutrition, and patterns of Turkana lifestyle associated with child care and general behavior.

Infant and child health. Reproductive success depends not only on successful gestation and parturition, but also on survival and normal growth during infancy and childhood. Anthropometric surveys to assess growth of nomadic children and adults in body size and composition began in 1981 and were continued through 1994. Most measurements were reported from cross-sectional studies, but some data were longitudinal (42–44). Nomadic infants and children have a slow growth pattern and are shorter than United States children (based on National Center for Health Statistics reference values) (45) until adulthood, when Turkana and Americans are equal in height. In contrast, weight is very low by United States standards, falling consistently close to or below the United States fifth percentile. At all ages from late infancy and beyond, Turkana children and young adults are slender in physique.

Body composition and reproduction in women. Although Turkana are tall as adults, they are very lean with limited fat stores and small muscle mass. This pattern results from limited food energy availability (but high protein intakes) superimposed on seasonal variation in food availability. Consequently, women, who already have low energy reserves (in the form of body fat), experience depletion of fat reserves during the childbearing years between ages 20 and 50 when pregnancy and lactation place high demands on dietary energy. For example, an average Turkana woman has a completed fertility of seven live births (5.25 years of cumulative pregnancy) (39) and 18 months of breast feeding for each of the seven infants (10.5 years of cumulative lactation) (46). This amounts to her food energy needs being substantially elevated for about 15 years, or half of her reproductive life. Tests were made to determine whether the elevated energy requirements were associated with reproduction (pregnancy and lactation) or age changes: parity was the most significant covariate (47) (Fig. 2). There is also evidence (48) that birth weights of late parity nomadic infants are low, suggesting that low body fat mothers may produce late parity infants who are at a higher risk of mortality. This process may contribute to the moderate-to-high infant mortality (9–14%) that indirectly leads to increased fertility by early termination of breast feeding (with death of the infant), rapid return to ovulation, and early conception (38, 40).

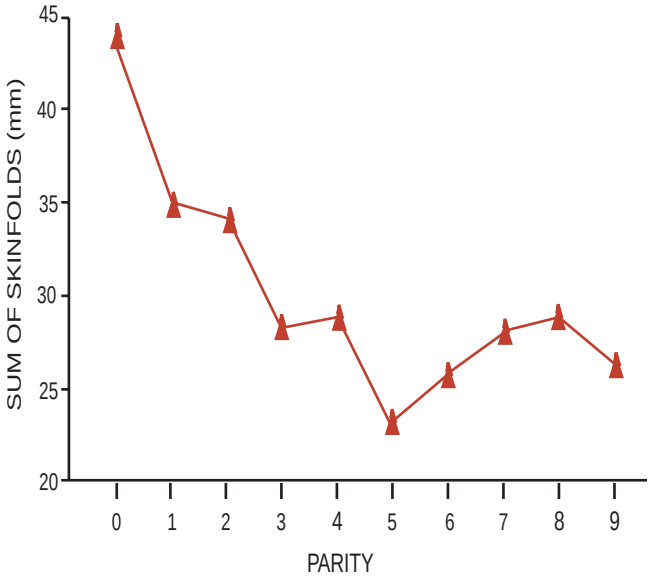

FIG. 2. Relationship between amount of body fat (sum of four skinfolds) in Turkana women, and parity (number of live births) (47).

The value of integrated studies of Turkana. There are several important and fundamental findings from this research that are unlikely to have been (*i*) uncovered in a Western population and (*ii*) uncovered in the absence of integrated studies. First, what is the basis for the high fertility in Turkana women when both year-round and seasonal dietary stress and depletion of energy reserves throughout their lives exert pressure on their reproductive capacity? Despite these stresses, Turkana have low pregnancy losses and are able to carry a substantial proportion of fetuses to term (36), and mean full-term infant birth weights are within the normal range for healthy babies, 3,250 g (48). The basis for our findings of high female fertility is grounded in the knowledge of Turkana behavior and culture, environmental variation, and food availability (including livestock management), gestation and pregnancy loss, infant health and feeding, and maternal body composition. Second, what is the basis for health and growth of Turkana children? Infants and young children are breast fed for about a year and a half with high-energy butterfat supplementation, are provided with a high-protein diet, and shown priority for food when it is in limited supply (49, 50). Here, data on Turkana diet, maternal health, cultural values, infant feeding patterns, and infant and child care and growth provide the bases for our understanding of very complex processes of reproduction, health, and child development.

Natural Experimental Models: Modernizing Populations

As small-scale traditional populations rapidly vanish by undergoing significant change through contact with and assimilation into larger, more cosmopolitan communities, investigating them in unaltered natural settings soon may be impossible. Factors such as migration and population movement to and from a modernizing population become a major mechanism for change for both the donor and recipient populations (Fig. 3). Social and cultural practices undergo change, and behavioral modification usually ensues. Such factors and events lead to environmental modification with exposure to new environmental circumstances, within a temporal context. Likewise, the original gene pool of the population may undergo an increase or decrease in variability, from a relatively homogenous gene pool to a larger heterogeneous one. This paradigm, built on comparative change, represents one of

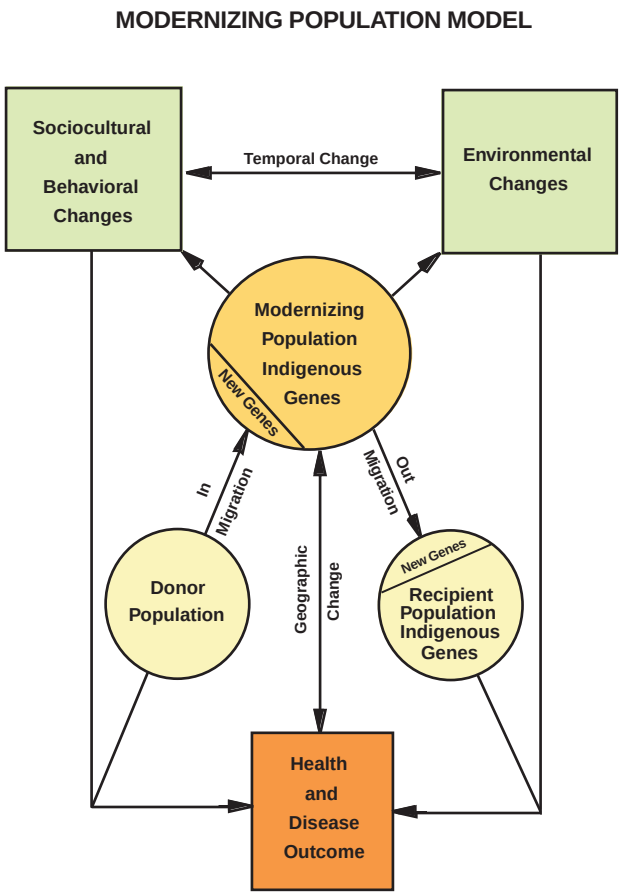

FIG. 3. Schematic of a natural experimental model in modernizing populations. The model is built on change and comparison of change across the same population temporally and/or across different populations. The major components of the model include: sociocultural and behavioral changes, environmental modification in a temporal context, migration and population movement, a redistribution of genes, and an exposure to novel events and conditions, all of which either could induce, ameliorate, or enhance specific risk factors for health and disease outcomes.

the most interesting and scientifically important models for the study of health and disease as we enter the next millennium.

Examples of Change. Several well-known examples of this model represent seminal studies for the kinds of population-based research designs that might be developed in the future, using well-planned natural experimental models rather than designs that are more opportunistic. An example of such a well-planned study is the Samoa Migration Project (13), designed to explore the effects of modernization on the health and well being of a Pacific Island population. It provided new insights into the way such studies could be designed and the factors that were likely to be important during the transition to modernization and the biological and behavioral measurements of such change. The model often was manipulated to address both long-term and short-term outcomes, with repercussions not only for the local populations, but also for modernizing populations worldwide. Other examples of this paradigm are studies of amyotrophic lateral sclerosis (ALS) and parkinsonism-dementia in the Mariana Islands, which represent a dramatic change in the patterns of these diseases with increased acculturation and contact (12, 51). Because these disorders have several of the same hallmark brain lesions as Alzheimer's disease, (e.g., neurofibrillary tangles), they are of direct relevance to the epidemiology, etiology, and mechanisms of pathogenesis of Alzheimer's disease, as well as parkinsonism and ALS worldwide. It is change, therefore, that drives the modernizing model in general, and the Samoan and Guam paradigms in particular. Modernizing models, therefore, that take advantage of naturally occurring cultural transitions within a genetically similar group can be used to identify acute and chronic disease patterns, particularly as they relate to the adoption of new and different lifestyles. Below is an example of this paradigm currently under study that may have global as well as local and regional health outcomes in the future.

Viliuisk Encephalomyelitis (VE) Among the Yakut. Today, there is a growing potential for rapid global spread of dangerous human pathogens (52–56). Guarding against these emerging and re-emerging pathogens is one of the most important goals of modern microbiology. During the past three decades, examples of infectious agents causing new infectious diseases in humans include: Borellia causing Lyme disease (57); hantaviruses causing Hantavirus Pulmonary Syndrome (58); Ebola virus causing a very deadly form of hemorrhagic fever (59, 60); HIV causing AIDS (61); human papilloma virus causing cervical cancer (62); and prions causing transmissible spongiform encephalopathies, including kuru (2, 63) and most recently, new variant Creutzfeldt-Jacob disease, which is likely the direct result of eating contaminated beef from cattle with "Mad Cow Disease" (64, 65). The existence of such pathogens in small-scale, traditional as well as modernizing populations poses a health threat to all humanity.

The modernizing paradigm that follows represents a newly emerging, unique disease, VE, which manifests as a progressive neurodegeneration of unknown etiology. Although VE currently is limited to a relatively small, relatively isolated, but modernizing Yakut population in east-central Siberia, it now is spreading from its original endemic area in the Viliui valley (population 10,000), where it has been known for at least a century, to a more densely populated cosmopolitan area (population 200,000), as a result of recent human migration and population movement within the region.

Historically, the Yakut (Sakha) people, a traditional hunting, fishing, trapping, and pastoral culture, are thought to have migrated to Siberia from Mongolia and populated the Lena-Aldan region around 1200 AD (66). Russian colonization and smallpox epidemics in the 17th century probably forced significant numbers of Yakut people from the Lena-Aldan valley northward where they assimilated with the Evenki (reindeer herders) in the Viliui valley. Evidence suggests that VE has been an endemic disease in the Viliui valley probably for centuries, initially among the Evenki, the original indigenous population, and subsequently in the genetically mixed Evenki-Yakut population where the disease is called bokhoror, a word for "stiffness" in the Sakha language (67, 68).

In contrast, the Yakut people back in the Lena-Aldan valley never knew of VE before World War II and unlike the Viliui river Yakut people, the Lena-Aldan valley population did not have a folk name for this disease. By 1990, 33 of 130 Lena-Aldan valley villages that previously were disease free, had developed cases of VE. Among those who left the Viliui region, the risk of developing disease remained high, but was about 60% less than for the Viliui population (69). Conversely, migrants to the Viliui valley had a prevalence rate of approximately 150/100,000 population, a rate similar to indigenous Viliui residents in the endemic area (69). Currently, all migrants represent 38% of registered VE patients who were born outside of the Viliui valley. Secondary cases in nonmigrants (in both genetic and nongenetic relatives), living in the same household as migrants, also have been documented.

Communication and contact between previously isolated Siberian villages have increased dramatically in the 1960s and 1970s, resulting in a change in the distribution pattern of VE. Decreased isolation and increased contact with the outside world, coupled with increased freedom of indigenous people to travel from Yakut villages to places like Japan, Alaska, Korea, China, and throughout Russia, eventually may lead to increased health risks and emerging disease worldwide.

During the 1970s, an intensive and comprehensive investigation of VE was initiated, including epidemiological, clinical, pathological, genetic, and experimental studies. Nearly 1% of the adult population died of VE each year in the Viliui valley (69). Affected individuals often attribute the onset of disease with falling into cold water while pursuing a traditional outdoor lifestyle, subsequently developing a severe febrile illness. The average age at onset is between 35 and 40 years with the youngest known case now thought to be 11 years of age and the oldest 61 years (69).

The disease manifests in three clinical phases: (*i*) an acute phase lasting a few days to several weeks; (*ii*) a recurrent, exacerbative, subacute phase lasting 2 months to 2 or more years; and (*iii*) a chronic, fully developed, clinical phase that lasts 2–6 years (Fig. 4). Death can ensue in any of the three phases. Longer durations up to 25 years recently have been documented (unpublished data). Patients initially present with symptoms of fever, headache, chills, vomiting, somnolence, or delirium in the acute phase. As the course slowly progresses in some patients, they develop clearly defined neurologic symptoms that include a spastic paraparesis, bradykinesia, dysarthria, and a progressive dementia. Early in the disease course, there is a lymphocytic pleocytosis and elevated protein in the cerebrospinal fluid (CSF) that declines with the progression of the disease over many years (Fig. 4). Neuropathologically, there is a spectrum of change depending on whether the patients are acute, subacute, or chronic at the time of death. The hallmark neuropathological changes included thickened and fibrotic meninges, necrotic cortical lesions throughout the brain, neuronal loss, lymphocytic infiltration, and gliosis (69–78). These findings, along with the clinical symptoms, support a chronic infectious etiology (70, 76).

VE also demonstrates some familial clustering. Of nearly 200 affected families interviewed, 24 had two or more cases that represent both first- and second-degree relatives and nongenetically related members of the household (69). Inbreeding coefficients for affected and nonaffected families were very low and were not significantly different. Thus, it is likely that transmission is horizontal rather than vertical in such families; although an argument for genetic susceptibility cannot be ruled out.

Early attempts to isolate and identify the causative agent from brain and CSF were largely negative, as was the inoculation of VE tissues into cell culture, rodents, and nonhuman primates. Although infectious agents were isolated, they subsequently were found to be contaminants (79–81). More recent attempts have included the inoculation of a wide variety of primary and continuous cell lines, both neuronal and nonneuronal, and numerous experimental animals of different species (unpublished data). Some animals developed neurological symptoms 10–14 months postinoculation, but all second-passage animals were clinically negative. Likewise, testing of serum and CSF from VE patients has included a broad search for antibodies against nearly 40 viral, microbial, and parasitic pathogens (unpublished data).

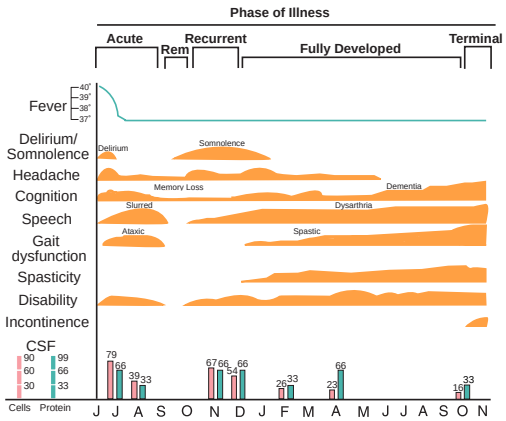

FIG. 4. Schematic of the progression of clinical symptoms of a Yakut patient with VE. The symptoms and their duration and progression are typical for the disease. Rem, remission. (Modified from Lev Goldfarb, Neurogenetics Unit, National Institute of Neurological Disorders and Stroke, National Institutes of Health, with permission).

There is compelling evidence that VE is a communicable, chronic, infectious disease with a pattern of dissemination and contact characteristic of leprosy, tuberculosis, and other latent and chronic infections (69, 70, 82). The Viliui valley is far north of the well-known tick-borne encephalitis belt in southern Siberia, and ticks in this region are extremely rare (unpublished data) and therefore unlikely to be involved in disease transmission. The current research initiative on VE represents a renewed attempt to pursue an infectious etiology, even though other scenarios such as susceptibility gene(s) and an autoimmune response cannot be excluded at this time. The scientific burden that remains is to elucidate and characterize the cause, determine the mechanisms of spread, and assess the potential health risk to neighboring or accessible populations worldwide.

Current and future research efforts in this fragile and marginally inhabited environment will address five main initiatives: (*i*) the early detection and ascertainment of cases and the clinical and pathological characterization of these cases in its three clinical forms; (*ii*) anthropological and epidemiological studies concentrating on social and behavioral mechanisms of spread, including case-control and migration studies; (*iii*) further attempts, using nonfrozen, fresh VE tissues, to isolate and characterize a pathogen or nonhost DNA from blood, CSF, and central nervous system tissues, particularly from acute and subacute cases; (*iv*) attempts to isolate and characterize a pathogen from nonhuman hosts in wild and domestic animals and birds; and (*v*) molecular and genetic studies to search for susceptibility genes and point mutations using large numbers of molecular genetic markers. These five VE initiatives form the core of a large-scale, multidisciplinary, collaborative research effort between the Sakha National Institute of Health in Yakutsk, the World Health Organization, and international collaborators worldwide (82).

Natural Experimental Models: Modern Populations

The final class of natural experimental models is an offshoot of the modernizing model that takes advantage of the microenvironmental variation and subpopulation differentiation inherent in technologically advanced societies. These models use the naturally occurring compartmentalization of individual lifestyles and residential patterning within the otherwise complex urban setting (Fig. 5) and have evolved from an interest in the development of chronic diseases, particularly those that are associated with the adoption of modern, Western lifestyles.

Psychosocial stress has been posited as a causative factor in some of these chronic degenerative disease states in modern Western societies, which are defined from cut-points in continuously distributed physiologic traits (83). These thresholds are determined from measurements taken under standardized conditions, because the functions they represent (such as blood pressure and hormone levels) fluctuate continuously to adjust body systems to rapid changes in the internal and external environment. Evolutionarily, the adaptive value of these traits most probably derives from the ability to change to fit circumstances, yet the determination of whether disease (pathology) is present in them often ignores this mutability (84).

Standard epidemiological studies using linear modeling techniques have examined the effects of environmental and behavioral factors on the health of urban Western populations. They posit that various aspects of lifestyle, often termed psychosocial stressors, increase the risk of developing threshold-defined chronic disorders. The problem with these analyses is that they often do not consider the variation in the biological functions that define the disorders (85) and treat the modern urban setting as a singular seamless environment. In reality, the dynamics of life in urban environments, particularly in modern Western populations, is characterized by a structuring of activities, such that the

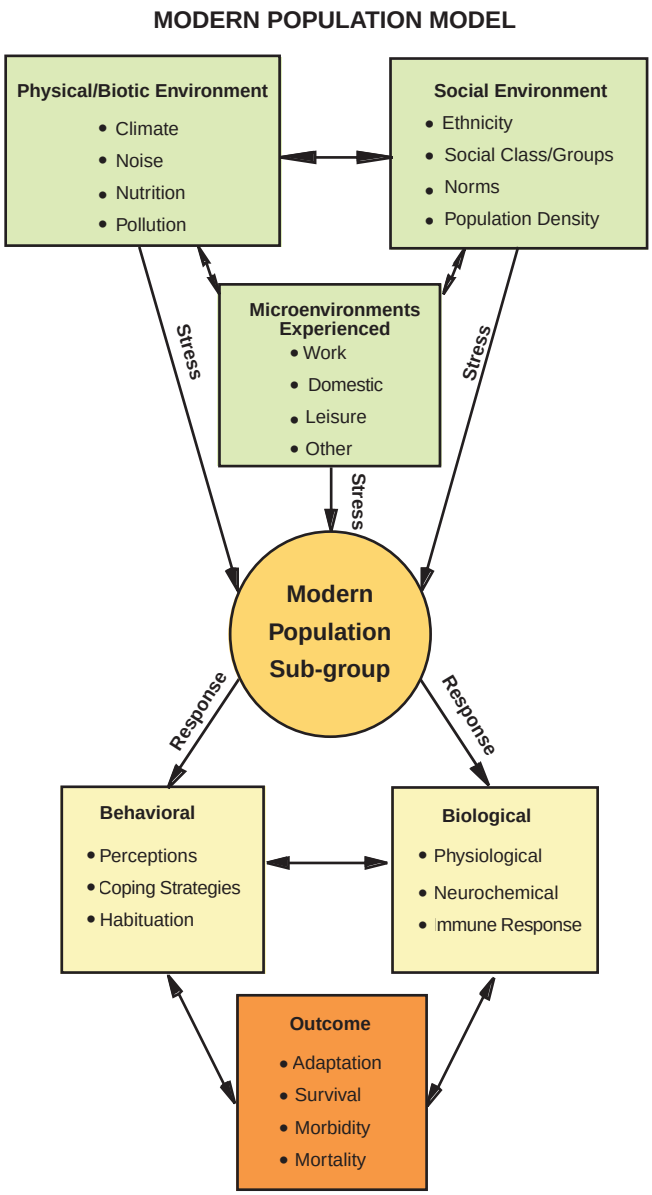

FIG. 5. Schematic of a natural experimental model in modern populations. The model is constructed on the premise that modern groups are affected by pervasive physical, biotic, and social stressors, but also must contend with situation-specific stressors as microenvironmental conditions vary. The combination of pervasive and dynamic stressors alter biological and behavioral responses, which may enhance survival in the short term, but which ultimately lead to mortality.

"microenvironments" defined by the social and geographic circumstances, where economic, domestic, and leisure activities of the individual occur, are different (85–87). Thus, microenvironment-specific stressors that may contribute to chronic disease development do not pervade the totality of life, but rather are encountered in a structured way, depending on the pattern and type of microenvironments experienced by the individual (85, 88). Physiologic traits are variable, and the environmental lifestyle stressors that affect them are sporadically encountered. Consequently, epidemiological risk assessments that relate standardized measures to fixed characteristics may be uninformative or even misleading in determining the contribution of psychosocial stressors to chronic disease pathology (85). A reliable way to assess the relationship between dynamically varying traits and changing microenvironments is to examine multiple measurements taken in the different settings. A useful approach is one that focuses on the individual rather than on the trait or environment. That is, by following individuals through different microenvironments, it is possible to identify individual stressors and examine how they affect biological responses (85).

Ethnic Comparisons in Modern Environments. Designs that take advantage of circumstances that differentiate ethnic enclaves within the total social fabric of modern populations are an example of a modern subpopulation model. These enclaves, or ethnic groups, do not fit traditional definitions of distinct, isolated populations given the high degree of gene flow among them. In fact, they often are more genetically heterogeneous than groups living in more traditional settings. However, there often is some degree of group-level genetic difference between the enclaves and surrounding peoples, differences that tend to be greater in first-generation immigrant or second-generation communities. There is also a shared culture within the ethnic group that is reflected in common patterns of behavior and values, although the biological and cultural diversity within these groups also is considerable.

Comparisons of biological measures in ethnic groups within or between microenvironments are useful in determining the effects of behavioral changes that occur as the groups cope with psychosocial processes, such as the transition from traditional to modernized lifestyles, occurring either *in situ* or through migration. Investigations that evaluate migrant groups in modern Western settings attempt to identify behavioral factors specific to intercultural interactions that contribute to chronic disease development. An example of a research project that examined the health effects of modern living was the Samoan Migration Project (13). As mentioned previously, this project studied the effects of modernization among recent migrants to the U.S. and New Zealand. People living in areas characterized as traditional (such as rural villages in Western Samoa) and modernizing (urban areas of American Samoa) were compared with Samoans in modern settings (urban areas of Hawaii and California) (89). In short, Samoan migrants experienced increases in adiposity (90, 91), catecholamine (chiefly norepinephrine) excretion rates (92, 93), and blood pressure (94, 95) in conjunction with the adoption of modern Western urban lifestyles. Although most of the research involved convenience samples, many of the immigrant Samoans lived under similar demographic conditions, such as in public housing projects in Honolulu (94).

A similar study focused on catecholamine and blood pressure variation and lifestyle stress among Filipino-American immigrants to Hawaii. Earlier investigations of Filipino-American immigrants to Hawaii showed that those with an intermediate level of contact with American society had higher 24-hr catecholamine/excretion rates than immigrants with either low or high levels of contact (96). This submodel used a design that incorporated use of a community where all of the participants lived in a single housing development and shared low-income status, but varied in type of employment, length of time since immigration, and many other characteristics. More recent research on lifestyle stress has examined ethnic differences between Filipino-American and Caucasian women by using an opposite design in which all participants shared a common occupation (nurses and nurses' aides) and workplaces, but varied in place of residence in the city of Hilo, HI (97). Significant differences in how behavior affects blood pressure also were found between Filipino-American and Caucasian women: for example, Caucasian women had significantly elevated systolic and diastolic blood pressure while doing household chores as compared with other activities; but there was no such elevation among Filipino-American women. Those who have lived in the U.S. for the longest period of time had significantly elevated catecholamine excretion rates and greater daily blood pressure variability than shorter-term immigrants (unpublished data). These differences highlight the importance of culture in the relationship between psychosocial stress and blood pressure variation (97).

Finally, these types of comparative studies of the daily variation of blood pressure and catecholamine excretion rates between

ethnic groups help define the risk for cardiovascular disease associated with group-specific lifestyle factors. However, it should be emphasized that the ethnic enclaves that exist within complex modern societies are heterogeneous groups. Simply making racial comparisons without appropriate designs for evaluating and controlling for variation, as often is done in medical research, may lead to incorrect conclusions about disease processes as traditional racial categorizations ignore the genetic or cultural variation within human ethnic groups (98).

Psychosocial Stress and Blood Pressure in New York City. A third example of a modern subpopulation model can be illustrated in the study of hypertension. Hypertension is defined from a cut-point in the distribution of standardized seated blood pressure measurements (99) and is pathologically high if it exceeds the threshold of 140/90 mm Hg. It is important that blood pressure pathology be understood as it represents a marker for or an underlying factor in the development of cardiovascular disease, the single highest cause of mortality in Western populations (100).

Biomedical anthropologists and human population biologists concern themselves with understanding human variation, and their input is critical in determining the boundaries between adaptive and pathological variation in blood pressure as well as other varying physiological traits. An important part of deciding what is a pathological response is determining what is appropriate variation associated with adaptation. Therefore, the question that may be asked in attempting to understand blood pressure pathology is "What is the normal adaptive response to the things that people do, experience, and think every day and the stress that these things cause?" The paradigm for this inquiry is a biopsychological synthesis of Selye's concept of the general adaptation syndrome (101), which provides a framework for studying adaptive responses that lead to degenerative diseases (84, 102).

An example of how blood pressure has been investigated in a dynamic context is a recent study of life stress in secretaries and laboratory technicians in New York City (103). A total of 121 healthy women participated in this study. Each wore an ambulatory monitor that took blood pressure every 15 min over the course of one 24-hr workday while at work, while commuting, and while at home, and every 30 min while sleeping. The pattern of hourly blood pressure averages were analyzed with regard to whether work or home was considered the most stressful microenvironment experienced on the day of study (Fig. 6). Work-stressed women had substantially higher pressures at work, a later commuting peak and a more precipitous drop in pressure from work to home than women who found home more stressful. Further analyses of subsets of the women suggested that having children and being married affected the perceptions of work and home stress, such that home-stressed women were more likely to be married and to have children (18). What these data showed is that the typical conditions of life profoundly affected how blood pressure varied and that the 140/90 mm Hg hypertension Rubicon often is crossed by most adults as a consequence of their usual daily behavior. Therefore, the data dramatically demonstrated that limiting analysis only to a single measurement taken under standardized conditions (as would be the case in typical epidemiological surveys) likely misses the true effects of stress at work or home on blood pressure and the potential role of this stress in cardiovascular pathology.

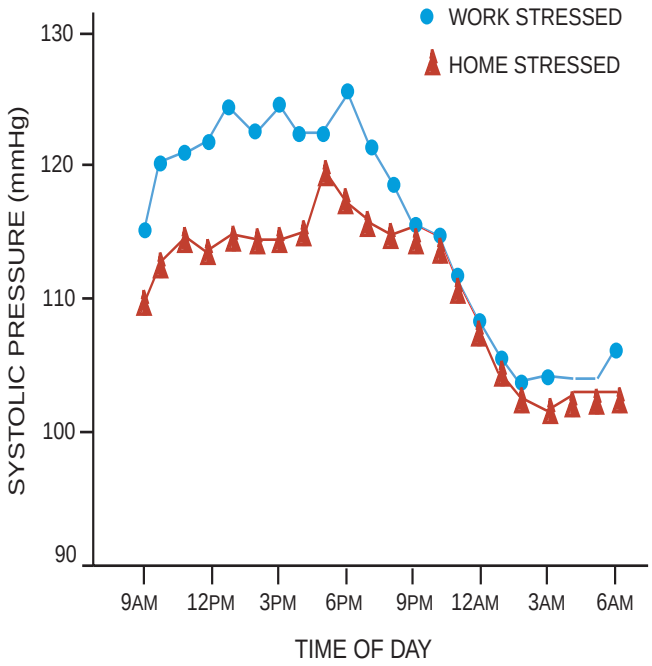

FIG. 6. Comparison of the pattern of systolic blood pressure variation among female secretaries and laboratory technicians, depending on whether work or home was perceived as more stressful (103).

The Value of Natural Experimentation

The three population models (traditional, modernizing, and modern) would appear to have an evolving importance in helping to frame and explain biomedical questions of local as well as global significance. The specific examples presented represent current research efforts. Yet, the three models are much more generalized than the specific examples presented. They provide a frame of reference, a theoretical construct in which to develop research thinking and answer problems. All three models use the population as the basic unit of study, use opportunistic and problem-oriented approaches, and use genetic, environmental, socio-cultural, and behavioral components as major determinants of health and disease outcome. Each of these models therefore represents major integrated methodological approaches that combine the biological, medical, and social and behavioral sciences toward the resolution of new as well as long-standing questions across disciplinary lines. We believe that such models already have contributed greatly to our understanding of health and disease outcomes, and with appropriate refinement and manipulation, they should help to generate new scientific knowledge and discovery well into the next millennium.

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