Coll. Antropol. **28** (2004) 2: 509–540
UDC 612.017:613.1:614.4
Original scientific paper

Environmental Stress and Adaptational Responses: Consequences for Human Health Outcomes

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A B S T R A C T

With the dramatic pace of modernization of the world's population, human adaptation as a theoretical construct and paradigm will likely become a focal scientific issue involving scientists from many disciplinary areas during the 21st Century. Macro and micro environments are in rapid flux and human populations are exposed to rapid change. The concept of adaptation, at least in the field of biological anthropology and human biology, will likely remain tied to evolutionary processes and concepts of selection and fitness. In this paper, we discuss the theoretical constructs of adaptation and adaptability and select three current examples from our ongoing research that involve studies of adaptation and evolutionary processes in modernizing populations in different locations worldwide.

Key words: *Hypoxic Stress, Altitude, HIF, Prion Diseases, Kuru, Co-Evolution, Reproduction*

Dedication

This paper is dedicated to Paul and Thelma Baker who for two generations trained and inspired young graduate students to pursue the study of human biological adaptation within the field of Anthropology and Human Population Biology.

Received for publication October 22, 2004

Introduction

Human Adaptation and Adaptability

Interests in human biological adaptation and acclimatization to the environment have a long historical perspective dating back at least to Aristotle[1]. What we mean by terms such as adaptation, acclimatization, and environment has been the source of great discussion and controversy in and of itself. In order to understand humans as biobehavioral beings requires that they be understood, first, as highly variable individuals who differ by age, gender, genetic makeup, history, population identity, and a host of other ways, and second, as creatures who must continually adjust to a social and cultural as well as a biological and physical mix of environments[2]. It may be convenient to separate the biological and behavioral aspects of human life as an aca- demic exercise in understanding, yet the adaptive process does not distinguish between the two. Behavior is biology and *vice versa*, and adaptation integrates these two conditions of life.

In the fields of biological anthropology and human biology, the concept of adaptation is closely bound to evolutionary processes, biological models, health, and ecology[3–5]. Adaptation can be thought of as a universal concept to assist in our understanding of human behavior and biology in a variety of contexts, including the sociocultural context. As a fundamental concept in evolutionary theory, adaptation is tied closely to related concepts of selection and fitness. However, adaptation need not only be studied in an evolutionary context, it also can be studied in the context of individual coping mechanisms, biobehavioral adjustments to stress, relative merits of different strategies, physiological and behavioral flexibility, and developmental plasticity. As Harrison[6] suggested, »adaptive processes operate to maintain physiological, behavioral and developmental homeostasis.« Evolutionary process may be implied in these studies, but evolution is not always a major consideration. Scientific interests can be directed toward understanding mechanisms of adjustment or patterns of variation, including processes that contribute to or limit variation.

Adaptability literally means »the ability to adapt,« yet the term has much broader application. As Baker[4] noted, the term *human adaptability* began only to be used widely during the years of the International Biological Programme (IBP) when the Human Adaptability Component of this program was in operation. At the beginning of the IBP, Weiner[7,8] conceptualized the field of human adaptability as a world--wide comparative study of the ecology of humankind, greatly needed because of the »... vast changes [that] are affecting the distribution, population density, and ways of life of human communities all over the world... [and that can be] measured in terms of health, fitness and genetic constitution.« Baker[9] identified human adaptability as »... the basic biological flexibility of human populations... [involving]... biological responses, which include biochemical, physiological, and behavioral components.« Human adaptability research, then, should focus efforts on ways in which human populations adapt biobehaviorally to their environments. Excellent reviews of human adaptability perspectives from the 1960s are by Baker[10], Lasker[11], Weiner[12], and more recently by Ulijaszek[13].

Adaptation as an Explanatory Paradigm

If one of the principal goals of human biology is to explain human biobehavioral variation, then one of the most effective means to do so is through an understanding of human patterns of adaptation. There are at least two fundamental ways to deal with adaptation. First, it can be applied simply as a perspective that as-

sists in understanding and in scientific explanation. The concept of adaptation has considerable explanatory power and can be used to understand complex relationships that cannot be conceptualized by other means. Second, specific studies can be designed in an attempt to demonstrate an adaptation or process of adaptation. In this case, an experimental approach is taken where hypotheses are formulated and tested. Adaptation, however, should not simply be used as »...the 'common sense' default assumption« [14]. Gould and Lewontin[15] correctly criticized those who consider adaptation as the *only* explanatory paradigm of evolutionary process, and cited allometry, scaling, pleiotropic by-products, and random effects as alternate explanations for what might appear to be adaptations. Those practitioners of what Gould and Lewontin call the »adaptationist programme« consider nearly everything as an adaptation and exclude alternative explanations. They were also highly critical of attempts to study adaptation in anything less than the whole organism. It should be clear, however, that Gould and Lewontin in no way reject the concept. Rather, they argue that it is often applied incorrectly, which involves poor logic and bad science, and leaves an opening for unnecessary attacks on the concept. Nearly five decades ago, Lewontin[16] identified a major problem in dealing with the concept when he stated that »There is virtually universal disagreement among students of evolution as to the meaning of adaptation.« To some extent, this is still true, although modest progress has been made since then.

Baker[3,10,17] wrestled with some of the issues that troubled Gould and Lewontin[15]. He identified two kinds of adaptive responses to stress: the first, called cultural and bio-adaptational universals, dealt with the needs of all members of our species (e.g., to eat, sleep, rest, learn); the second was a function of different environments producing different stresses and variation in adaptations to these different stresses (e.g., altitude, temperature, disease). With this framework, exploration of adaptive mechanisms under the second category does, to some degree, address the criticism that »adaptationists« consider *all* responses as adaptive« by focusing on the stresses that are most likely to contribute to population variation. This can be achieved by beginning scientific inquiry with the environmental stress rather than with a morphological, physiological, or behavioral characteristic (as a presumed response to that stress).

Mazess[18,19] addressed these and other problems of human adaptation in a discussion of what he called »adaptive domains.« Adaptive domains are referents used to assess relative benefit and necessity in evaluating adaptation at the level of the individual organism. The nine domains that were identified included: *reproduction*, *health*, *nutrition*, *nervous system*, *growth and development*, *resistance and cross-tolerance*, *physical performance*, *affective function*, and *intellectual ability* (a tenth domain, *sociality*, might be added as an important human attribute). The interactive and biobehavioral nature of these adaptive domains becomes quite clear if we look at »reproduction.« All other domains must be in relatively healthy states to facilitate normal reproduction. Mazess also raised the issue of adaptation at different levels of the biological hierarchy, that is, at the level of: cellular structures, the cell, tissues, organ systems, the organism, population, biotic community, ecosystem, and biosphere. Human behavioral units might be included in a hierarchy for exploration of adaptation, as well. They could include: ideas, individuals, family, ethnic group, society, region, nation, »humanosphere.« Each level becomes the environment of the next lower level in the series, to pro-

duce a hierarchy of environments and units of adaptation. Mazess suggested that each level of the hierarchy would have different criteria for assessing relative benefit, and hence, adaptive value. For example, important criteria for assessing the *population* as a unit in the hierarchy are size, density, distribution, composition, and persistence. Population, in this case could mean anything from a small group to our entire species. Multiple levels of adaptation are also consistent with contemporary, although controversial, understanding that there are multiple levels of selection[20].

Approaches to the Study of Human Adaptation

There are numerous areas in which human adaptation to the environment can be investigated in humans within a biobehavioral framework. In environmental physiology, considerable work has been done on adaptations of humans to stressful environments (heat, cold, altitude). Although there has been some interest in among-population variation, much of the environmental physiology research focused on physiological mechanisms with small samples of individuals tested. Adaptation and disease, and adaptation in reproduction and fertility in specific contexts are two other major research areas extensively studied by human biologists. Rather than giving an overreaching review of all the work on human adaptation over the past century, we will concentrate on emerging aspects of these three evolving research areas that attempt to understand adaptation and adaptational processes in human populations in Africa, Asia and the Pacific Basin, and Europe, specific examples of which will follow in the next section. As will be seen, it is difficult to determine what the consequences, if any, of some of these natural experiments might be in adaptational and evolutionary terms. But, what is clear is that some adaptational events have clearly led to survival and reproductive success of the populations, while others may not be known for some time as these natural experiments continue to play out on the stage of both a modernizing and modern world[21].

Adaptation and Stress

The concept of adaptation as used by environmental physiologists has had considerable influence on the thinking of many human biologists[5,22–24]. With the exception of C. Ladd Prosser[25,26] few physiologists had dealt with human adaptation in an evolutionary context. Rather, they focused on physiological systems and their responses to environmental stress. The kinds of environmental stresses explored include: thermal (heat and cold), hypoxic (high altitude), nutritional (low calorie and protein), and physical work (exercise).

»Stress« is a concept that has been used widely and has many meanings. At the simplest level of agreement, stress involves some environmental stimulus that produces a reaction in a living organism that may be either favorable or unfavorable to the organism. The term, *stress*, has been used in the literature both as an environmental stimulus and as the response to an environmental stimulus, which has added some confusion to understanding the concept. Ideas of *adjustment*, *coping*, *accommodation*, *adaptation*, *balance*, and *homeostasis* have been applied in studies of stress. The basis for present theory dates back to Claude Bernard[27] who identified the ability of all living creatures to maintain the constancy of their internal environment (*milieu interne*), and Walter Cannon[28], who coined the term *homeostasis* and defined some of the body's mechanisms of self-regulation in the face of external environmental variation. Cannon[29] also defined the flight or

fight emergency response that involved the sympathetic adrenal medullary system. The later work of Hans Selye[30] further defined the involvement of the endocrine system via the pituitary-adrenocortical axis.

Selye's[30] work on the non-specific response (strain) to environmental stressors led to his definition of the *General Adaptation Syndrome*. This was defined as a three-stage reaction beginning with an alarm stage, leading into a resistance stage, and ending with an exhaustion stage if the stressor (and strain) persists and the organism is unable to maintain the defensive responses. Selye's studies of stress define what might be identified as very acute responses to noxious stimuli usually involving behavior. Stress also may be thought of more broadly as a reaction (strain) of the human body to environmental forces (stressors) that perturb the body and lead to deviations in homeostatic states. Here, the homeostatic regulatory mechanisms are the principal means of combating stress in the organism. It is also the case that these homeostatic mechanisms are, themselves, capable of adjustment according to the duration and intensity of the environmental stressors. This process of »fine tuning« of the specific homeostatic mechanism may be thought of as *adaptation*.

The idea of *homeostasis* has been broadened in recent years by a reconceptualization of the way that homeostatic systems interact within the whole body. Sterling and Eyer[31] defined *allostasis* as a principle identifying »stability through change,« that is: »to maintain stability an organism must vary all the parameters of its internal milieu and match them appropriately to environmental demands.« Where *homeostasis* suggests a dynamic steady state maintained by negative feedback for a single system, *allostasis is* a more dynamic and interactive process where »...variation is achieved by multiple, mutually reinforcing neural and neuroendocrine mechanisms that override the homeostatic mechanisms«[31]. Homeostatic »set points« are continually shifting to accommodate changes in other internal systems in response to external stimuli/stresses.

A simple model to illustrate the principal relationships between environmental stress and various responses is presented in Figure 1. Here, any force from the environment (stress) has the potential to produce strain in the human organism. Strain, then, can be defined as a »deviation from homeostasis« or dynamic steady state that requires a human response. The response may be highly favorable to the human, and either reduce the strain itself or reduce or remove the stress. Such a favorable response may be viewed as an adaptation that restores the organism to a state of normal function by employing appropriate feedback controls. A means of adaptation may also involve a shift to a new homeostatic level. If the response is not successful in its feedback patterns to strain and stress, then the organism can be said to be unable to cope with the environmental conditions. This may lead to a chronic state of maladaptation that can be termed »poor health,« or even total failure of the system and death of the organism. In addition, maladaptation may resu-

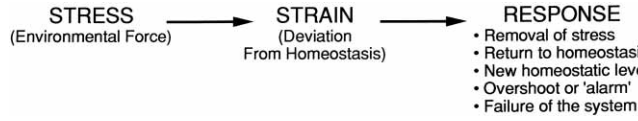

Fig. 1. Elementary model to demonstrate environmental stress, strain, and variable responses.

lt from overcompensation of homeostatic controls (an »overshoot« effect).

Within the framework of *allostasis*, poor health or adaptability may be defined as a state of limited responsiveness[31]. *Allostatic load* is then identified: »...as a measure of the cumulative physiological burden exacted on the body through attempts to adapt to life's demands«[32]. Here, *strain* may be identified as a chronic deviation from homeostasis (as in vascular hypertension) that produces stress, and consequent strain in other homeostatic systems[33].

Models are particularly useful in human physiology where interests are focused on effects of exercise or climatic effects on the human body. An example of climatic stress is *hypoxia* produced by decreased partial pressure oxygen at high altitudes. Since hypoxia stresses the human physiological system most intensely during strenuous physical activity, it is possible to reduce the stress by becoming inactive or by resting. Obviously, this is only a short-term behavioral adaptation, since human residents of high altitude mountain zones cannot cease all subsistence activities and still hope to survive. Other physiological mechanisms must therefore come into play to improve oxygen transport and oxygen delivery to the tissues and organs, and to restore oxygen homeostasis of working muscle[34], and the study of these mechanisms is best done through a »system science« approach. These mechanisms involve feedback controls in the heart, lungs, blood, and the circulatory system. It is also the case that the chest and lungs and the right side of the heart of individuals who have lived at high altitude since infancy are larger than in sea level residents[35,36]. These permanent size differences might be considered morphological or structural adaptations to high altitude, and they are likely to result from gradual developmental changes. Under the assumption that humans were exposed to an approximate sea level environment during the course of most of their evolutionary prehistory, then adaptations to high altitude hypoxia have clear evolutionary implications.

Early attempts in human physiology and biological anthropology were made to define patterns of adaptation as either (1) genetically specified, (2) developmental (ontogenetic adaptation), or (3) short-term, reversible, seasonal, or flexible (acclimatization)[11,37,38]. Although physiologists have seldom worked in this area, attempts by anthropologists to demonstrate genetic adaptation (with evolutionary implications) in human physiological systems have generally failed. It is quite clear to most investigators, however, that all physiological systems and adaptive patterns operate within fixed genetic limits[26]. Hence, we cannot just think of genetic or environmental adaptations: rather, we might conceptualize the process as either genetically inflexible and highly specified or genetically flexible and highly modifiable by environmental experiences (gene-environment interactions).

Developmental patterns of adaptation have been explored most commonly by anthropologists[24,39–44] in conjunction with their interests in child growth. An important point concerning environmental influences and developmental changes during growth is that many are not reversible and set limits on short-term acclimatization or adaptive responses that can be made during adulthood. Some of these processes are discussed in the section that follows.

Adaptation to Hypoxic Stress in Western China

There are no other environmental conditions that lend themselves to a »natural experiment« of human adaptability better than those that exist at high altitude. Hypoxia is a ubiquitous stress from which indigenous high altitude populations can-

not escape. It has significant physiological consequences to newcomers, and has been associated with reductions in fertility and increases in pathologies that lead to mortality[35,45,46]. It thus possesses all the characteristics necessary for the operation of natural selection on human populations. This was recognized over a generation ago by pioneers in the application of evolutionary biology models to human populations[47]. But the large number of studies that have taken place among high altitude populations living in the Andes of South America, in the Himalayas and on the Tibetan Plateau of Asia since the 1960's have produced a much more complex picture than was originally envisioned. The emerging picture of indigenous high-altitude groups is that they not only posses physiological and anatomical differences from lowlanders, but also differ from each other. While some of these differences may be genetic[48,49], many others seem to be related to ontogenic adjustments made to hypoxia[36] and other stressful conditions (particularly poor nutrition) that exist at high altitudes[50,51].

Most studies of indigenous high altitude population biology have focused on what appear to be unique physiological systems associated with oxygen extraction, transport and utilization, or on atypical anatomical features, particularly thorax dimensions. To understand the origins of the anatomical and physiological characteristics of high-altitude populations in an evolutionary context, the primary strategy has been to compare indigenous adults to adult sojourners from low altitude. The presumption, of course, is that any changes that occur among sojourners after exposure to high altitude would reflect short-term adjustments to hypoxia, not genetic adaptation. It is also possible to extend this model to include an analysis of long-term adjustments that may be made during the growth period, when both anatomical and physiological systems have greatest capacity to adjust to environmental conditions. Only those phenotypic differences that remain after accounting for the effects of both short-term and long-term (developmental) phenotypic adjustments, can potentially be attributed to genetic, or adaptive, differences between populations. Studies of this sort in the Andes and at other high altitude locations have indicated that individuals from low-altitude populations exhibit a number of long- and short-term ventilatory and hemodynamic changes, including increased minute volumes (and consequent elevations in al-veolar PO_2), reduced hypoxic ventilatory response (HVR), increased erythropoiesis, increased capillarization, increased myoglobin concentration, and increased mitochondrial number[46]. But, differences in thorax dimensions, pulmonary function[52], and probably in red cell numbers[41] persist between indigenous Andean groups and lowland sojourners, even those who have been born and raised at high altitude. For these phenotypes, the characteristics of high altitude populations may reflect genetically-determined adaptive differences compared to low altitude groups or in some cases high altitude pathologies[41].

Differences between Andean and Tibetan high altitude populations

One of the most intriguing results of high altitude research over the past two decades has been the realization that indigenous Tibetans appear to have smaller thoraxes, lower hemoglobin concentrations, greater HVRs, higher SaO_2, and lower incidences of chronic mountain sickness than Andeans. This has led to the hypothesis that Tibetans possess a superior (or at least different) adaptation to high altitude hypoxia than Andeans[53,54]. This hypothesis has been tested by studying, for the first time, the growth of indigenous Tibetan and lowland Han (Chinese) children who were born and raised at

high altitude[42–44,55–57]. Following models used in the Andes, it was thought that Han-Tibetan anatomical and physiological similarities during the growth period would demonstrate that development under hypoxic conditions is more important than genetic factors in explaining high altitude phenotypes. Our effort is the first to compare the growth of Han children born and raised at high and low altitudes. If hypoxia is more important than genetics in determining physiological phenotypes, Han children growing up at high altitude should exhibit significant phenotypic differences from Han children growing up at low altitude. Conversely, the persistence of phenotypic similarities among Han children at different altitudes, and/or the existence of differences between Han and Tibetan groups born and raised at the same high altitudes, would indicate that the two groups may exhibit genetically different responses to hypoxia.

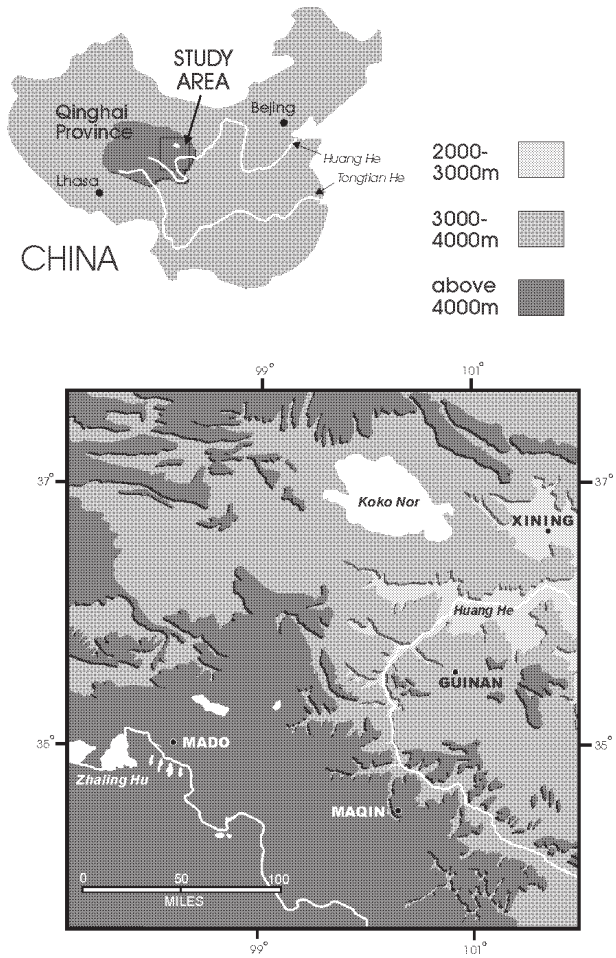

Fig. 2. Map of research area in Qinghai Province, Western China.

Fig. 3. Field laboratory for processing blood samples from children, adolescents and adults at 3200 m near the village of Guinan in Qinghai Province, Western China.

The study was carried out in Qinghai Province, western China, where a large number of first and second generation Han (Chinese) migrants from low altitude live in close proximity to indigenous Tibetan populations. Nearly 1,600 Han and Tibetan children, adolescents and adults who were born and raised in three economically similar rural towns (Guinan at 3200 m, Maquin at 3800 m, and Mado at 4300 m) were studied. Figure 2 shows the location of these towns South and East of Xining, the Capital of Qinghai Province. In addition, 894 Han children, adolescents and adults at low altitude were studied near Beijing, 238 first generation Han migrants to high altitude, and another 531 children, adolescents and adults of mixed Han-Tibetan parentage and other ethnic groups at high altitude (Figure 3).

Morphological growth of Han and Tibetan children and adolescents at high altitude

Our analysis of morphological growth indicates that Han children and young adolescents growing up at high altitude are shorter and lighter at every age than Han growing up at low altitude[43,56]. On the other hand, older adolescents and adults are similar in height; but, at these ages, low altitude Han weigh more than high altitude Han. It appears that this is a cohort effect, related to the recent, uneven economic development in China[58]. During the 15 years preceding our study, nutrition and growth appear to have improved more rapidly at low altitude than at high altitude[43]. The greatest differences in body size and composition occur among younger individuals who have grown up since the initiation of economic reforms in the 1980's, essentially in different nutritional environments at different altitudes. Conversely, the least difference occurs among older individuals who grew up prior to the economic reforms, in similar nutritional environments, regardless of altitude. The existence of proximate increases in food at low altitude could explain why older Han there are considerably fatter and heavier than those at high altitude, but are no taller.

The body size characteristics of Qinghai Tibetans are similar to those of Han throughout the growth period: the avera-

ge heights, weights, body fat and muscle masses of children and adolescents from both groups are significantly below low altitude US and Chinese standards[42,43,57]. Between 3200 m and 4300 m, altitude differences in body size are sporadic among Han and Tibetans alike, and are not consistent with expectations based on hypoxia-caused growth retardation. That is to say, in those age groups where altitude differences in body size do occur, children at 3800 m or 4300 m tend to be larger than those at 3200 m. Along with the cohort effect described above for Han, this seems to indicate that differences in nutrition may contribute to different growth patterns, even under the hypoxic conditions that exist in Qinghai. In this regard, our data correspond with growing evidence of poor nutrition on the Qinghai-Tibetan Plateau leading to high rates of nutritional deficiency syndromes and growth stunting[59–63]. Thus, among Han and Tibetan children and young adolescents living in Qinghai, as among Quechua and Aymara in the Andes[50,51,64–66], poor nutrition may play a larger role than hypoxia in determining slow growth at high altitude.

Differences in thorax and lung function growth between Han and Tibetans at high altitude

When altitude differences in stature, body fat and muscle mass are controlled statistically, there are few altitude differences in mean thorax diameters and circumferences of low altitude Han compared to Han at 3200 m and 3800 m. Thus, there is no support for the hypothesis that lowland children who grow up in an hypoxic environment experienced enhanced growth in thorax width, depth or circumference as a way of compensating for lower PO_2. On the other hand, Han children and adolescents at high altitude, while shorter than those growing up at low altitude, have longer sitting heights (i.e., shorter legs) relative to stature[44]. Since sitting height serves as a crude measure of chest length[67], this may indicate greater relative growth in thorax length among Han children and adolescents at high altitude. However, this pattern also corresponds to expectations based on nutritional differences between altitudes. Because of improved nutrition, children from recent generations in lowland China are taller than those of previous generations due to relatively greater leg length, not because of proportional increases in both thorax and leg length[68]. Altitude differences in diet among Han children and adolescents could therefore explain the altitude differences in relative sitting height. Adults, unlike children and adolescents, show similar statures and similar relative sitting heights at all altitudes. This also would be expected if, as explained earlier, adults at all altitudes experienced similar diets while younger. In Qinghai, therefore, the existence of relatively longer thoraxes among younger Han could be a serendipitous effect of nutrition and not a consequence of developmental adaptation to hypoxia.

In general, Han-Tibetan differences in thorax dimensions are much more significant than Han-Tibetan differences in body size[57]. Tibetans have larger thorax circumferences than Han, although ethnic differences in thorax shape are not the same in both males and females. At almost all ages, Tibetan males exhibit significantly greater chest depths than Han males; but there are no significant ethnic differences in chest width among males. Tibetan females, on the other hand, exhibit significantly greater chest widths than Han females; but the chest depths of both groups are generally similar. Han of both genders have longer sitting heights (both absolutely and relative to stature) than Tibetans, which may indicate ethnic differences in thorax length. The existence of clear ethnic differences in horizontal

chest dimensions, and the possibility of ethnic differences in thorax length is a strong indication that Han and Tibetans exhibit fundamentally different patterns of thorax growth at high altitude. Given the overall similarity in the growth of body size among Han and Tibetans, differences in thorax growth probably reflect genetic differences in the control of chest growth under hypoxic conditions.

As might be expected, the greater chest widths among Tibetan compared to Han females, and the greater chest depths of Tibetan compared to Han males are associated with greater lung function among Tibetans compared to Han. On the average, between the ages of 6 and 29 years, Qinghai Tibetans show forced vital capacities that are about 5 to 7 percent above those of Han born and raised at high altitude. This difference occurs despite the fact that Han have longer sitting heights (and possibly, therefore, longer lungs) than Tibetans, and despite the fact that Han growing up at high altitude exhibit small-to-moderate increases in lung volumes relative to Han growing up at low altitude[44]. Figures 4 and 5 show the differences in forced vital capacity (relative to stature) between Han and Tibetan males and females at 3800 m; but neither group exhibits significantly greater lung functions at 4300 m or 3800 m compared to 3200 m; and Tibetan-Han differences in lung function are consistent at all altitudes. It is difficult to escape the conclusion that (potentially genetic) ethnic differences in thorax growth produce ethnic differences in lung function. Furthermore, lung function is increased in Tibetans compared to Han, despite gender differences in thorax shape. Thus, regardless of whether Tibetans exhibit increased thorax depth (as among males) or increased thorax width (as among females), the result is a comparable increase in lung function relative to Han.

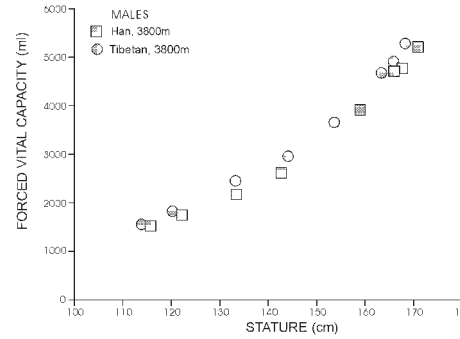

Fig. 4. Relationship between forced vital capacity and stature among Han and Tibetan males, ages 6–29 years, at 3800 m.

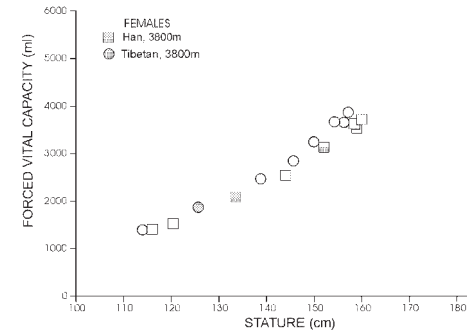

Fig. 5. Relationship between forced vital capacity and stature among Han and Tibetan females, ages 6–29 years, at 3800 m.

Differences in hematological growth between Han and Tibetans at high altitude

There also appear to exist differences between Han and Tibetans in hematological characteristics, particularly at 3800 m and above[55]. But, this difference is apparent only beginning at adolescence. At 3200 m, not only are there no hematological differences between Han and Tibetan children, adolescents and young adults, but Han and Tibetan males and females of all ages show [Hb] and hematocrit values that are well within normal limits of

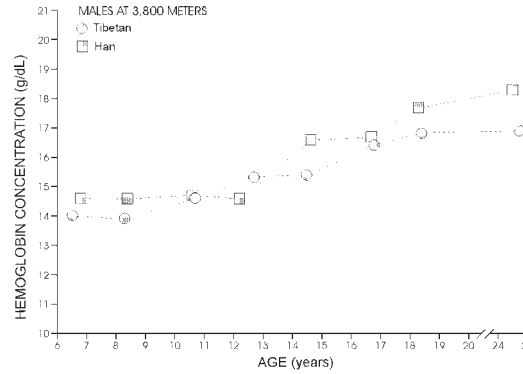

Fig. 6. Average hemoglobin concentration of Han and Tibetan males between the ages of 6 and 29 years, at 3800 m. Data are aggregated by 2-year age groups for individuals between 6 and 19 years, and as a single 10-year age group for individuals 20 through 29 years.

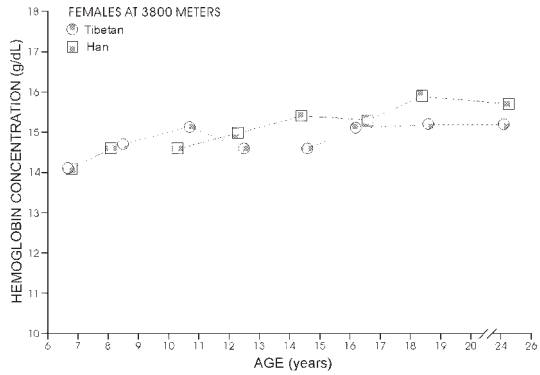

Fig. 7. Average hemoglobin concentration of Han and Tibetan females between the ages of 6 and 29 years, at 3800 m. Data are aggregated by 2-year age groups for individuals between 6 and 19 years, and as a single 10-year age group for individuals 20 through 29 years.

similarly aged low-altitude Americans. However, the affect of altitude on the hematological characteristics of both groups is clearly discernable at 3800 m and 4300 m. At 3800 m, hematological values for both Han and Tibetan males and females are elevated compared to individuals at 3200 m, and values for each age-group are at or above the low altitude, US 95th percentile. Male Tibetans at 4300 m show higher hematocrit (but roughly equivalent [Hb]) values compared to male Tibetans at 3800 m. Both [Hb] and hematocrit of male Han children are higher at 4300 m compared to 3800 m. Even though the hematological characteristics of both Han and Tibetan show an altitude affect above 3200 m, the Han seem to exhibit an age and altitude interaction that does not exist among Tibetans. This is evident when children ages 13 and younger are compared to adolescents and young adults ages 14 through 29. Prior to age 14, the hematological characteristics of Han and Tibetan children at 3800 m and 4300 m are similar (Figures 6 and 7); but, beginning in

early adolescence, a divergence between the two groups appears to exist. Among individuals aged 14–29 years, mean hematological values of Han are greater than those of Tibetans.

Even though *mean* hematological values of Han adolescents and young adults at 3800 m and at 4300 m are significantly greater than those of Tibetan adolescents and young adults, there is considerable overlap in the distribution of both [Hb] and hematocrit between the two groups. Since many Han and Tibetans have similar hematological characteristics, it is important to understand why some Han appear to exhibit a tendency toward elevated hematological characteristics and others do not. Understanding individual variation in hematological characteristics may require deciphering the relationships between variation in HVR, variation in SaO_2, and variation in erythropoietic response. For example, if differences in ventilatory sensitivity to hypoxia play a role in determining hematological characteristics[69], then the Han-Tibetan differences in [Hb] and hematocrit that begin during adolescence at 3800 m may reflect differences in hypoxic ventilatory response that begin at the same time. As is the case for other low altitude populations[70,71], as well as for high altitude Quechua[72], Han residents at high altitude may undergo a »blunting« of hypoxic sensitivity during adolescence, causing a relative increase in [Hb] and hematocrit. Han adults who migrated to Lhasa (3,658 m) as children show reduced HVR compared to Han adults who migrated after adolescence[73]. In contrast, young adult Tibetans appear to posses a hypoxic sensitivity similar to that of newcomers to high altitude[73]. Since Tibetans do not experience an adolescent »blunting« of HVR[49], this might explain their generally lower [Hb] and hematocrit values compared to adolescent and young adult Han.

Future Research in Qinghai

These interesting possibilities form the basis of our future research in Qinghai. One important study would be to »track« longitudinal changes in HVR, SaO_2 and erythropoiesis during adolescence. Repeated measurements of the same adolescents over a five-year period will help determine the range of individual Han and Tibetans differences in erythropoietic growth patterns. This first-ever longitudinal study of physiological growth should therefore help resolve whether the erythropoietic and ventilatory responses to hypoxia are essentially the same for many Han and Tibetans, and whether all individuals (Han and Tibetans) who show elevated [Hb] growth during adolescence show a corresponding reduction in the ventilatory response to hypoxia. In the end, a better understanding of the nature of individual variation within and between groups should make possible a clearer appreciation of the extent of Tibetan physiological uniqueness.

One explanation for the distribution of [Hb] and hematocrit between the two populations may be that individual variation in HVR and/or SaO_2 and/or erythropoiesis are inherited[48,49,74]. A second future project would involve research on the genetic mechanisms that underlie individual physiological differences. The focus of this project would be an investigation of variation in the structure, activation or action of hypoxia-inducible-factor (HIF), a recently discovered protein that seems to regulate many of the genes that appear to encode responses to hypoxia. Hypoxia prevents HIF-1 complex from being degraded, thus enabling its activation of erythropoietin, vascular endothelial growth factor (VEGF), various components of gylcolytic metabolism and peptides that appear to affect the vascular development of the lung in hypoxic conditions[75–78]. Indeed, while the mechanisms for oxygen sensing and hypoxic-transcriptional gene

activation are not completely understood, it has been suggested that they may be shared by many (if not all) cells[75]. It is conceivable that there exist polymorphisms in the structure of the HIF-1 complex, in the enhancer (or hypoxia-responsive-element) regions of genes such as the one that controls erythropoietin, or in the way hypoxia affects the ubiquitination or stabilization of HIF-1.

Investigating these possibilities in Tibetan versus Han populations could provide a clue as to the underlying control of different [Hb] or ventilatory responses to hypoxia. Beall et al.[79], has already demonstrated that Tibetans show increased concentrations of NO in exhaled air. Expression of the gene encoding inducible nitric oxide synthase that generates NO is induced by hypoxia in an HIF-1 dependent manner in some cell types[77]. Molecules that function as NO donors have also been reported to stabilize HIF-1[80], although large concentrations may inhibit such stabilization. Thus, the exciting possibility exists that it may be possible to determine a genetic mechanism explaining individual and population differences in physiological function at high altitude.

The Qinghai research project has the potential for identifying genetic adaptations at high altitude. This research supports the hypothesis that Tibetans have genetically different responses to hypoxia than low altitude groups. However, this study and those of others[53,54] also indicate that there is a substantial range of individual variation in thorax size, lung function, the ventilatory response to hypoxia, hematological characteristics, and SaO_2. Understanding how individuals may differ in their functional responses to hypoxia is just as important as deciphering the genetic basis for this variation. If it can be demonstrated that individuals with particular phenotypes actually function better under hypoxic conditions than others, we will have the first real evidence that natural selection may be operating on complex physiological systems at high altitude.

Adaptation and Disease

One of the newest emerging research areas in biomedical anthropology and human population biology is what has been termed evolutionary or Darwinian medicine[81]. It is a reasonable assumption and consistent with Darwinian theory of evolution that all forms of disease, whether infectious, hereditary or degenerative, are subject to the processes of natural selection and adaptation to the environment. This has been best documented for infectious host-parasite relationships in which interactive processes and competition produce an environment of intense selection[82]. Clearly, the discovery of human adaptation to sickle cell anemia and the resulting protection against malaria was a major landmark in the development of this emerging area. Another is our increasing awareness and knowledge about the evolutionary implications of antibiotic resistance and an understanding of the evolution of parasite virulence and co-adaptation of host and parasite[82]. All of these issues can be studied at the population level.

The complex process of human response to infectious disease is an ideal model for adaptation. It involves co-evolutionary transformation of host/parasite resistance, and adaptation that may include genetic changes in both organisms or adaptations at other levels. Although these are not known for most infectious diseases, there are probably hereditary factors in resistance and susceptibility (genetic adaptation), developmental factors through behavior, health and immune status (developmental adaptation) in resistance, and short-term adaptation factors linked to health. There is even a body of information to suggest that negative emotio-

nal status can affect the immune system and increase susceptibility to disease or limit recovery when disease is present (psychoneuroimmunology)[83].

Our best example, within this framework, is the epidemiology of malaria. Here the patterns of adaptation to the disease are extraordinarily complex, with several organisms (parasite, mosquito, humans), several levels of adaptation, and a broad lifetime of exposure for many peoples in the tropical world. At the genetic level of adaptation, the hemoglobin variants that produce sickle-cell anemia, thalassemia, and other forms of hemoglobin variant anemias, also lead to varying degrees of serious anemic illness, and often death, when these conditions are produced by genetically homozygous states. The heterozygous condition, on the other hand, provides some protection against the *Plasmodium* parasite that causes malaria[84]. What is most important is that this genetic adaptation that reduces malaria susceptibility and severity is most helpful to children with immature immune systems. Hence, those with the phenotype that helps them survive repeated malaria assaults during childhood, have the time to develop their own immune systems that will, in turn, help them to combat malaria as adults. Among adults who are exposed to malaria and having survived childhood exposures, there are three levels of defense against (or adaptation to) malaria: (1) the genetic level with hemoglobin variants, (2) the immune system level, and (3) the short-term response level, where an individual's health and behavior can profoundly influence exposure and depth of infection. Current research by Lum and Colleagues in Vanuatu and Africa is addressing the interaction and genetics of Plasmodia, Anopheles, and humans in hyperendemic areas of Malaria[85–87] with an attempt to understand the evolution of drug resistance[88].

A second new and exciting example involves the discovery of the role of genetics and environment in helminthic infections among the Jirel population of Nepal whereby genes on human chromosomes 1 and 13 have a significant affect on *Ascaris* infection[89,90]. *Ascaris* infections occur in a quarter of the world's population, significantly affecting nutrition, growth, and development. It is known that helminthic infections are not distributed uniformly in human populations, but are more characteristically over-distributed in a small portion of individuals, often with a familial pattern of distribution[89]. Using 444 members of a single Jirel pedigree, evidence for *Ascaris* worm burdens has been found to be associated with loci on chromosomes 1 and 13, and perhaps 8 as well, and candidate genes have been identified[91]. These data are the first to link genes influencing susceptibility to *Ascaris lumbricoides* infection, showing that 80% of the total worm burden is attributable to 20% of the infected individuals. Thus, we have another demonstration of genetic susceptibility to infectious disease, and a mechanism to identify susceptible individuals, not only for possible intervention, but also for understanding principles of co-adaptation, selection, and evolution.

A third example from the chronic disease realm concerns the so-called »diseases of civilization«: cardiovascular disease (CVD), hypertension, adult onset diabetes (non-insulin dependent diabetes mellitus-NIDDM), obesity, and cancer. Within the United States today, these diseases are endemic with most at very high levels. Since most of these disorders are older-adult diseases, there are implications of life style causality (CVD, hypertension, NIDDM, obesity, certain cancers) and changes in the immune response with aging (some cancers) that are linked to a changing environment. This changing environment in Western nations (having accelerated following world war II)

includes increased environmental toxins, reduced human physical activity, abundant food, commercial encouragement of excess food intake, and an increased stress level associated with lifestyle[21,33,92]. Hence, this changing environment has disrupted human homeostatic systems of health and well-being, or according to Harrison's[93] framework, has reduced the biobehavioral fitness (adaptive status) of individuals.

There is another dimension to such changing environments and reductions in patterns of adaptation. Non-Western peoples are also changing life styles and developing »Western« diseases. The impact of a modernizing environment on the health of people from traditional societies appears even more disruptive than it is on Western peoples. A case in point is Polynesian migrants from Pacific islands to Hawaii and other Western sites[94,95]. Samoan migrants to Hawaii and California have the greatest obesity of any population in the world and show increasing incidence of diabetes, hypertension, and CVD[95]. Likewise, the rate of hypertension in adults on Saba Island, in the Netherlands Antilles in the Caribbean is more then 50%, the highest in the world[96].

In 1962 James Neel postulated a genetic theory to explain the extraordinarily high prevalence of diabetes among certain population groups[97–99]. Although never fully confirmed, Neel suggested a genetic adaptive system designed to enhance energy utilization and body fat storage during periods of food abundance as a compensation for weight loss during periods of food scarcity. The modern state of consistent and abundant food availability is thought to stress the pancreatic system and lead to diabetes in »susceptible« individuals[100]. These same individuals who are susceptible to obesity and diabetes in the new environment of food abundance, were well adapted to the old environment of fluctuating food availability.

Finally, the immune system, which is exquisitely designed (through natural selection) to deal with disease stress at the genetic, developmental, and short-term levels of adaptation, is being affected by the new life styles of modernization. Stresses from toxins, the pace of modern life, excess intakes of fat, and other factors are contributing to immune impairment, and increased susceptibility to a variety of diseases. HIV infection producing acquired immunodeficiency syndrome (AIDS) is another wrinkle in the fabric of the adaptive immune system, where components of the immune system itself are impaired[101]. Here, the adaptive defenses against AIDS, caused by a highly mutable RNA virus, and against many other infectious diseases may be lost, and mortality rates are often extremely high. Although we have come a long way in understanding mechanisms of interventions and prevention, we have much to learn, not only about AIDS, but also about the adaptive nature of the immune system.

Co-Evolution, Adaptation and Prion Diseases

Today, there is a growing potential for rapid global dissemination of dangerous pathogens emerging from diverse sources[82,102–105]. The existence of such pathogens in nature and/or endemic to isolated and modernizing human populations is potentially harmful to all of humanity and can result in major epidemics of fatal disorders. One of the most interesting issues regarding human adaptation and adaptability to infectious or transmissible diseases yet to be studied in any significant way is adaptation and evolution of »infectious« proteins (prions) or prion diseases. The study of human transmissible spongiform encephalopathies (TSEs)[106] arose from D. Carleton Gajdusek's historic and landmark work on kuru in the mid 1950s in a remote area of the Eastern Highlands of Papua New Guinea. With

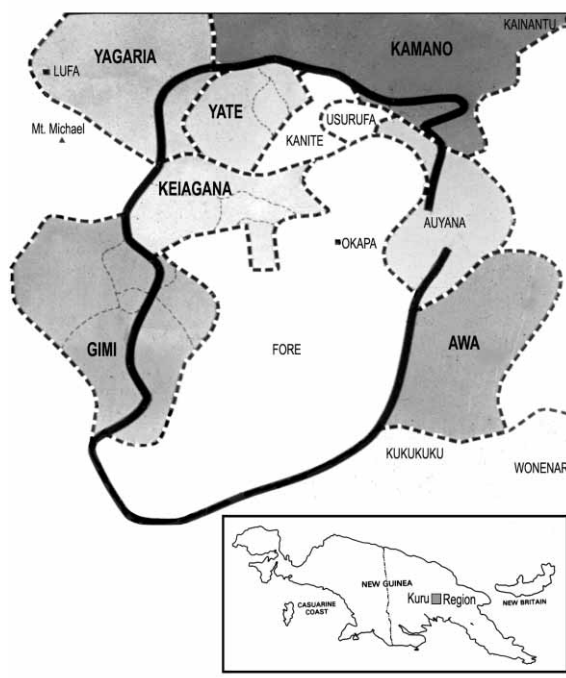

Fig. 8. Insert map showing the approximate location of the kuru region in the Eastern Highlands of Papua New Guinea. The larger map is a linguistic map of the region at the height of the kuru epidemic with the highest prevalence found among the Fore linguistic group, particularly those in the South Fore region. Photo courtesy of D. Carleton Gajdusek.

an Australian Medical Officer, Vincent Zigas, they brought to the medical and scientific world's attention for the first time a description of an epidemic of a uniformly fatal neurodegenerative disorder among the Fore linguistic group that killed over 3,000 people[107]. The kuru epidemic peaked during the mid 20th century and subsided to near extinction by the end of the century.

Kuru. The list of seminal discoveries made in small population isolates as noted above is headed by Gajdusek's work on kuru and his resultant discovery of new mechanisms for the origin and dissemination of infectious disease[108]. His recognition by the Nobel Foundation in 1976 underscores the global importance of this research, which has shown that naturally occurring disease models are more than just exotic phenomena with only local application and interest. Recently, and most unusually, a second Nobel Prize was awarded in 1997 to Stanley Prusiner for his characterization of the infectious agent or prion found in kuru and other TSEs, again emphasizing the evolving importance of this group of unconventional agents[109]. The investigation of kuru opened the floodgates to one of the most controversial and novel scientific discoveries of our time, with perhaps one of the most promising opportunities to investigate host-parasite relationships and the evolution and potential co-adaptation of this fascinating group of transmissible agents.

Fig. 9. Kuru children and adults in various clinical stages of their disease at the Okapa Hospital in the Fore region of Papua New Guinea. The three adult women standing are still ambulatory and use long wooden sticks for support. The children in the lower right cannot stand alone and some cannot sit without support. Photo courtesy of D. Carleton Gajdusek.

Kuru is a subacute, uniformly fatal, degenerative disease of the CNS that affected some 160 villages in a population of 35,000. First described more than 45 years ago in an early contact stone-age Neolithic society in the Eastern Highlands of New Guinea[107], more than 80% of the 3000 deaths from kuru occurred in the Fore linguistic group, particularly in the South Fore region (Figure 8). In some villages 50% of all deaths were from kuru. The clinical course is progressive and relatively uniform, leading to total incapacitation and death, usually within 3–9 months. At its height, kuru was epidemiologically the most prevalent cause of death among the Fore people. It affected essentially all ages beyond infancy and was common in children of both sexes (Figure 9). Adult women were particularly prone to the disease – an epidemiological pattern that was determined by culturally specific practices of transmission via ritual cannibalism. There was a marked excess of deaths among females with a F:M ratio as high as 3:1 or even higher in some villages, a sex ratio change that led to a change in the social structure from a polygynous to a polyandrous society, with a concomitant change in the division of labor[110]. Traditionally, women cultivated gardens and cared for small children, cooked, and cared for pigs, which were an integral part of highland New Guinea society. Men cleared the gardens, made fences for pigs, hunted, and occasionally waged war. The Fore were originally a polygynous society, but by 1960 polygyny was rare because of kuru and the influence of missionaries in the region. With the dramatic loss of women, which led to motherless nuclear families, men began to perform the role of both mother and father. In this changing South Fore society, a role change occurred and they began cooking food and tending to children, pigs, and the gardens. The loss of women due to kuru changed the sex ratio, and indeed the whole »social fabric of the society« [111].

Kuru can be traced only as far back as the beginning of the 20th century[112]. However, a systematic decline by age group in the frequency of kuru occurred since 1960. First, kuru was no longer seen in

pre-adolescent children, then no longer in adolescent and young adults, and only several cases in middle-aged adults as said exist[110]. Thus, there is a near total disappearance of the disease from the world[113]. Kuru is not transovarian or transplacental and no child born to a kuru mother ever contracted kuru after the cessation of cannibalism, an important evolutionary consideration[114]. The decline was clearly coincident with the cessation of ritual cannibalism as a rite of mourning and respect for dead kinsman.

When a kuru or other relative died, rites of mourning were carried out before the body of the victim was consumed. After the funeral, the victim's maternal kin dismembered the body in a sugar cane field using a bamboo knife and stone axe, resulting in conjunctival, nasal, and skin contaminations and oral inoculation of women and their accompanying babies and small children, by handling highly »infectious« brain tissue[110,112]. The brain was removed and eaten, usually with little cooking. When cooking did take place, the method varied. In high incidence areas, it would be cut in small pieces and steamed in a bamboo tube with vegetables. It was solely the job of women to dismember and prepare the body for cooking and distribution among the women. Adolescent boys and adult men usually did not participate in these ritual feasts. When men did occasionally eat human flesh, it was seldom that of women, and they usually only consumed muscle where the »infectious« agent or prions are found in low titer[110].

The Fore explanation for disease was sorcery. Relatives of the victim sought out the person they believed responsible, to get them to remove the curse, to kill them, or to extract a payment for the misdeed. The origin of kuru is not known, but it is possible that kuru resulted from a sporadic case of Creutzfeldt-Jacob disease (CJD) as the index case to the epidemic in a cannibalistic society that accentuated the risk immeasurably. Ultimately, it was behavioral intervention that relieved the population of this terrible burden, and the cessation of human cannibalism was through the efforts of missionaries and government administrative controls and not the direct result of medical intervention.

Creutzfeldt-Jacob disease and the mad cow epidemic. Creutzfeldt-Jacob disease is a rare, usually sporadic, sometimes iatrogenic, pre-senile dementia found worldwide, with 10% of cases having a familial form. Typically, patients present clinically with a rapid global dementia and marked progressive motor dysfunction[110,115]. The disease, like kuru, is usually fatal in less than a year. CJD was the second human spongiform encephalopathy discovered to be transmissible to both humans and experimental animals.

Both diseases are caused by prions or »infectious proteins« that have an altered conformation (folding) that acts as a nidas and induces normal host precursor protein to adopt a host form of the abnormal protein according to two different theories[109,110]. A prion may act like a nucleating agent or »missionary« capable of converting chemically identical normal precursor proteins to fold abnormally, a conversion of a soluble protease sensitive lyphophillic alpha configuration to an abnormal insoluble hydrophobic beta-pleated sheet configuration that is protease resistant. Thus, »propagation« of the protein can occur under this scenario without the need for a nucleic acid, an idea first proposed by Griffith more than three decades ago[116].

The current epidemic of bovine spongiform encephalopathy (BSE) or mad cow disease in Europe likely has its origin from a two-century-old disease of sheep and goats called scrapie [117]. Although the story is complicated and parts still specu-

lative, prions from scrapie-infected sheep may have crossed the species barrier to cause BSE. The epidemic began in the UK where scrapie in sheep is commonly found, and where carcasses rendered from scrapie sheep in the mid 1980s were included in the processing of livestock feed. About the same time, the usual rendering process was changed, which probably allowed the survival of scrapie prions in feed that orally »infected« cattle. Experimentally, BSE as well as scrapie can be transmitted orally to cattle and sheep[118,119]. Subsequently, BSE was shown to be the likely cause of a variant of CJD (vCJD) as a result of ingestion of contaminated beef[120,121], although an inquiry panel in the UK hypothesized that vCJD resulted from a spontaneous mutation in a single cow that was rendered into the food chain. Although, BSE in the UK has dramatically decreased since the mid 1990s, some 200,000 symptomatic, and an additional 4.5 million asymptomatic cattle have been destroyed, bringing the beef industry in the UK to near economic destruction[120,121]. Thus, with a likely species barrier breach and bovine neocannibalism, we have two concurrent epidemics with an initial lag phase of approximately five years between the two, BSE and vCJD. A third potential TSE epidemic, unrelated to the current epidemics in Europe, is emerging in farmed and free-ranging deer and elk in the U.S. and Canada, called chronic wasting disease (CWD).

Chronic wasting disease. CWD in deer and elk, first recognized more than three decades ago[122,123], appears to be spreading across eight states in the Western U.S. and southern Canada, and as far East as Wisconsin. The disease was first identified in captive deer in Colorado and has now spread to wild populations of both mule and whitetail deer in five states and Saskatchewan. The spread (or recognition) of CWD was slow to start and led to the reported destruction of nearly 15,000 deer and elk[124] as a means of containment, even though only a small percentage were likely infected. Although there is no direct evidence today that ingestion of deer or elk with CWD has infected humans, at least five cases of CJD in young people in the U.S. in their 20s and 30s, similar in age to vCJD victims in Europe »infected« with prions from BSE, have been uncovered, a number of whom ate venison[125].

Clinically, animals with CWD lose weight, salivate enormously, have strange behavioral alterations, and die[122,123]. Although the origin and transmission of CWD are not yet known, the spread could be associated with browsing on the same range as animals with CWD, or though breeding of captive deer and farmed elk. The link to humans, although small, could take place by eating contaminated meat, and spread perhaps by commercial processing of deer meat scraps into deer hamburger where contaminated and uncontaminated meat would come in contact with eachother, particularly during the grinding procedure. Oral transmission of TSE has been shown to occur not only in kuru, scrapie (in sheep), and transmissible mink encephalopathy, but also in natural and experimental BSE and CWD[118– 121,126,127].

In CWD, the species barrier was breached from deer to elk, but the conversion of CWD prions to human prions has not yet been proved[125,128]. From a genetic perspective, prion (PrP) genotypes of captive and free-ranging elk with CWD show a polymorphism (methionine/leucine) at codon 132 that is associated with variable CWD susceptibility. This codon corresponds to the polymorphism at codon 129 in humans. Elk homozygous for PrP at codon 132 (methionine/methionine) were found to be over represented in both free-ranging wild elk as well as in farmed elk with CWD[129]. Interestingly, elk homozygous for leucine/leucine at codon 132 we-

re found to be free of CWD. O'Rourke et al.[129], imply that selective breeding of leucine/leucine homozygotes resistant to CWD may become necessary as has been suggested to control scrapie in sheep[130]. What effect this would have on the long-term survival of this genotype and other polymorphic forms in wild populations is not known. Such breeding may increase resistance to CWD, the immediate problem, but throw out of balance the naturally evolved genetic structure of wild elk populations, making them highly susceptible to genetic or other disease burdens in the future. Whether anthropogenically manipulated or not, the fascinating issues of co-adaptation of this group of agents and their co-evolutionary consequences may be an extremely significant and emerging research issue for the future.

The current epidemic of CWD, if allowed to proceed unchecked, may have devastating implications, not only for wild populations of deer and elk, but perhaps prions from CWD animals will continue to cross the species barrier converting host precursor protein in widely different wildlife species or in humans. Although evolutionary processes are likely to be short circuited through anthropogenic intervention, we should again take advantage of yet another emerging model of disease, concurrently posing a threat to the health of wildlife, and perhaps human populations in North America.

Implications for Evolution and Adaptation to Prion Diseases

Perhaps the most interesting question from an evolutionary and adaptability point of view is whether or not the Fore population of New Guinea ever adapted to kuru and the prospects for adaptation to vCJD in Europe. With respect to kuru, we know that the Fore people adapted behaviorally and socioculturally to this intense disease stress by »inventing« kuru sorcery, which led to the Fore explanation of the disease. This sociocultural explanation of the disease allowed the Fore to potentially stop or check its occurrence; that is, once the sorcerer was identified, negotiations were opened with the sorcerer to lift the curse, and if that failed, to extract some just payment for generating the curse or initiating reprisal murder of the sorcerer, not necessarily in that order.

Biologically, there is evidence to support a differential genetic susceptibility for the timing of the onset of kuru with the most »adapted« or resistant individuals having a later onset and longer duration of disease, and thus, surviving through reproductive age. We know that nursing infants and children were likely infected by remaining at their mother's side during ritual cannibalism. The estimated minimum incubation time of 4–5 years and a maximum of 40–45 years are based on the youngest and oldest patients who developed kuru[114]. Molecular studies of TSEs have demonstrated multiple mutations in the PrP gene on chromosome 20, the gene that encodes the prion protein[131]. At position (codon) 129 of the PRNP (PrP) gene, a methionine/valine polymorphism occurs, the homozygous methionine/methionine genotype that has been shown to be associated with an earlier age at onset and shorter duration of disease in kuru patients[132]. In a follow-up study, it was further established that methionine/methionine genotype carriers were the first to be disproportionately eliminated from the population, and the less susceptible genotypes, methionine/valine and valine/valine, had an older age at onset and longer duration of disease[133]. Homozygous valine/valine individuals probably had the longest incubation time and the oldest age at onset. The same increased susceptibility has been reported for CJD, and to date, all 120 plus individuals with verified vCJD have been homozygous for methionine at codon 129[134]. This scenario, of course, has great implications for

natural selection and reproductive fitness. Since we know from studies of kuru patients that individuals with the youngest age at onset are those homozygous for methionine/methionine at codon 129, we can predict the likely early loss (incomplete fertility) of methionine/methionine phenotypes from the Fore population.

Future research perspectives on Prions and Prion Diseases

The main scientific significance of kuru was that it led to the discovery of the cause of other human and animal TSEs, and to the novel discovery of a whole new group of biological agents termed infectious amyloids or prion proteins that are self-replicating without the presence of DNA or RNA, a biological heresy that changed our fundamental scientific thinking. It also gave us considerable insight into the recent outbreak of a new disease called bovine spongiform encephalopathy, or mad cow disease in Europe, caused initially by processing of contaminated sheep and cattle into protein supplements as an additive to cattle feed. Thus, most unfortunately, we have a new natural experiment in progress, perhaps akin to kuru, with the long-term susceptibility of a human population eating prion-contaminated beef. With it, we have a scientific opportunity not only to find ways to impede transmission and provide intervention regimes to patients afflicted with prion diseases, but also to attempt to understand the evolution of host-parasite relationships, mechanisms for cross-species barriers and breachings, and questions regarding virulence and attenuation, genetic susceptibility, and programmed onset, duration, and death.

Is there a slow process of host-parasite co-adaptation for prion diseases over the next 50 years, or will it depend solely on the genetic structure of the infected population and resultant age at onset and duration of disease, affecting completed fertility and Darwinian fitness? What are the adaptational and evolutionary implications in conversion of infecting prion to host prions that are recognized as »self«, and thus, not subject to an immune response against these conformationally abnormal proteins? What of a possible species barrier breach, prions from cervids (deer and elk) »infecting« cattle and now prions from cattle »infecting« humans? Is there evidence for molecular barriers limiting cross-species susceptibility to prion diseases as Raymond et al.[128] have suggested for CWD? By contrast, can species-specific prions develop an altered host range in cross-species adaptation as some experimental evidence suggests[120,121,135–137]? Passage of scrapie in cattle may have acquired an ability to infect other species (i.e., cattle and humans) even though scrapie is not naturally pathogenic to either. These questions are part of interactive models that remain an important force in determining health outcomes in traditional as well as in modernizing and modern populations worldwide, and a major driving force in the evolution and adaptation of our species[21]. It was the practice of endocannibalism that accelerated the transmission of kuru, human intervention that created the abrupt transformation of the epidemic by the cessation of cannibalism leading to the disappearance of the disease, and anthropogenically-induced bovine neocannibalism that led to the current epidemic of BSE and resultant vCJD in Europe.

Adaptation and Reproduction

Within the past two decades, patterns of human reproduction have begun to be explored within evolutionary, ecological, and adaptational frameworks. This has been accomplished by integration of ideas from social demography, physiology, endocrinology, medicine, exercise physiology,

nutrition, body composition, and growth and development[138–140]. This synthesis of Darwinian evolution, ecology, and reproduction, which led to remarkable gains in our understanding of human reproduction, has been produced largely by biological anthropologists, and human biologists with anthropological training. The bases for these advances in knowledge are unique anthropological perspectives that: (1) employ evolutionary, ecological, and adaptational frameworks to explain human variation; (2) embrace biobehavioral and biocultural approaches to understanding human adaptation to the environment; and (3) encourage Western and non-Western cross-population comparisons to investigate human population variation.

One of the earliest studies to explore the interaction of biology and behavior on reproductive function was conducted by Rose Frisch[141]. She argued that there was a »critical weight« that had to be achieved during adolescence in girls for menarche to be triggered. Over the course of her research, she modified this »critical weight hypothesis« to a »critical body fat hypothesis,« where young girls had to reach a given level of fat deposition (approaching the adult female pattern) before menarche would occur[142]. She also described, in a taxi to one of us (M.A.L.) in 1972, work that she was pursuing with female models who regularly experienced amenorrhea during dieting. Hence, although her work was severely criticized at the time, she was a pioneer in identifying early relationships among energy balance, body composition, and activity in adolescent girls and women. The most recent perspective on these relationships suggests that energy balance and storage (fat and muscle stores), activity levels, dietary energy intake, and reproductive energy needs interact in complex ways[143]. If energy intake is low, or fat stores are low, or physical activity is high, then reproductive function may be compromised through suppressed ovarian hormones or amenorrhea[144].

Another variable that has been shown to be of central importance in the fertility of non-Western peoples is breastfeeding[145,146]. One of the earliest studies to demonstrate the influence of breastfeeding duration and frequency on birth spacing and fertility was by Konner and Worthman[147] on the!Kung Bushman. Since that time, numerous studies have demonstrated similar relationships on Andean[148], Indonesian[149], Nepalese[150], New Guinea[151], nomadic Turkana[152], and many other populations. The relationships between fertility and breastfeeding patterns are influenced profoundly by food availability and diet, energy balance and stores, cultural traditions, environmental conditions, and random events, among others. There is much yet to learn about reproduction, ecology, and evolution within human populations.

The field is vast and central to our understanding of human evolution. It is, of course, the variation in reproductive performance (fertility) that is a primary means through which natural selection operates to preserve favorable heritable biological and behavioral variation. However, there is much more to successful reproduction than simply conception, implantation, gestation, and successful parturition[153]. Infants must survive, maintain good health, move through childhood to adolescence, and achieve sexual maturation with a combination of good emotional, intellectual, and physical health[2]. Hence, this new field of reproductive population science, although focusing on fecundity, fecundability, fertility, and infancy, really encompasses a greater part of the human life cycle. Below, we summarize a major research effort in this emerging area of reproductive population ecology.

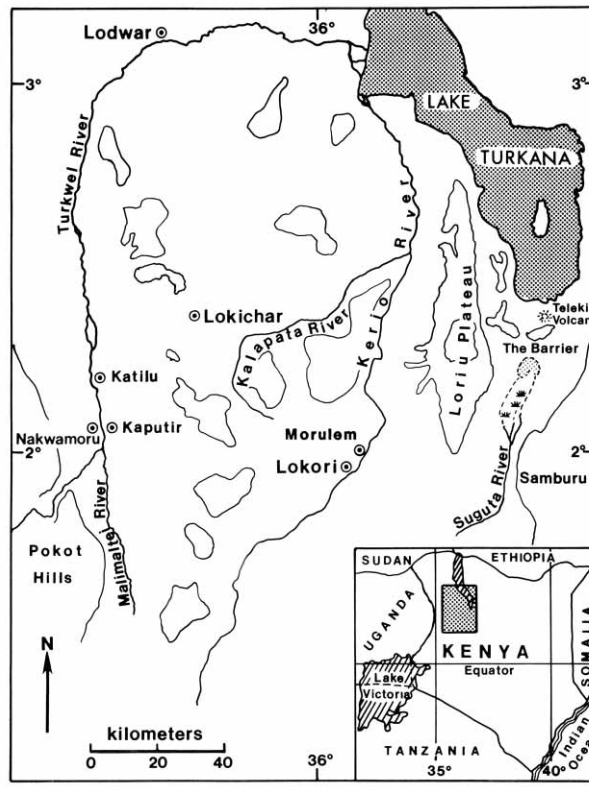

Fig. 10. Map of the southern region of Turkana District, Kenya[155]. Physical features include the Kerio and Turkwel River drainage systems, Lake Turkana, and the central mountain range. The capital of the district is the town of Lodwar. The wettest areas are to the west (Turkwel) and the driest areas are to the north.

Ecology and reproduction in nomadic Turkana Pastoralists

Nomadic Turkana pastoralists of northwest Kenya are, in many ways, an ideal population to serve as a model of the influence of the environment on human reproduction (Figure 10). They are linked closely to the semi-arid and seasonal savanna environment and are dependent on their five species of livestock (camels, cattle, goats, sheep, donkeys) for food and resources (milk, meat, blood, hides, and for trade). Human settlements and herds are moved frequently throughout the year in search of green vegetation to nourish the livestock. Reproductive performance of both people and livestock is crucial in this environment with limited resources: the young people provide labor for management and the livestock provide both food for their young animals and food for their managers. Balances must be maintained between numbers and demographic composition of people and numbers and composition of livestock[154]. All of these demographic balances must occur in an environment with high temperatures and intense solar radiation, marked seasonality in rainfall, limited moisture and

vegetation, frequent conditions of drought, and serious endemic diseases affecting both humans and livestock[155]. Research was conducted on this ethnic group (Ngisonyoka Turkana) by scientists of the South Turkana Ecosystem Project for more than 20 years: scientists included rangelands ecologists, social and biological anthropologists, population modelers, and biomedical personnel[156]. One of the major components of this integrated and multidisciplinary human ecological project was the study of reproductive performance, maternal health, and infant and child growth, results of which are summarized below.

Maternal health. Turkana women are tall and lean by worldwide standards and have limited energy reserves in the form of body fat. Body mass indices (BMI, a measure of robusticity) for Turkana women average between 17 and 18, which is in marked contrast to United States women whose BMI values fall between 22 and 26 kg/m^2 [157]. Hence, Turkana women have limited energy reserves in the form of body fat to support the demands of pregnancy and lactation. The lean physique of Turkana women is almost certainly a combination of genetics, high physical activity[158], and limited dietary energy intake (although dietary protein is abundant)[159]. Additional demands on these limited energy stores are made by pregnancy and lactation, which contribute to depletion of body fat reserves as women move through their reproductive lives[160]. Health care for women is limited to folk healing and infrequent access to clinics.

Fertility. The Turkana can be identified as a »natural fertility population,« that is, a population in which fertility is not governed by contraception or planned limitation[145]. Accordingly, in the Turkana, fertility (as measured by live births) is controlled by human reproductive capacity, and conditions of the physical, biological, and social environment. For example, the reproductive life span of women begins at about 20 years of age and ends sometime before 50 years of age because of a late menarche (age 16.5 years) and either menopause or death of the spouse. A high total fertility rate (TFR) for Turkana women is about 7 live births[161]. TFR is the sum of age-specific fertility rates. These fertility rates vary by season and according to productive (high rainfall and vegetation) and unproductive (drought and limited vegetation) years. Leslie and Fry[162] found a pronounced seasonality of Turkana births where many conceptions occurred when resources (milk production and other food) were in greater supply. This period of high conceptions was several months after the rainy season when vegetation had flushed, livestock had regained condition, milk production was high, and women had restored lost body weight. Similar environmental effects have been recorded for a series of years (1981–1984) where rainfall was very low and vegetation limited, in contrast to several years in which rainfall and resources were abundant (1987–1989). During the »poor« years, the TFR averaged 4.4 live births per woman over the reproductive span, whereas during the »good« years the TFR was 8.1 live births[161].

Pregnancy and gestation. Energy needs of pregnancy are minimally about 27,000 kcal for a full-term gestation without gains or losses in body fat stores[163]. Average weight gain during pregnancy for American and British women is about 12 kg, which usually entails some increased body fat storage. Turkana women, on the other hand, gain an average of only 6 kg[164,165]. Nearly all Turkana women in this study by Pike displayed losses in body fat stores during pregnancy, indicating that dietary intake was not meeting the

energy needs of pregnancy. Despite these maternal losses in body weight, mean birth weight of full-term infants was 3125 g, a value only about 300 or 400 g below average Western values. However, there is a cost. In the sample of Pike's 21 Turkana pregnancies and births, about one-third were pre-term.

Breastfeeding. As noted above, breastfeeding patterns influence birth spacing, and, hence, fertility, through the effects of lactational amenorrhea. Prolonged and intense breastfeeding will suppress postpartum ovulation and reduce fecundity, while at the same time, contributing immeasurably to infant health and well being. Turkana women breastfeed from 15 to 24 months, but supplement their infants with a variety of milk products, including butterfat as early as a few weeks after birth[166]. Pregnancy and lactation involve trade-offs among the variables of long-term maternal health, pregnancy and birth-spacing, and infant care and feeding[152]. The long period of lactation in Turkana women extends the birth interval by suppressing ovulation and allowing the breastfeeding infant to get a good (or adequate) nutritional start toward childhood. At the same time, seven full-term pregnancies, each with a 20-month period of lactation, will exert a substantial energetic cost and contribute to depletion of energy reserves during the Turkana women's reproductive years (on average, nearly 17 years either pregnant or lactating).

Fig. 11. Turkana women and children sitting in a sheltered day hut. (Photo courtesy of Paul W. Leslie.)

Infant and child growth. Survival to reproductive age in Turkana children entails maintenance of adequate nutrition, and avoidance of disease and accidents (Figure 11). Infant mortality (birth to one year of age) is between 9 and 14 percent and child mortality (birth to age 15 years) is between 15 and 24 percent[167]. Infants show growth faltering in weight at about 6 months, but are close to Western standards throughout infancy and early childhood[168]. Throughout childhood and adolescence, Turkana boys and girls are lean and somewhat shorter than Westerners, but catch up to Americans in stature by adulthood, although adult height is not achieved until the late teens in girls and the early 20s in boys[169]. Hence, in the Turkana physical growth to adulthood tends to be prolonged, and sexual maturity occurs late in both girls[170] and boys[171]. These growth and maturation patterns are likely the result of limited food energy resources, both seasonally and in the long term, but with high intakes of protein.

Adaptive perspectives

In the trade-offs between maternal health, reproduction, and child develop-

ment, the Turkana show adaptive responses to a highly fluctuating and stressful environment with limited resources. When food resources are abundant, fertility is high and other indicators of health are positive. All of the parameters linked to reproduction and health are sensitive to environmental variations, demonstrating high levels of adaptability in these nomadic pastoral residents of the dry savanna.

Conclusions

We have selected and summarized three themes that represent our current efforts in human adaptation research and have proposed what we feel are interesting and emerging issues to be addressed during the early part of the 21st Century. The epistemological discussions of human adaptation will likely continue and intensify in the future. Perhaps the reason that the concept of *adaptation* has sparked so much controversy over its definition, its identification, and its measurement is that, as a process in living creatures, it is so fundamental, yet so complex in its many manifestations[38,172]. One kind of controversy exists between the »adaptationists,« that is, those who »claim that natural selection is the only important cause of the evolution of most nonmolecular traits and that these traits are locally optimal,« and those who claim that other evolutionary processes are equally important[172]. Another controversy is between evolutionists who believe that the primary unit of selection (and adaptation) is the individual[173], while others believe in »multi-level« evolution[174]. Other controversies center on just how specific patterns of adaptation can be demonstrated or empirically defined[175]. Each of these areas of scientific controversy fall within the evolutionary realm. Phenotypic patterns of adaptation, on the other hand, are being explored in several behavioral and biological sciences within the context of *Allostasis* or interactive homeostatic systems. All areas of exploration, the genetic-evolutionary-generational and phenetic-individual-lifetime, are important in understanding human adaptation to our increasingly complex environment. In the future we expect that the concept of adaptation as applied to human populations will become increasingly important and multidisciplinary as the vast majority of the world's populations undergo the rapid process of modernization.

Acknowledgements

The authors wish to acknowledge in memoriam the many years of support and dedication given to the Qinghai Project by the premiere Chinese pediatrician and neonatologist Chin Chen-Ting. Without her years of effort, our research in China would not have been possible. The authors also wish to thank Jean Farrand for her administrative and technical assistance during all phases of our research over the past seven years. Support for research in China and Kenya was provided through the National Science Foundation (NSF) and the Wenner-Gren Foundation for Anthropological Research; and in Papua New Guinea, through the National Institutes of Health (NIH). All research involving human subjects was reviewed and approved by respective institutional review boards in both the U.S. and host countries.

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OKOLIŠNI STRES I ADAPTACIJSKI ODGOVOR: POSLJEDICE ZA LJUDSKO ZDRAVLJE

S A Ž E T A K

Uzimajući u obzir dramatično brzinu modernizacije svjetske populacije, ljudska adaptacija kao teorijska tvorevina i paradigma vjerojatno će biti u centru interdisciplinarnih znanstvenih istraživanja u 21. stoljeću. Mikro i makrookoliš brzo se mijenjaju i ljudske populacije izložene su brzim promjenama. Koncept adaptacije, barem na području biološke antropologije i humane biologije, vjerojatno će ostati usko vezan uz procese i koncepte evolucije, prirodne selekcije i sposobnosti. U ovom radu opisujemo teorijske osnove adaptacije i prikazujemo tri primjera iz trenutnih istraživanja koja uključuju adaptaciju i evolucijske procese u populaciji koja se modernizira, na nekoliko lokacija širom svijeta.