



The Dawn of Darwinian Medicine

Author(s): George C. Williams and Randolph M. Nesse

Source: *The Quarterly Review of Biology*, Vol. 66, No. 1, (Mar., 1991), pp. 1-22

Published by: The University of Chicago Press

Stable URL: <http://www.jstor.org/stable/2830330>

Accessed: 13/08/2008 12:10

---

Your use of the JSTOR archive indicates your acceptance of JSTOR's Terms and Conditions of Use, available at <http://www.jstor.org/page/info/about/policies/terms.jsp>. JSTOR's Terms and Conditions of Use provides, in part, that unless you have obtained prior permission, you may not download an entire issue of a journal or multiple copies of articles, and you may use content in the JSTOR archive only for your personal, non-commercial use.

Please contact the publisher regarding any further use of this work. Publisher contact information may be obtained at <http://www.jstor.org/action/showPublisher?publisherCode=ucpress>.

Each copy of any part of a JSTOR transmission must contain the same copyright notice that appears on the screen or printed page of such transmission.

---

JSTOR is a not-for-profit organization founded in 1995 to build trusted digital archives for scholarship. We work with the scholarly community to preserve their work and the materials they rely upon, and to build a common research platform that promotes the discovery and use of these resources. For more information about JSTOR, please contact [support@jstor.org](mailto:support@jstor.org).

# THE QUARTERLY REVIEW of BIOLOGY



## THE DAWN OF DARWINIAN MEDICINE

GEORGE C. WILLIAMS

*Department of Ecology & Evolution, Division of Biological Sciences,  
State University of Stony Brook, Stony Brook, New York 11794-5245 USA*

RANDOLPH M. NESSE

*Department of Psychiatry, University of Michigan Medical School,  
Room C440, Med-Inn Bldg., 1500 E. Medical Center Dr.,  
Ann Arbor, Michigan 48109-0840 USA*

### ABSTRACT

*While evolution by natural selection has long been a foundation for biomedical science, it has recently gained new power to explain many aspects of disease. This progress results largely from the disciplined application of what has been called the adaptationist program. We show that this increasingly significant research paradigm can predict otherwise unsuspected facets of human biology, and that it provides new insights into the causes of medical disorders, such as those discussed below:*

*1. Infection. Signs and symptoms of the host-parasite contest can be categorized according to whether they represent adaptations or costs for host or parasite. Some host adaptations may have contributed to fitness in the Stone Age but are obsolete today. Others, such as fever and iron sequestration, have been incorrectly considered harmful. Pathogens, with their large populations and many generations in a single host, can evolve very rapidly. Acquisition of resistance to antibiotics is one example. Another is the recently demonstrated tendency to change virulence levels in predictable ways in response to changed conditions imposed incidentally by human activities.*

*2. Injuries and toxins. Mechanical injuries or stressful wear and tear are conceptually simpler than infectious diseases because they are not contests between conflicting interests. Plant-herbivore contests may often underlie chemical injury from the defensive secondary compounds of plant tissues. Nausea in pregnancy, and allergy, may be adaptations against such toxins.*

*3. Genetic factors. Common genetic diseases often result from genes maintained by other beneficial effects in historically normal environments. The diseases of aging are especially likely to be associated with early benefits.*

*4. Abnormal environments. Human biology is designed for Stone Age conditions. Modern en-*

*The Quarterly Review of Biology, March 1991, Vol. 66, No. 1.*

© 1991 by The University of Chicago Press. All rights reserved.

0033-5770/91/6601-0001\$01.00

*vironments may cause many diseases — for example, deficiency syndromes such as scurvy and rickets, the effects of excess consumption of normally scarce nutrients such as fat and salt, developmental diseases such as myopia, and psychological reactions to novel environments.*

*The substantial benefits of evolutionary studies of disease will be realized only if they become central to medical curricula, an advance that may at first require the establishment of one or more research centers dedicated to the further development of Darwinian medicine.*

#### INTRODUCTION

**M**EDICAL EDUCATION stresses physics, chemistry, and those branches of biology that deal with proximate mechanisms. Application of this knowledge to biology and medicine has resulted in impressive advances in the prevention and treatment of human disease. Evolutionary biology, however, has not been emphasized in medical curricula. This is unfortunate, because new applications of evolutionary principles to medical problems show that advances would be even more rapid if medical professionals were as attuned to Darwin as they have been to Pasteur.

In one sense, physics and chemistry may furnish a complete explanation of all events in the human body, from subatomic aspects of cellular metabolism, to the mechanical characteristics of the skeletal system, to the cognitive mechanisms that regulate behavior. For instance, there are seven vertebrae in the neck. Can physics and chemistry explain that? Yes, in an important sense. These vertebrae arise by a series of developmental events of a material nature, very much the realm of the proximate sciences of physiology and embryology.

In another important sense, however, the answer is no. A complete explanation of how seven cervical vertebrae are normally produced by a human zygote leaves untouched the question of why that zygote's DNA should be so programmed. Why is it not organized to produce six or eight cervical vertebrae? And why should the zygote be capable of producing a functionally adequate neck at all? These last two questions find their answers in the Darwinian concepts of phylogeny and natural selection, respectively. Such answers are not alternatives to answers from physiology and embryology, they are answers to different kinds of questions.

This review presents the current status of natural selection as a predictive theory of human biology, and illustrates its application to four categories of causes of disease. The first is infection: conflicts between pathogens and

their human hosts and the adaptations with which both contestants attempt to influence the outcome in their own favor. We suggest that an evolutionary taxonomy of manifestations of infectious disease must underlie any attempt to understand such conflicts, and that an appreciation of the implications of the rapid evolution of pathogens may help with the solution of some public health problems. We then turn to the understanding and treatment of physical injuries that result from mechanical or chemical agents. We next consider genetic disease, and genetic factors that affect susceptibility to disease, especially those maintained by pleiotropic effects that offer benefits in youth but exact a cost later in life by increasing susceptibility to the diseases of aging. Finally, we consider how differences between present circumstances and the environment of evolutionary adaptedness may contribute to diseases of civilization including deficiency states, toxins from various natural and artificial sources, and some behavioral and psychological disorders.

#### NATURAL SELECTION AS A PREDICTIVE THEORY OF HUMAN BIOLOGY

An evolutionary explanation, of the history and current utility of some feature of some organism, always implies more than the observations that suggested the explanation. The implications constitute predictions of the results of investigations and may thereby lead to new discoveries. The relentless operation of mutation pressure, Mendelian genetics, selection, and other Darwinian factors for hundreds of millions of years in every lineage means that organisms must have certain features and not others. The most universally reliable expectation is of a near maximum for a gene's ability to get itself replicated. An intuitively useful if not entirely accurate restatement is that selection maximizes the abilities of organisms to gain genetic representation in future generations. This is substantively different from older "wisdom of the body" or "survival of the fittest" notions, and can lead to different and counter-

intuitive expectations. Selection need not maximize fitness in the vernacular sense of strength, health, and longevity. It does not necessarily enhance the welfare of the species or the happiness of the individual. In fact, many of the capacities for suffering seem to have been shaped by natural selection to serve special adaptive functions.

The expectations generated by applying evolutionary theory to particular problems often constitute hypotheses testable by experimental, comparative, or other kinds of investigations. When such testing confirms predictions, it often results in the discovery of phenomena that would not have been noticed without the aid of the theory. Failure of a prediction often results from some easily identified error of reasoning or information. More rarely, a negative result discloses an instructive anomaly that offers a starting point in a quest for more refined understanding.

This kind of interaction between evolutionary theory and the field and laboratory work of biologists was exemplary in the work of Darwin and has continued ever since. It has become a conspicuous part of biology in the last two decades, often in the special form recognized as the *adaptationist program* (Gould and Lewontin, 1979; Mayr, 1983). Adherents of this program, when confronted with a biological phenomenon, try to envision it as an aspect of an adaptation. An adaptation is some sort of biological machinery or process shaped by natural selection to help solve one or more problems faced by the organism. The phenomenon may be interpreted as a necessary component of the imagined machinery, or as an unavoidable cost of the machinery, or some incidental manifestation of its operation. The prediction is then made, or at least implied, that other necessary components must be there, and that an appropriate investigation will disclose their presence. Thus, the adaptationist program predicts otherwise unsuspected adaptive processes that can be searched for and, if found, described.

This search can start either with a trait or a function. An observed trait gives rise to hypotheses about its possible usefulness. For instance, the ampullae of Lorenzini are organs in the heads of sharks. Hypotheses about their functions ranged from regulation of buoyancy to simply filling empty space. When the deci-

sive experiments were done, the organs were found to respond to tiny electrical currents. They enable sharks to detect electrical effects of the heartbeats of potential prey buried in the sand (Wissing et al., 1988). When the adaptationist program proceeds in the other direction, an observed capability gives rise to a search for its physical basis. Migrating birds, for example, have long been known to have remarkable navigation abilities. This led to the hypothesis that they might be able to detect magnetic fields, a possibility confirmed by the disorientation of birds with magnets attached to their heads (Keeton, 1971). This finding led to a further search for the bird's magnetic compasses, a search that disclosed magnetic particles in the skulls of certain species (Beason and Nichols, 1984).

The adaptationist program has been enormously fruitful in the fields of ecology and animal behavior, and in the study of life cycles. The examples in Table 1 are a sample of those in a single volume of a single journal (*Evolution*, Vol. 42) published in 1988. *The American Naturalist*, *Animal Behavior*, *Evolutionary Biology*, and many other journals could have served as well. Predictions were selected that could be easily stated in the limited space of a table. They were further selected to illustrate the diversity of phenomena discovered through use of the theory.

#### INFECTIOUS DISEASE

##### *A Darwinian Approach to Symptoms, Signs, and Treatment*

Even when making a transition from another species to human hosts, an infectious agent has a long evolutionary history that must have maximized its ability to achieve its own survival and reproduction despite elaborate host defenses (many examples reviewed by Gotschlich, 1983). Parasites interact with their hosts in complex ways, and a first step towards understanding this interaction is use of a valid classification of the associated phenomena. We suggest the following terms and categories, summarized in Table 2, an elaboration of Ewald's (1980) proposals:

- (1) *Direct damage* to host tissues caused by the infectious agent. Gonococcal bacteria eroding joint tissues is an example.
- (2) *Impairment* of host function resulting from

TABLE 1

*Examples of the use of the theory of natural selection to predict the existence of phenomena otherwise unsuspected*

All examples are from Volume 42 of *Evolution*, published in 1988. A “+” indicates that the prediction was confirmed, a “-” that it was refuted. Both appear where results were mixed or not simply characterized as confirmation or refutation of the prediction. Different species or different localities, for example, might give different results.

Page	Authors	Predictions	Result
19	Shine	Aquatic and terrestrial snakes should differ in mass and position of ovary or young	+
160-161	van der Haven et al.	Ant sex ratios will vary as a function of polyandry, resources, and other factors	+
173-175	Roeloffs & Riechert	There should be high levels of kinship within social spider colonies	+
239	Parker	There should be great variation in resistance to pathogens in a legume	+
294	Sillen-Tullberg	Distastefulness of caterpillars must have broader taxonomic distribution than gregariousness	+
303-304	Sillen-Tullberg	Caterpillar gregariousness must have a broader taxonomic distribution than warning coloration	-
306	Schnebel & Grossfield	Flies with high reproductive output early in life should have reduced longevity	-
404	Burd & Allen	Tall teosintes will have higher male/female ratio	+
545	Gwynne	Measures of katydid female reproductive success will vary as a function of quality and number of spermatophores provided by male	±
571	Nonacs	Social insect queen number will vary as a function of ecological and genealogical factors	+
626-627	James et al.	Fruit flies should thrive better on normal host plant than on an alternative	-
661-663	Etter	Snail colors should be adaptive in relation to temperature stress	+
661-663	Etter	Snail colors should be adaptive in relation to predation	-
689	Snyder et al.	Mouse hemoglobin structure will vary as a function of habitat altitude	+
708-709	Service et al.	Increased longevity in <i>Drosophila</i> must result in depressed early fitness	+
718-719	Moran & Whitham	Relative frequencies of one- and two-host life histories of an aphid will vary geographically	+
775	Newman	Toad tadpoles should be able to anticipate and respond to pond desiccation	+
935	Payne & Westneat	Female sparrows with fitter mates will have fitter young	-
969-970	Zuk	Female crickets will prefer older males and those with fewer gregarine parasites	+
1021	Kawecki	High-rank male fish will spend more time assessing possibly parthenogenetic females	+
1048-1049	Linhart	Competition within and between plant species should result in different adaptations	+
1090	Joshi & Mueller	Crowded <i>Drosophila</i> will have evolved more rapid feeding behavior	+
1101	Krebs & West	A female butterfly should prefer cryptically colored over mimetic males	+
1190	King	Wasp offspring sex ratio will vary in relation to host size	+
1190	King	Wasp female reproductive success will vary in relation to host size	+
1200	Crespi	Thrips offspring sex ratio will vary in relation to anticipated food abundance	+

TABLE 2  
*A classification of phenomena associated  
 with infectious disease*

Observation	Beneficiary
1. Direct damage to host tissues	Neither
2. Impairment of host	Neither
3. Repair mechanisms	Host
4. Compensatory adjustment to impairment	Host
5. Hygienic measures	Host
6. Host defense	Host
7. Evasion of host defenses	Pathogen
8. Attack on host defenses	Pathogen
9. Trophic effects of parasite	Pathogen
10. Pathogen dispersal mechanisms	Pathogen
11. Pathogen manipulation of host adaptation	Pathogen

the damage. The distinction between damage and impairment may prove useful. Decreased ability to clear toxins is an impairment that results from damage to the liver. Decreased fleetness is an impairment from damage to joint tissues.

(3) *Repair mechanisms* used by the host to rectify the damage. The clearest example is regeneration of lost tissues. Ability to regenerate varies according to the normal likelihood of the usefulness of such capabilities. Skin regenerates quickly, the lining of the gut even faster, and severed nerves can gradually regrow to connections a meter from the site of injury. By contrast, heart muscle and the central nervous system have feeble repair capacities. Injuries at these sites are so often fatal that natural selection cannot develop or maintain capacities for regeneration (Williams, 1966: 83-87). The risk of cancer must also limit the capacity for tissue regeneration, if increased ability to regenerate makes cell division less controllable (Sager, 1989). Mechanisms for the restraint of maladaptive growth confine regeneration to those tissues where they are most needed.

(4) *Compensatory adjustments* made by the host to mitigate impairment. For example, when damaged lungs cannot adequately oxygenate the blood, there is a secondary increase in blood hemoglobin concentration (Vander et al., 1990:307). Increased use of the left hand may compensate for infection in the right.

(5) *Hygienic measures* used by a potential host to avoid infection. Such defenses start long before infection begins. The revulsion toward odors associated with bacterial decomposition helps to prevent ingestion of pathogenic agents. The special capacity to learn a conditioned nausea response to odors previously associated with sickness is likewise protective against pathogens (Rusiniak et al., 1976). People avoid intimate contact with obviously ill associates (Hart, 1990). Behavioral tendencies to defecate and urinate some distance from a dwelling may serve to decrease infection. Because the initiation of an infection is a complex process, there can be no sharp separation between defenses against contagion and defenses against an established pathogen. The importance of grooming and other antiparasite behaviors is reviewed by Hart (1990). Vomiting, coughing, and sneezing, and associated rhinorrhea and increased bronchial secretion, if initiated soon enough, may prevent establishment of a pathogen.

(6) *Host defenses* that expel, destroy, or sequester the pathogen. Cough, sneeze, rhinorrhea, vomiting and diarrhea expel pathogens. The system that mediates fever and inflammation both expels and destroys foreign matter, while the immune system more specifically recognizes and destroys pathogens. Pathogens that cannot be destroyed are often sequestered, as in the tubercles that the body forms around certain bacilli.

(7) *Evasion* of host defenses is commonly observed in parasites (Gotschlich, 1983). The mimicry of host molecular structures by helminth integument is well known (Capron et al., 1987). Some bacteria, such as certain streptococci, have evolved antigenic structures so similar to human antigens that an immune response to them may also damage the body's own tissues (Burgio and Ugazio, 1975). Rheumatic fever results when such antibodies attack the heart, Sydenham's chorea from antibodies that damage the basal ganglia. *Trypanosoma brucei*, the protozoan that causes African sleeping sickness, escapes the immune system by changing its antigenic coat every few days, just one step ahead of the body's ability to manufacture new antibodies (Donelson, 1988; Donelson and Turner, 1985). Hamilton et al. (1990) argue that the host-parasite arms race has been a key factor, all through plant and animal evolution, in



illustrates use of the adaptationist program to make medically important and heuristically useful predictions. Our ignorance about the effects of aspirin on upper respiratory infections and influenza illustrates the blind spots that result from neglecting evolutionary considerations.

Another defense is sequestration of iron. Plasma iron levels may fall to 20 percent of normal during initial stages of infections, as iron is bound more tightly to protein and sequestered in the liver (Weinberg, 1984, 1989). The plasma iron decrease has sometimes been viewed as a deficiency to be treated by dietary supplements. In fact, the sequestration of iron deprives bacteria of a vital mineral and works synergistically with fever. Weinberg (1984) reviews the harmful medical consequences of interfering with this mechanism. The prescription of aspirin and an iron supplement for infection blocks two interdependent evolved defensive systems.

There are dangers of blocking other defensive systems as well. For instance, routine prescription of antidiarrheal agents for shigellosis causes delayed recovery, increases complications, and slows eradication of the bacteria from the bowel (DuPont and Hornick, 1973). The effects of decongestants on upper respiratory infections seem to have escaped study. A theoretical framework for interpreting the host-parasite conflict encourages much needed investigation of such treatments.

Nonetheless, there are times when it is useful to interfere with the body's defenses. They were evolved for Stone Age conditions, and technological substitutes may be preferable. Severe cough may do more harm than good if antibiotics can quickly suppress an infection. But decisions about the appropriate use of such technologies should be informed by an understanding of the evolutionary nature of the host-parasite contest.

#### THE HOST-PARASITE ARMS RACE

Bacterial pathogens may complete a million cycles of fission within the lifetime of one human host, and there may be more pathogens in one individual than the earth's human population. Even in one host, a pathogen can be expected to produce highly improbable mutations many times and to evolve significantly in response to even minute selection forces. This

could happen even if the bacterial populations and rates of reproduction were one percent of what they actually are. Populations of protozoans and some parasitic helminths may also evolve important changes during their residence within one host. It has been realized for many years that some bacteria rapidly acquire high levels of antibiotic resistance (reviewed by Saunders, 1984) and that resistant strains can locally replace susceptible ones in a few weeks (Ewald, 1988:222). A less commonly appreciated phenomenon, the evolution of virulence, will be emphasized here.

Conventional wisdom has it that prolonged host-parasite association leads to a gradual reduction in virulence, with obligate mutualism as the final stage of extended association (Dobzhansky, 1951). Because host death removes the parasite's means of livelihood, it is thought that parasites will be selected to minimize damage to the host. Modern work on host-parasite coevolution challenges this expectation. Natural selection can increase or decrease virulence, depending on a variety of factors. Conditions for the evolution of very low virulence, and especially of mutualism, are rather stringent (Gill and Mock, 1985; Massad, 1987).

The idea that parasites will normally evolve so as to reduce virulence is defective for several reasons. First, it fails to appreciate the rapidity of parasite evolution. Pathogen characteristics should almost always be near their evolutionary equilibria. Pathogens will seldom be in transition between virulence levels, unless ecological circumstances have recently changed. Invasion of a novel host would be an outstanding example of such an ecological change. Another kind of error is failure to appreciate that pathogen adaptations, especially for dispersal to new hosts, may come to depend on coughing, diarrhea, or other host defenses that are activated only as a result of appreciable virulence. Ewald (1987, 1988, 1991) and Ewald and Schubert (1989) have reviewed the published data on host-parasite coevolution in an effort to understand virulence. Their main predictions are: (1) Virulence, in pathogens with insect or other animal vectors, will tend to be high in the human host and low in the vector. Human tissues provide the resource base, the vector merely a way of getting to another resource base. Any damage to the vector would decrease its effectiveness in dispersing the pathogen. By con-

trast, the prostration of a human host, whether it recovers or not, may make it more accessible to the vectors. A dense pathogen population implies high virulence but it also increases the likelihood that an adequate number of propagules will be taken up by the vector for its infection and transport to the next human victim. This is in contrast to diseases spread by personal contact between diseased individuals. Virulence high enough to immobilize the victim may reduce contact with other individuals and transmission of the pathogen. Diseases spread by contact are expected to be less virulent than those spread by vectors.

(2) For similar reasons, diseases transmitted mainly by inanimate vectors, such as water, will be more virulent than those spread by personal contact, at least if an immobilized host releases pathogen propagules to the water supply or other agent of transmission. Here again a dense (highly virulent) population of the pathogen will be able to release the large numbers of propagules needed to overcome dilution effects and increase the rate of infection of new hosts. No such dilution need be overcome when contact contagion spreads the pathogen.

(3) The same principles apply to what Ewald calls *cultural vectors*, such as may operate in hospitals. Hospital workers or equipment rapidly transmit propagules from infected to uninfected patients. This is not contagion by personal contact, because the workers do not normally become infected. Diseases with this sort of hospital transmission, such as puerperal sepsis or neonatal diarrhea ought to be more virulent than related diseases spread by personal contact in the population at large.

(4) Changes in mode of transmission will have predictable effects on virulence. A disease spread mainly by personal contact in a peasant society may come to be spread mainly by water in a primitive urban community. If so, it should quickly evolve a greater virulence. Substituting a hygienic water supply will not only curtail the spread of the disease, but also cause it to evolve reduced virulence, as has been demonstrated for cholera (Ewald, 1988).

(5) Parasites transmitted mainly to offspring will be the least virulent. Any curtailment of host survival or fecundity is a cost to the pathogen in direct proportion to its reliance on this vertical transmission. It is only among organisms with a high frequency of transmission to

host offspring that there is a high proportion of really benign or mutualistic symbionts. If transmission is entirely from parent to offspring, contagion is functionally equivalent to heredity. Population genetics might thus be viewed as a specialized branch of epidemiology.

Ewald reviews an impressive mass of data on human and animal diseases (see especially 1988: Table 1; in press: Tables 1 and 2), that confirm predictions made from his theory. He also points out the likely fruitfulness of various kinds of research, such as the monitoring of virulence evolution during disease outbreaks, and the use of experimental animals to test his models.

Ewald mentions (e.g., 1988:117), but does not emphasize, within-host competition between pathogens, another ecological factor that we would suspect to be important in the evolution of virulence. Within-host variation in virulence is little studied but is known to occur. De Nooij and van Damme (1988) showed markedly different virulences for fungus samples from different parts of the same plant. As an extreme example of within-host selection of virulence, imagine two pathogen clones competing within a host. One uses optimal exploitation, which results in the maximum number of propagules dispersed during the lifetime of the host. The other uses maximal (lethal) exploitation, which converts host resources to propagules at the maximum possible rate. The host will disperse more of the lethal type than its restrained competitor. The cost of the host's death is borne equally by the two competitors, whereas only the more virulent benefits from a greater rate of transmission. Mayr (1988:120-121) advances a similar argument.

In highly virulent cases of cholera and shigellosis propagules may be dispersed at more than a hundred times the rate in less virulent cases (Ewald, 1988:217). The host's final output of both strains, of course, may be less than the long-term output from the less virulent type when it is the sole exploiter. The evolutionary outcome will depend on relative strengths of within-host and between-host competition in pathogen evolution. This is a clear example of group vs. individual (clone) selection for altruism, for which many formal models have been proposed (e.g., Nunney, 1985; Wilson, 1987; De Nooij and van Damme, 1988). A particularly dramatic example of clone selection is

provided by plasmids that generate a toxin that kills the bacterial cell they inhabit and nearby bacteria that are not infected with these plasmids. Plasmids in other bacteria generate a protein that protects against the toxin. The genes that cause some plasmids to generate the toxin give a selective advantage to their kin whose bacterial hosts benefit from the elimination of competitors (Maynard-Smith, 1978; Eberhard, 1990).

Competition between species or clones of one species within a host results in the evolution of greater virulence than would be favored with only one strain of one pathogen. The magnitude of the increase depends in complex ways on the magnitude of virulence variation and the levels of clonal diversity within and between hosts. The complexity does not preclude a qualitative prediction: diseases that result from single infections of each host will be less virulent than those that normally arise from multiple infections from different sources.

Mutation is another, but slower, way to produce genetic diversity within a host. Only quite early in a host's incubation of a bacterial pathogen, when the total count is in the millions or less, is the pathogen likely to be genetically homogeneous. Thereafter, various mutants will be competing with the ancestral type. The great majority of these mutations will be eliminated by selection, but a small minority will increase competitive ability and survive. Such differences generated by mutation are likely to be minor compared with those produced by multiple infection. Whatever its origin, the clone that more rapidly converts host tissues into more of itself will come to predominate within the host. The expected steady increase in virulence will be reversed only as a result of improved host defense, either natural or artificial.

Lusso et al. (1990) found that genetic recombination between HIV strains produced a new form with increased virulence in tissue culture. While decreased virulence is to a patient's advantage, it also offers a longer symptom-free period and thus increased opportunity for transmission to new hosts. Retroviruses in general can evolve rapidly (Doolittle et al., 1989) and evolution of increased resistance to an effective AIDS drug is now documented (Larder et al., 1989). Also of concern is the possibility that some strain will evolve more efficient transmission.

Wallace (1989) has suggested another possible problem. Individuals with severely suppressed immune systems provide an abnormally benign environment for invading pathogens. The presence of large numbers of such people could provide a "stairway" to human pathogenicity for organisms that have not previously caused human disease. Having gained access, they might rapidly evolve adaptations for exploiting the new host and evading its remaining defenses. These adaptations, in turn, might make it easier to invade uncompromised hosts.

#### INJURIES, BREAKDOWNS, AND TOXINS

##### *Mechanical Damage*

Healing of mechanical damage is less complex than eliminating an infection, because it is not a contest between two organisms with divergent interests. Only the first five categories of symptoms in Table 2 are relevant: damage, impairment, repair, compensatory adjustments, and processes analogous to the hygienic precautions. The remaining six relate to special host-parasite interactions that apply only to injuries that provide parasites access to host tissues.

An evolutionary perspective suggests the value of distinguishing among several kinds of repair mechanisms and secondary adjustments. Repairs include both rebuilding of damaged tissues and other processes that indirectly aid in repair. Increased temperature associated with inflammation might be one example of indirect aid (Kiestler, 1984; Boorstein and Ewald, 1987), along with mechanisms that restrict use of damaged parts, such as pain and swelling. Their initiation by injury is presumably optimized for Stone Age conditions. Now, artificial restraints and advice from physicians may substitute for pain to discourage activity. Swelling that is bothersome or physiologically costly can often be safely blocked by medication and local cooling.

As a specific example, consider the usual sprained ankle. Blood escapes from damaged tissues to cause a bruise. This and increased extravascular fluid contribute to local swelling. Histamine and other diffusible products of the injured tissues initiate the process that attracts phagocytes and other mobile cells, some of which start removing damaged structures and synthesizing their replacements.

An evolutionary biologist, and adaptation-conscious physiologists and pathologists (Vander et al., 1990:599-640), would ask a number of questions about the pathophysiology of a sprain. To what extent is swelling merely an incidental result of the trauma, and to what extent is it an adaptation to immobilize the joint or to otherwise favor healing? What harmful consequences may result from limiting swelling? What is the role of each cell type in the repair program and how are these roles coordinated for the efficient achievement of the repair? Are the repair processes influenced by temperature, and is healing fastest at a certain temperature? What exactly is the mechanism that results in pain, and is the pain adjusted to the expected need for immobilization under normal conditions of human ecology? Is local pain supplemented by more general injury-induced effects on motivation (lethargy and malaise)?

Reliable answers to such questions would facilitate design of a program of therapy. Evolved mechanisms that produce pain or malaise can be suppressed in favor of artificial substitutes: splints, wrappings, wheelchairs, and sick-leave. Cellular mechanisms of repair and related processes that facilitate their action should be augmented unless there is reason to think them already optimal. Thus, the assumption that the increased temperature is adaptive would preclude routine application of ice unless well-designed studies confirmed its benefits.

There can be no sharp distinctions among injury, injurious wear and tear from abnormal usage, and normal wear and tear, but an evolutionary perspective can aid in deciding what uses are normal. For instance, osteoarthritis mainly affects those joints that received increased use and loading with upright posture — especially the back, knees, and ankles. Sitting for long periods dramatically compresses the lumbar disks and can be regarded as abnormal usage. Other joints, by contrast, are overdesigned for current demands and therefore less prone to osteoarthritis — especially those of the shoulders, arms, and metacarpals (Hutton, 1987). Yet even an overdesigned joint can be damaged by abnormal usage. An example is carpal tunnel syndrome caused by hypertrophy of the fascia over the median nerve at the wrist. It results from repeated wrist twistings of the sort that are often necessary for carpenters.

Some adaptations for the avoidance of injury are analogous to hygienic precautions against infectious diseases. The actual mechanisms of injury avoidance and infection avoidance are quite different, of course, but in both cases we are prepared to avoid some kinds of modern dangers much better than others. For instance, tissue damage elicits spinal reflexes that cause withdrawal before the information even reaches the brain. Likewise, defensive action is initiated when specialized sensors detect pressure, excessive strain, or thermal stress. There are, however, no detectors for PCBs or for most of the electromagnetic spectrum. Lack of precursor detectors would make it difficult for natural selection to create protective mechanisms against such hazards.

Other adaptations to prevent injury are cognitive and behavioral. For instance, snakes and other objects of common phobias are by no means random, but seem to represent “prepared fears” of stimuli associated with danger in previous generations (Marks, 1987). Similarly, the changes associated with a panic attack are not an autonomic storm, but a carefully coordinated pattern that is adaptive in life-threatening situations (Nesse, 1988a).

Psychological and physiological responses to danger are particularly intriguing since their adaptive significance and evolutionary origins have long been recognized (Cannon, 1929), but they also contribute to the etiology of various diseases (Winer, 1977). Why do stress responses cause disease? and why, if stress responses make the organism function more effectively, hasn't natural selection shaped continuous expression of these responses? One reason is that stress arousal is calorically expensive, and another is that an organism in a state of arousal may be less capable of dealing effectively with everyday tasks. A third explanation is the possibility that certain useful components of the stress response also interfere with metabolism or damage bodily tissues. Such components will be retained by natural selection only if their expression can be restricted to situations when the damage or disruption they cause will be more than outweighed by the benefits they offer — in short, if expression can be limited to emergency situations.

The stress response is an example of an inducible defense (Harvell, 1990). An analysis of its costs and benefits may help to explain why

extended states of stress cause disease. Some physiological changes are components of the stress response precisely because they cause damage. Increased secretion of adrenal steroids has long been associated with stress, but many of their actions seem to be the opposite of what one would expect. For instance, steroids decrease inflammation and increase susceptibility to infection, but the opposite would seem appropriate in the face of danger. An adaptive view of the functions of the adrenal cortex suggests that they may have been shaped by natural selection specifically to protect the body against other components of the stress response (Munck et al., 1984).

Post-traumatic stress reactions, though often pathological in modern circumstances, may sometimes be adaptive. When Ayla's first attempt at hunting almost assigned her the role of prey rather than predator, she ruminated about the attack and how it might have been better dealt with or, better yet, avoided (Auel, 1980). It was surely adaptive for her to enter a special state of unpleasant arousal in response to stimuli such as the weapon she had tried to use that suggest the possible recurrence of a similar life-threatening situation (Behrs, 1990).

### *Toxins*

Which substances are and which are not toxic results largely from the action of natural selection on both producers and potential victims of toxins. Our typically catholic tastes imply the ability to detoxify a wide variety of chemicals. Recent preoccupation with possible dietary toxins has focused on novel substances. This is in accord with evolutionary thinking; there is no reason to expect that we have evolved mechanisms for dealing with even moderate amounts of nickel, organic mercury, PCBs, or recently invented insecticides (Calabrese, 1985). Not in accord with evolutionary thinking, however, is the belief that it should be possible to find a perfectly natural, perfectly safe, toxin-free diet.

Plants defend themselves against herbivores mainly by synthesizing toxic chemicals, which may comprise 10 percent of the dry weight of some plant products (Abelson, 1990). Vegetables all contain at least trace amounts of such toxins (Ames and Gold, 1989). The complex chemicals that make coffee so appealing are

toxins that protect coffee seeds from insects and small mammals. We can safely consume vegetables and even coffee because we have evolved effective detoxification mechanisms. Also, like many other animals, we prefer diverse diets. This avoids overloading any particular detoxification mechanism (Janzen, 1978; Curtin and Chivers, 1978) and helps to provide all needed trace nutrients. No diet is perfectly safe; all are compromises arising from the plant-herbivore arms race. This has important implications for current efforts to develop plant strains that require less pesticide protection. Artificial selection for such disease-resistant plants should make it possible to reduce pesticide use, but we must expect such selection to increase the concentrations of natural plant toxins.

Profet (1988; in press) reviews extensive evidence that the nausea and taste aversions of the second to fourteenth weeks of pregnancy are not epiphenomena, but adaptations that protect the embryo and fetus against toxins. The embryo is especially susceptible from the second to fourteenth week to toxins that affect tissue differentiation. Pregnant women especially avoid substances with bitter tastes, which are reliable cues to the presence of plant toxins. Miscarriages are more common in women who do not experience pregnancy sickness.

Profet (1991) also argues that the IgE system that mediates allergic response must serve some specialized defensive function, and she marshals evidence that it protects against toxins. Her arguments suggest a need for investigations of suppressing the symptoms of allergy without removing the cause. It is worth asking if long-term antihistamine use increases the rate of cancer in tissues exposed to pollen toxins.

### GENETIC FACTORS IN DISEASE

#### *Single-Locus Genetic Diseases*

Almost all genetic mutations are deleterious and selection purges some of these in every generation. Their prevailing frequencies reflect the balance of mutation pressure and adverse selection. Because mutation rates are usually orders of magnitude lower than selection coefficients, abnormal genes tend to be rare. They most often manifest themselves in inbred populations or those established by small numbers of founders (Diamond, 1988). Darwinian theory has little to contribute beyond what is al-

readily widely understood about such rare genetic diseases.

In contrast, genetic diseases with appreciable frequency, perhaps higher than one in twenty thousand (Diamond, 1989), are likely to require another kind of evolutionary explanation. Apparently abnormal genes with high frequencies are likely to have some adaptive benefits. Even diseases that severely depress both biological fitness and perceived well-being may be caused by genes with subtle beneficial effects, perhaps in other individuals or other stages of development.

It has long been known that sickle-cell anemia afflicts people who are homozygous for a gene that protects against malaria in the much more numerous heterozygotes (Allison, 1954). It has more recently been realized that other hemoglobinopathies and glucose-6-phosphate dehydrogenase deficiency may also be maintained because they augment resistance to malaria (Diamond, 1989). A dramatic illustration of evasion of host defense is the ability of some malarial organisms to make their own glucose-6-phosphate dehydrogenase (Usanga and Luzzatto, 1985).

Peptic ulcer is associated with a genetic elevation of pepsinogen-1. Petersen and Rotter (1983:77) argue that "The evolution of hypersecretory forms of peptic ulcer may be a consequence of selection by infectious disease agents for higher gastric proteolytic activity." They review substantial evidence for the protective effects of high proteolytic activity against bacterial infection, and suggest that selection for high pepsinogen-1 production may have resulted from the prevalence of tuberculosis in recent centuries. This raises the possibility that antacid use may predispose to some bacterial infections.

#### *Senescence*

Much of modern medicine addresses diseases of senescence, but evolutionary analyses have had little impact. Many physicians assume that such a deleterious trait could not have been shaped by natural selection. Even some influential gerontologists discount the possibility that life span can evolve by natural selection (Sacher, 1982). This ignores the substantial work in the last few decades on life-history evolution (Rose, 1985).

The most important advance is recognition

that genes causing senescence can be favorably selected if they also have beneficial effects early in life (Medawar, 1952; Williams, 1957; Hamilton, 1966; Rose, 1990). Because the force of selection is stronger at earlier ages to which larger numbers survive, a gene that causes substantial morbidity and mortality during the tail end of the expected life span in the wild may nonetheless be favored if it has even minor earlier benefits. Conversely, a gene that prevents or repairs the abnormalities of aging will not be selected for if it imposes even small costs early in the life span. Senescence may also result from deleterious genes that act so late in life that they are never subject to selection in the natural environment. The relative importance of these genes and pleiotropic genes may differ substantially between species (Nesse, 1988b).

The diseases of senescence are not limited to gross afflictions such as Alzheimer's disease and osteoarthritis, but include all progressive impairments of adaptive function that occur after the age of earliest reproduction. They include declining sensory and motor performance, increased susceptibility to infection, autoimmune diseases, many endocrine disorders, arterial diseases, and most kinds of cancer (Fries and Crapo, 1981). Any changes that decrease fitness late in the expected life span under natural conditions but have not been eliminated by natural selection are likely to result from genes with beneficial effects earlier in life, perhaps effects that may even be essential. There is evidence for such pleiotropic benefits for hemochromatosis (iron retention) and for pepsinogen-1-related peptic ulcer (pathogen resistance) (Albin, 1988). Cytokines may be examples of gene products that produce early benefits at steadily increasing later costs (Marx, 1988).

Gout may be an instance of the presumably less common situation in which genes are selected for later benefits despite possibly earlier costs. Damage from free radicals is a cause of aging; uric acid is an effective scavenger of free radicals; and mean plasma uric acid levels for a species are strongly correlated with its maximum life potential. Thus the loss in humans of uricase, which converts uric acid to allantoin in other mammals, may not be a defect, but an adaptation that increases longevity at the cost of increased susceptibility to gout.

Are there benefits from genes that contribute to Alzheimer's disease, osteoarthritis, atherosclerosis, and other diseases of aging? Searches for early benefits from the genetic bases of such conditions become especially important as we gain the capacity for genetic surgery. Therapeutic alterations of genotypes of specific tissues for the cure of disease in affected individuals holds great promise, but we must begin looking now for possible benefits of the genes to be changed. Germ-line alteration should be approached even more cautiously (Friedman, 1989). If we naively assume that ridding the population of the genetic capability for Alzheimer's disease is an unconditionally desirable goal, we might incidentally eliminate unsuspected benefits.

Two recently prominent lines of gerontologic research suggest that senescence can be retarded by dietary restriction and by decreasing DNA damage (Weindruch and Walford, 1988; Miller and Hadfield, 1990). Major effects depend on severe calorie reduction begun early in life, although detectable benefits can arise from even moderate restriction begun in adulthood. A Darwinian perspective suggests caution in interpreting these findings. The human developmental system was selected to make optimum use of the range of dietary abundance under Stone Age conditions. Abundant nutrition permits rapid maturation and higher reproductive success than would be possible under a restricted diet. Dietary restriction that lengthens mammalian life spans also decreases fertility (Weindruch and Walford, 1988). A comparable effect is seen in spiders (Austad, 1989). The practical lesson is that there are costs of delaying senescence by dietary restriction. It may not be worth the costs for cowboys, dancers, athletes, or those who want high fertility in the usual parental years.

We also suggest that caloric restriction and associated reduction in DNA damage will not affect some aspects of senescence. For example, one set of adult teeth was presumably enough for the normal human life-span in Stone Age conditions. Elephants, however, may have as many as six sets of teeth in a lifetime (Diamond, 1990). Developmental programming also limits replacement or repair of brain cells, nephrons, and heart valves. There may be similar limitations even at the molecular level. We suspect that dietary restric-

tion may achieve some benefits for people in their seventies and eighties, but we doubt that it will much affect maximum human longevity.

The public and many physicians continue to view senescence as a single disease of uniform etiology, and to hope for and look for a cure. Yet a century of enormous progress in medical science, and decades of major effort in gerontological research, have failed to produce any increase in maximum human life span or support for any central proximate mechanism that might be changed in ways that slow aging (Bell, 1984). An evolutionary approach strongly suggests that senescence has diverse interwoven developmental causes with a polygenic basis, and that no cure, in the sense of correction of one or a few genes or other causes, will be possible. The fountain of youth is a fantasy, but it should still be possible to augment and prolong youthful vigor and postpone some degenerative changes.

#### ABNORMAL ENVIRONMENT

##### *The Environment of Evolutionary Adaptedness*

Adaptations are produced and maintained only in the range of environments in which selection takes place (Endler, 1986). For humans, the physical environment of evolutionary adaptiveness is probably that of the Pleistocene savannah (Orians, 1980). The socioeconomic environment consisted of small groups of relatives hunting, gathering, mating, raising children, and responding to threats and opportunities provided by neighboring groups (Eaton et al., 1988; Campbell, 1985). The unique ability to use culture to adapt to diverse and changing environments enabled human populations to grow enormously, spread widely, and adapt technologically to a great range of conditions (Cavalli-Sforza and Feldman, 1981).

In the past ten thousand years, we have largely created our own environments, by the domestication of plants and animals and by the industrial and technological revolutions. These advances have led to the virtual elimination, in many parts of the world, of many of the most enduring and prominent agents of selection, such as starvation, parasites, and infectious diseases. There can be no doubt that people are, on the average, substantially healthier to a greater age than their predecessors.

Yet many of the diseases now confronted by medicine in technological societies are "diseases

of civilization" (Eaton et al., 1988). They are either caused by differences between our current environment and the environment we evolved to live in, or they are aspects of senescence that have been uncovered by preventing earlier causes of mortality. The effects of recent increases in mean life span have changed medicine more than many people realize. For instance, since 1900, 80 percent of mortality from causes other than senescence in the United States has been eliminated (Fries and Crapo, 1981:73). An individual who could somehow escape senescence would, on average, live seven times as long as is now possible (Nesse, 1988b), a fact that may explain why people are so intent in their determination to extend the life span, despite the pessimistic lessons of history and evolutionary theory.

Before dealing with specific diseases that result from novel aspects of our environment, we would like to emphasize again that our health has been immensely improved by medical advances and other environmental changes. Current rates of mortality and morbidity in economically advanced societies allow no challenge to this conclusion. We do not advocate a return to any earlier way of life, but only the recognition that some net improvements of modern civilization are mixed blessings.

#### *Nutritional Deficiencies and Excesses*

Historically, nutritional shortage may have been a major cause of human disease and indirectly, from socioeconomic competition and strife, a source of much additional distress. These phylogenetically normal conditions still prevail in some cultures, but there may be important differences between the stresses of modern and Stone Age poverty. Today's economically stressed populations are almost entirely agricultural and industrial and subsist on highly abnormal diets that may result in trace-nutrient deficiencies that must have been rare in more normal environments. The undernourished, in the Stone Age, probably suffered most often from inadequate protein and fat, less often from a shortage of calories, and only rarely from trace-nutrient deficiencies that cause such diseases as rickets and scurvy (Johnston, 1987; Cassidy, 1980).

This conclusion presupposes that early human habitats and diets nearly always provided needed minerals. A needed organic compound

can be an essential nutrient only if it is present in excess in the normal diet. Even an occasional shortage of a metabolite will favor retention of the ability to synthesize or conserve it. If a synthetic ability is entirely lost, selection will favor instincts of habitat selection and life-style that assure qualitatively suitable diets. For example, since the ability to synthesize ascorbic acid was lost, as a result of an abundant supply of this vitamin in a largely frugivorous diet, subsequent evolution of dietary preferences has been constrained by the necessity of ingesting a critical minimum of certain kinds of plant tissues. It is unlikely that there will ever be a purely carnivorous higher primate. These arguments are developed in detail by Charnov (1984) and Scriver (1984).

Special dietary preferences also evolved because of the high value of certain scarce resources, like fat, salt, and sugar. Our normal motivational systems interact with their abundance in our modern environment to result in extraordinarily high intake. Because our bodies are poorly prepared for such plenitude, new diseases have emerged. Tooth decay, rare in native societies, is largely a consequence of extended exposure of teeth to sugar. Atherosclerotic disease and increased risk of cancer are associated with high levels of dietary fat. The relationship of salt intake to blood pressure remains uncertain, but hypertension is rare in some inland tribal groups with low-salt diets (Intersalt Cooperative Research Group, 1988).

Human motivations and metabolism are programmed to store fat reserves in times of plenty for later times of shortage. A tendency to minimize physical activity may also be adaptive for minimizing expenditure of such reserves. The variability in these processes may be great, with some individuals, who have what Neel (1982) calls *thrifty genotypes*, now especially vulnerable to diabetes and obesity (see also Knowler et al., 1983). They store calories more efficiently than others, but never benefit from the episodes of famine to which they are especially adapted. Attempts to restrict food intake voluntarily may be interpreted by the regulatory mechanism as uncertain food availability; in such situations, binges of eating would be adaptive (Nesse, 1984). It appears that repeated increases and decreases in weight may slow metabolism and increase the set-point for body

weight (Hill, et al., 1988). Such a response would be quite appropriate in the face of wide variations in food availability, but directly opposes the goals of modern dieters. Early identification of individuals at risk for eating disorders and alerting them to their special vulnerabilities may be helpful.

Accumulation of increased fat stores in pregnancy is evidently an adaptation to ensure adequate milk for the infant, even if food becomes scarce (Frisch, 1988). Inadequate fat stores set off a mechanism that stops ovulation, thus preventing conception at times when insufficient food is available to sustain the costs of pregnancy and lactation (Wasser and Barash, 1983; Profet, 1991). Pong (1981) provides a well-reasoned account of the evolution of adiposity in general, and of the human example in particular, with special attention to the anatomical distribution of fat reserves in relation to age and sex. Extending this work to the problem of how diet regulation mechanisms are impaired by our unnatural environment should assist our understanding of anorexia and bulimia (Volland and Volland, 1989).

Vitamin D is synthesized in skin exposed to sunlight. The spread of humans to forested, often overcast, and seasonally cold regions, such as central and western Europe, and the thermally adaptive use of clothing in such habitats, may have selected for reduced skin pigmentation as a way of maintaining adequate supplies of vitamin D. Russell and Russell (1983) discuss this and related matters, and point out that rickets was common among black but not white children in northern U.S. cities until the 1930s, when vitamin D supplementation of milk was initiated. They also suggest that the heterozygous state for phenylketonuria may be advantageous in vitamin D synthesis and that this may explain the increased frequency of this gene in fair-skinned populations. They also propose that the special ability of adult Europeans to digest lactose may relate to the capacity of dairy products to partially substitute for the role of vitamin D in calcium metabolism.

Excess nutrition is a dramatic aspect of our abnormal environment, but current efforts to help people to control their weight rely on further environmental changes. The use of artificial sweeteners has increased dramatically even though their use does not seem to assist weight control (Stellman and Garfinkel, 1986). There

has been little consideration of the long-term effects of artificially stimulating taste receptors, and thus eliciting endocrine and physiological responses appropriate to sugar intake, without actually providing it. The same issue will certainly arise as imitation fats become widely available.

#### *Other Diseases from Modern Environments*

While artificial foods stimulate peripheral gustatory and olfactory receptors, psychotropic drugs induce pleasure by direct actions on brain mechanisms. Alcohol and tobacco have long been available, but distillation of alcohol and the invention of cigarettes dramatically increased health risks. Complications from alcohol and tobacco addiction now account for a substantial proportion of disease and health-care expenditures in industrialized countries. Opioids and cocaine were also used for centuries, perhaps with only moderate medical and social costs, but new delivery methods, especially the invention of the hypodermic needle and crack cocaine, have created new epidemics.

Finally, new pharmaceutical agents developed in the past 30 years now allow physicians to relieve symptoms of psychosis, anxiety, depression, and other kinds of mental suffering. Some of these agents, especially amphetamines and benzodiazapine-like drugs, are reinforcing and cause pharmacologic and psychological dependence. These addictions are diseases of civilization. We simply were not evolved to resist substances that directly stimulate reward mechanisms in the brain. Genetically based tendencies to use drugs are not interpreted as biological abnormalities, but as quirks that result in maladaptive behavior only as a result of special environmental abnormalities. With this in mind, it is possible to ask, in an evolutionarily sophisticated way, why some people use drugs and others do not. All psychotropic drugs change how people feel. To better understand drug use, we will need to understand the evolutionary functions of the emotions (Thornhill and Thornhill, 1989; Nesse, 1990). In the meantime, the Darwinian physician presumes that the emotions have been shaped to maximize fitness, and therefore, that any drug that disrupts them will often disrupt normal adaptive capacities. Better understanding of the evolutionary functions of the emo-

tions will provide guidance about when the use of particular psychotropic drugs is advisable.

Myopia is another disease of civilization, one that shows much genetic variability. Teikari et al. (1988) showed high levels of concordance for both monozygotic and dizygotic twins in respect to myopia, and Karlsson (1986) found evidence for a strong single-locus effect. This evidence for genetic control is hardly evidence against decisive environmental causation. A serious handicap with a high heritability, such as myopia, could not possibly persist under natural conditions. Corrective lenses were invented far too recently to have allowed a substantial increase in genes that cause myopia. This argument is supported by the dramatic myopia increase in native groups newly subjected to formal education in childhood (Young et al., 1969). Myopia may be a fine example of a disease that is strongly heritable, but is seen only in a special environment.

Recent research on the development of myopia in experimental animals has revealed an exquisite adaptation: eye growth is regulated by the kind of usage and the quality of retinal images received (Raviola and Wiesel, 1985). Each eye grows independently and different parts grow differentially to keep images in focus (Wallman et al., 1987; Schaffel et al., 1988). The strong genetic factor in myopia most likely reflects differences in the sensitivity of the mechanism that regulates eye growth. None of the experimental data derive from human subjects, and conflicts among some results even within the same species indicate that many issues await resolution (Angela Brown and Howard C. Howland, pers. commun.). Still, an evolutionary approach gives reason to be optimistic about the possibility of preventing or reducing myopia. For example, could it be that the burden of myopia would be dramatically reduced if children's books had large print and wide margins, and if schools made more frequent use of larger, more distant reading materials, such as posters and blackboards?

Patterns of child rearing and acculturation have changed so dramatically that many children may not receive the minimum amounts of certain kinds of stimulation. Psychiatrists and psychologists have appropriately emphasized the importance of the early mother-child interaction and attachment (Bowlby, 1969; Ainsworth et al., 1978; Trevathan, 1987), and

studies continue about the psychological and intellectual effects of extended early exposure to day-care by strangers. Less emphasis has been given to such factors as family size, loss of availability of extended family, and lack of consistent early exposure to groups of peers. The hunter-gatherer child, playing with other children in a clearing between huts under the casual supervision of several related adults, may be having developmentally significant experiences that are not available to a child in even the best day-care center or single-family dwelling.

There are strong genetic predisposing factors for many of the diseases of modern civilization. Examples include obesity, myopia, hypertension, substance abuse, atherosclerosis, and adult-onset diabetes mellitus. These genetic factors have often been characterized as "defects," but they might better be called "quirks," since they have probably been of little biological detriment (or possibly of some benefit) until recent generations when individuals have been exposed to certain novel circumstances. A genetic tendency to overeat sweets is of little consequence when sugar is scarce and extensive exercise is involved in meeting basic needs; if famines are frequent, it might even be advantageous. A preference for fats will mainly be adaptive when calories and fat are scarce and few people live into their sixties. The strong genetic factors in myopia and dyslexia will remain latent until literacy becomes a necessary accomplishment. It will be valuable to understand the nature of the genetic variations that make some individuals especially susceptible to these diseases. An adaptive analysis reveals the fundamental distinction between such genetic quirks (genes of little cost in the natural environment), genes that impose costs that are worth their biological benefits, and true genetic defects that are necessarily rare and maintained by mutation pressure.

#### HOPES AND PRACTICAL SUGGESTIONS

Disease looks different from an evolutionary perspective. Infection is not a happenstance encounter with another organism, but an arms race between host and parasite, with extraordinary elaborations of weapons, strategies, defenses and counterdefenses. Trauma is not a mere matter of damaged tissue, but of the failure of protective mechanisms, the yielding

of the soma at weak spots, and repair processes that have been shaped and constrained by natural selection. Genes that cause disease are not just the result of mutation, but may be selected for known or unknown benefits, such as the vigor in youth that may result from genes that later cause aging. Environmental abnormalities, not limited to changes in the last few generations, are major causes of common diseases, often in interaction with genetic "quirks" that are harmless in the environment of evolutionary adaptedness. For all four causes of disease, an evolutionary perspective adds another dimension to proximate explanations.

We are only at the dawn of Darwinian medicine. Although evolutionary theory has long been the foundation for many branches of biology, adaptationist analyses are just beginning to be applied in medicine. We expect them to grow rapidly in number and explanatory power, and to make major contributions to future progress in the understanding of disease.

One might ask why this is happening now, but it may be more edifying to ask why evolutionary theory was not fully applied to medicine decades ago. We predict this will eventually be a topic for historians of science, but our present guess is that the delay resulted mainly because scientific medicine arose during the heyday of logical positivism, with its condemnation of all implications of purpose. This was transmitted to many physicians, who remain suspicious of adaptationist arguments. Another reason, also worthy of the attention of historians of science, is the surprising slowness of evolutionary biologists to provide useful theory. The historians may well marvel that the role of kinship in evolution was not seriously examined until 1964. While some branches of biology have made rapid strides as a result of testing evolutionary as well as proximate explanations, the evolutionary approach has so far provided few benefits to medicine.

Many people seem to think that an adaptationist approach is based on the assumption that organisms are perfect. This is a misconception. It is true that the adaptationist holds the power of selection in high regard and is skeptical of explanations that take quick refuge in proposed defects in the organism. Paradoxically, however, the adaptationist is also particularly able to appreciate the adaptive compromises that are responsible for much disease.

Walking upright has a price in back problems. The capacity for tissue repair has a price of cancer. The immune response has a price of immune disorders. The price of anxiety is panic disorder. In each case, natural selection has done the best it can, weighing benefits against costs. Wherever the balance point, however, there will be disease. The adaptationist does not view the body as a perfect creation, but as a bundle of compromises. By understanding them, we will better understand disease.

Medical research should benefit substantially from an adaptationist approach. While most researchers well understand the basics of evolution and apply them intuitively in their work, more explicit evolutionary explanations should facilitate the study of proximate abnormalities. Some current medical research seems a bit like trying to understand a clock's malfunction by analysing all its gears, without daring to ask about their function. A dirt-in-the-gears analogy can be misleading in relation to genes that cause senescence or cancer. Such genes should be suspected of having beneficial effects in most individuals most of the time. A search for such benefits may lead to ways of augmenting them. We look forward to the day when research articles routinely address both evolutionary and proximate explanations. We look forward to textbooks that include, in addition to the traditional sections on Epidemiology, Etiology, Pathophysiology, Diagnosis, Course and Treatment, another section on Evolutionary Considerations.

Clinical practice will also benefit from an evolutionary perspective. We hope that Darwinian medicine never becomes a sect or a rallying cry for a branch of medicine. Instead we hope that the addition of an evolutionary perspective can help to integrate every practitioner's knowledge as it is applied to individual cases. This has immediate practical utility when considering what to do about a low iron level in a person with a chronic infection, whether to suppress the cough in a person with pneumonia, or when to adopt new technology. For instance, when chest X rays came into common use, some physicians believed that an enlarged thymus caused susceptibility to infection and prescribed radiation treatments to shrink the thymus. Now, people who received such treatments have a risk of thyroid cancer 45 times greater than that of controls (Shore

et al., 1985). This tragedy might have been prevented either by distrust of radiation because it is a novel environmental factor, or by the presumption that a complex organ like the thymus must serve important adaptive functions. Those who see the body as a machine designed by a careless engineer are prone to therapeutic hubris. The antidote is a deep understanding of each organ's phylogeny and functions, as well as its ontogeny and structure.

At present, evolutionary considerations are included haphazardly in medical curricula, often with inappropriate apologies for their "speculative" or "teleological" nature. Such misconceptions will not be corrected until evolutionary medicine is taught, like other aspects of biology, by specialists. It should be taught by those who can communicate a view of the organism as a complex and interrelated bundle of adaptations and compromises designed to maximize reproduction in competition with conspecifics and other organisms. It should be taught by those who see evolution as the framework that can link diverse aspects of medicine.

There is already widespread dissatisfaction with the disjointedness of medical curricula organized along traditional departmental lines, but there are also difficulties with alternatives organized according to bodily systems or clinical problems. In contrast to such artificial devices, evolution provides a natural framework for a conceptually cohesive medical curriculum. While awaiting such curricular innovation, we recommend that medical students receive at least 20 hours of instruction specifically on Darwinian theory, human evolution, and the functional analysis of organ systems. In addition, lectures in other basic sciences should routinely address the phylogeny and adaptive significance of the systems under discussion. We believe that such curricular changes would provide a payoff in a new generation of physicians with a deeper understanding of disease.

Major reform of medical curricula is difficult. Lecture schedules swell with burgeoning knowledge about proximate causes, and departments compete for scarce time to present this knowledge. Departments organized around the traditional medical sciences are rarely able

to support the study of evolutionary hypotheses. They lack both funds and mentors for the support of faculty who specialize in evolutionary aspects of medicine. The creation of Departments of Evolutionary Medicine is the natural solution to this problem, but few deans will accept the challenge of establishing a new discipline.

A more modest step in this direction would be the creation of interdisciplinary programs or institutes to advance the development of evolutionary medicine. Such institutes could include geneticists, physiologists, microbiologists, biochemists, anthropologists, and psychologists in addition to specialists in the various areas of clinical medicine. They would be charged with further developing the conceptual tools and standards of evidence necessary to formulate and test explicit evolutionary hypotheses at all levels of organization of the organism. They would write textbooks that address, for each disease, the evolutionary considerations that are missing from current presentations. Their work would soon demonstrate that evolutionary considerations are not speculations to be discussed by review committees that have finished allocating their funds, but fundamental scientific hypotheses that require rigorous testing if medicine is to realize the benefits of recent advances in evolutionary biology.

#### ACKNOWLEDGMENTS

We thank the J. S. Guggenheim Foundation, the Evolution and Human Behavior Program and the Department of Psychiatry at The University of Michigan, the Department of Ecology and Evolution of the State University of New York at Stony Brook, and the Department of Biology at Queen's University, Kingston, Ontario, for generous support and encouragement. For important criticisms and suggestions on the manuscript we are grateful to Angela M. Brown, Paul W. Ewald, Douglas J. Futuyma, John Hartung, Howard C. Howland, Kevin Kerber, Matthew Kluger, Isaac M. Marks, Cynthia S. Pomerleau, Marjorie Profet, James Sisson, Robert Smuts, Donald Symons, Brant Wenegrat, and two conscientious referees consulted by the editors of this journal. Contribution 776 from the Department of Ecology and Evolution, State University of New York at Stony Brook.

## REFERENCES

- Abelson, P. H. 1990. Medicine from plants. *Science*, 247:513.
- Ainsworth, M. D., M. D. Blehar, E. Waters, and S. Wall. 1978. *Patterns of Attachment: A Psychological Study of the Strange Situation*. Erlbaum, Hillsdale.
- Albin, R. L. 1988. The pleiotropic gene theory of senescence: Supportive evidence from human genetic disease. *Ethol. Sociobiol.*, 9:371-382.
- Allison, A. C. 1954. Protection afforded by the sickle-cell trait against subtertian malarial infection. *Brit. Med. J.*, 1:290-292.
- Ames, B. N., and L. S. Gold. 1989. Pesticides, risk and applesauce. *Science*, 244:755-757.
- Auel, J.M. 1980. *The Clan of the Cave Bear*. Crown, New York.
- Austad, S. N. 1989. Life extension by dietary restriction in the bowl and doily spider, *Frontinella pyramitela*. *Exp. Gerontol.*, 24:83-92.
- Baer, G. M. 1973. *The Natural History of Rabies*, Vols. I and II. Academic Press, New York.
- Beahrs, J. O. 1989. The evolution of post-traumatic behavior: Three hypotheses. Paper presented at The Human Behavior and Evolution Society, Annual Meeting, August 25-27, 1989, Evanston, Illinois.
- Beason, R. C., and J. E. Nichols. 1984. Magnetic orientation and magnetically sensitive material in a transequatorial bird. *Nature*, 309:151-153.
- Bell, G. 1984. Evolutionary and nonevolutionary theories of senescence. *Am. Nat.*, 124:600-603.
- Boorstein, S. M., and P. W. Ewald. 1987. Costs and benefits of behavioral fever in *Melanopus sanguinipes* infected with *Nosema acridophagus*. *Physiol. Zool.*, 60:586-595.
- Bowlby, J. 1969. *Attachment and Loss, Vol. 1 (Attachment)*. Basic Books, New York.
- Burgio, R. R., and A. G. Ugazio. 1975. How infection can trigger autoimmunity. *Infection*, 3:63-73.
- Calabrese, E. J. 1985. *Toxic Susceptibility: Male/Female Differences*. Wiley, New York
- Campbell, B. G. 1985. *Human Evolution*, 3rd ed. Aldine, New York.
- Cannon, W. B. 1929. *Bodily Changes in Pain, Hunger, Fear and Rage*. Harper, New York.
- Capron, A., J. P. Dessaint, M. Capron, J. H. Ouma, and A. E. Butterworth. 1987. Immunity to schistosomes: Progress towards vaccine. *Science*, 238:1065-1072.
- Cassidy, C. N. 1980. Nutrition and health in agriculturists and hunter-gatherers. In N. W. Jerome, R. F. Kandel, and G. H. Pelto (eds.). *Nutritional Anthropology*, pp. 117-145. Redgrave Publ. Co., Pleasantville.
- Cavalli-Sforza, L. L., and M. W. Feldman. 1981. *Cultural Transmission and Evolution: A Quantitative Approach*. Princeton Univ. Press, Princeton.
- Charnov, E. L. 1984. Why are there essential amino acids and other nutrients. *Evol. Theory*, 7:92.
- Curtin, S. H., and D. J. Chivers. 1978. Leaf-eating primates of peninsular Malaysia: The siamang and the dusky leaf-monkey. In G. G. Montgomery (ed.), *The Ecology of Arboreal Folivores*, pp. 441-464. Smithsonian Inst. Press, Washington, D. C.
- De Nooij, M. P., and J. M. M. van Damme. 1988. Variation in pathogenicity among and within populations of the fungus *Phomopsis subordinaria* infecting *Plantago lanceolata*. *Evolution*, 42:1166-1171.
- Diamond, J. M. 1988. Founding fathers and mothers. *Nat. Hist.*, 1988(June):10-13.
- . 1989. Blood, genes, and malaria. *Nat. Hist.*, 1989(February):8-18.
- . 1990. The cost of living. *Discover*, 1990(June): 62-67.
- Dobson, A. P. 1988. The population biology of parasite-induced changes in host behavior. *Q. Rev. Biol.*, 63:139-165.
- Dobzhansky, T. 1951. *Genetics and The Origin of Species*. Columbia Univ. Press, New York.
- Donelson, J. E. 1988. Unsolved mysteries of trypanosome antigenic variation. In P. T. Englund and A. Sher (eds.), *MBL (Marine Biology Laboratory) Lectures in Biology, Vol. 9 (The Biology of Parasitism: A Molecular and Immunological Approach)*, pp. 371-400. Alan R. Liss, New York.
- Donelson, J. E., and M. J. Turner. 1985. How the trypanosome changes its coat. *Sci. Am.*, 252:44-51.
- Doolittle, R. F., D.-F. Feng, M. S. Johnson, and M. A. McClure. 1989. Origins and evolutionary relationships of retroviruses. *Q. Rev. Biol.*, 64:1-30.
- Doran, T. F., C. De Angelis, R. A. Baumgardner, and E. D. Mellits. 1989. Acetaminophen: More harm than good for chicken pox? *J. Pediatr.*, 114:1045-1048.
- DuPont, H. L., and R. B. Hornick. 1973. Adverse effect of Lomotil therapy in shigellosis. *J. Am. Med. Assoc.*, 226:1525-1528.
- Eaton, S. B., M. Shostak, and M. Konner. 1988. *The Paleolithic Prescription: A Program of Diet, Exercise and a Design for Living*. Harper and Row, New York.
- Eberhard, W. G. 1990. Evolution in bacterial plasmids and levels of selection. *Q. Rev. Biol.*, 65:3-22.
- Endler, J. A. 1986. *Natural Selection in the Wild*. Princeton Univ. Press, Princeton.
- Ewald, P. W. 1980. Evolutionary biology and the treatment of signs and symptoms of infectious disease. *J. Theor. Biol.*, 86:169-176.
- . 1987. Transition modes and evolution of the

- parasitism-mutualism continuum. *Ann. N. Y. Acad. Sci.*, 503:175-306.
- . 1988. Cultural vectors, virulence, and the emergence of evolutionary epidemiology. *Oxford Surv. Evol. Biol.*, 5:215-245.
- . 1991. Culture, transmission modes, and the evolution of virulence with special reference to cholera, influenza, and AIDS. *Human Nature*, 2:1-30.
- Ewald, P. W., and J. Schubert. 1989. Vertical and vector-bone transmission of insect endocytobionts, and the evolution of benignity. In W. Schwemmler and G. Gassner (eds.), *Insect Endocytobiosis: Morphology, Physiology, Genetics*, pp. 21-35. CRC Press, Boca Raton.
- Freed, W. J., L. de Medinaceli, and R. J. Wyatt. 1985. Promoting functional plasticity in the damaged nervous system. *Science*, 227:1544-1552.
- Friedman, T. 1989. Progress toward human gene therapy. *Science*, 244:1275-1281.
- Fries J. F., and L. M. Crapo. 1981. *Vitality and Aging: Implications of the Rectangular Curve*. W. H. Freeman, San Francisco.
- Frisch, R. E. 1988. Fatness and fertility. *Sci. Am.*, 258 (March):88-95.
- Gill, D. E., and B. A. Mock. 1985. Ecological and evolutionary dynamics of parasites: The case of *Trypanosoma diemyctyli* in the red spotted newt *Notophthalmus viridescens*. In D. Rollinson and R. M. Anderson (eds.), *The Evolution of Host Parasite Interactions*, pp. 157-183. Academic Press, London.
- Gotschlich, E. C. 1983. Thoughts on the evolution of strategies used by bacteria for evasion of host defenses. *Rev. Infect. Dis.*, 5:S778-S783.
- Gould, S. J., and R. C. Lewontin. 1979. The spandrels of San Marco and the Panglossian paradigm: A critique of the adaptationist programme. *Proc. R. Soc. Lond. B*, 205:581-598.
- Hamilton, W. D. 1966. On the moulding of senescence by natural selection. *J. Theor. Biol.*, 12:12-45.
- Hamilton, W. D., R. Axelrod, and R. Tanese. 1990. Sexual reproduction as an adaptation to resist parasites (a review). *Proc. Natl. Acad. Sci. USA*, 87:3566-3573
- Harris, P. 1983. Evolution and the cardiac patient. 5: Origins of neuro-endocrine control of water and salt balance; 6: Origins of congestive cardiac failure. *Cardiovasc. Res.*, 17:437-445.
- Hart, B. L. 1990. Behavioral adaptations to pathogens and parasites. Five strategies. *Neurosci. Behav. Rev.*, 14:273-294.
- Harvell, C. D. 1990. Ecology and evolution of inducible defenses. *Q. Rev. Biol.*, 65:323-340.
- Hill, J. O., S. Thacker, D. Newby, M. N. Skykes, and M. Digirolamo. 1988. Influence of food restriction coupled with weight cycling on carcass energy restoration during ad-libitum refeeding. *Int. J. Obesity*, 12:547-555.
- Hussein, L., A. Arafah, and S. Gaafar. 1989. The vitamin B1 status among young Egyptian males in relation to infection with parasites. *Int. J. Vitam. Nutr. Res.*, 59:48-51.
- Hutton, C. W. 1987. Generalized osteoarthritis: An evolutionary problem? *Lancet*, 1:1463-1465.
- Intersalt Cooperative Research Group. 1988. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *Brit. Med. J.*, 297:319-328.
- Janzen, D. H. 1978. Complications in interpreting the chemical defenses of trees against tropical arboreal plant-eating vertebrates. In G. G. Montgomery (ed.), *The Ecology of Arboreal Folivores*, pp. 73-84. Smithsonian Inst. Press, Washington, D. C.
- Johnston, F. E. (ed.). 1987. *Nutritional Anthropology*. Alan R. Liss, New York.
- Karlsson, J. L. 1986. Genetics of myopia and associated mental traits. *Hereditas*, 105:205-208.
- Keeton, W. T. 1971. Magnets interfere with pigeon homing. *Proc. Natl. Acad. Sci., USA*, 68:102-106.
- Kierszenbaum, F., M. B. Szein, and A. A. Beltz. 1989. Decreased human IL-2 receptor expression due to a protozoan pathogen. *Immunol. Today*, 10:129-131.
- Kiester, E., Jr. 1984. A little fever is good for you. *Science* 84, 9:168-173.
- Kluger, M. J. 1986. Is fever beneficial? *Yale J. Biol. Med.*, 59:89-95.
- . 1991. The adaptive value of fever. In P. A. Mackowiak (ed.), *Fever: Basic Mechanisms and Management*, pp. 105-124. Raven Press, New York.
- Knowler, W. C., D. J. Pettitt, P. H. Bennett, and A. C. Williams. 1983. Diabetes mellitus in the Pima Indians: Genetic and evolutionary considerations. *Am. J. Phys. Anthropol.*, 62:107-114.
- Larder, B. A., G. Darby, and D. D. Richman. 1989. HIV with reduced sensitivity to zidovudine (AZT) isolated during prolonged therapy. *Science*, 243:1731-1734.
- Lusso, P., F. di M. Veronese, B. Ensoli, G. Franchini, C. Jemma, S. E. deRocco, V. S. Kalyanaraman, and R. C. Gallo. 1990. Expanded HIV-1 cellular tropism by phenotypic mixing with murine endogenous retroviruses. *Science*, 247:848-852.
- Mahmoud, A. D. 1989. Parasitic protozoa and helminths: Biological and immunological changes. *Science*, 246:1015-1022.
- Marks, I. M. 1987. *Fears, Phobias, and Rituals: Panic, Anxiety, and Their Disorders*. Oxford Univ. Press, New York.
- Marx, J. L. 1988. Cytokines are two-edged swords in disease. *Science*, 239:257-258.

- Massad, E. 1987. Transmission rates and the evolution of pathogenicity. *Evolution*, 41:1127-1130.
- Maynard Smith, J. 1978. The evolution of behavior. *Sci. Am.*, 239:91-101.
- Mayr, E. 1983. How to carry out the adaptationist program? *Am. Nat.*, 121:324-334.
- . 1988. Philosophical aspects of natural selection. In E. Mayr (ed.), *Toward A New Philosophy of Biology*, pp. 116-129. Belknap (Harvard Univ. Press), Cambridge.
- Medawar, P. B. 1952. *An Unsolved Problem in Biology*. H. K. Lewis, London.
- Miller, S. E., and M. B. Hadfield. 1990. Developmental arrest during larval life and life-span extension in a marine mollusc. *Science*, 248:356-358.
- Moss, J., and M. Vaughan. 1979. Activation of adenylate cyclase by cholera toxin. *Annu. Rev. Biochem.*, 48:581-600.
- Muller, H. J. 1948. Evidence of the precision of genetic adaptation. *Harvey Lectures*, 43:165-229.
- Munck, A., P. M. Guyre, and N. J. Holbrook. 1984. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocr. Rev.*, 5:25-94.
- Neel, J. V. 1982. The thrifty genotype revisited. *Serono Symposium*, 47:281-293.
- Nesse, R. M. 1984. An evolutionary perspective on psychiatry. *Compr. Psychiatry*, 25:575-580.
- . 1988a. Panic disorder. An evolutionary view. *Psychiatr. Ann.*, 18:478-483.
- . 1988b. Life table tests of evolutionary theories of senescence. *Exp. Gerontol.*, 23:445-453.
- . 1990. Evolutionary explanations of emotions. *Human Nature*, 1:260-284.
- Nunney, L. 1985. Group selection, altruism, and structured-deme models. *Am. Nat.*, 126:212-230.
- Orians, G. H. 1980. Habitat selection: General theory and applications to human behavior. In J. S. Lockard (ed.), *The Evolution of Human Social Behavior*, pp. 49-66. Elsevier Press, New York.
- Petersen, G. M., and J. I. Rotter. 1983. Genetic and evolutionary implications in peptic ulcer disease. *Am. J. Phys. Anthropol.*, 62:71-79.
- Pond, C. 1981. Storage. In C. R. Townsend and P. Calow (eds.) *Physiological Ecology: An Evolutionary Approach to Resource Use*, pp. 190-219. Sinauer, Sunderland.
- Profet, M. 1988. The evolution of pregnancy sickness as protection to the embryo against Pleistocene teratogens. *Evol. Theory*, 8:177-190.
- . 1991. The function of allergy: Immunological defense against toxins. *Q. Rev. Biol.*, 66:23-62.
- . In press. Pregnancy sickness as adaptation: A deterrent to maternal ingestion of teratogens. In J. Barkow, L. Cosmides, and J. Tooby (eds.), *The Adapted Mind: Evolutionary Psychology and the Generation of Culture*. Oxford Univ. Press, New York.
- Raviola, E., and T. N. Wiesel. 1985. An animal model of myopia. *N. Engl. J. Med.*, 312:1609-1615.
- Rose, M. R. 1985. Life history evolution with antagonistic pleiotropy and overlapping generations. *Theor. Pop. Biol.*, 28:342-358.
- . 1990. *Evolutionary Biology of Aging*. Oxford Univ. Press, New York.
- Rusiniak, K. W., J. Garcia, and W. A. Hankins. 1976. Bait shyness: Avoidance of the taste without escape from the illness in rats. *J. Comp. Physiol. Psychol.*, 90:460-467.
- Russell, W. M. S., and C. Russell. 1983. Evolutionary and social aspects of disease. *Ecol. Dis.*, 2:95-106.
- Sacher, G. A. 1982. Evolutionary theory in gerontology. *Perspect. Biol. Med.*, 25:335-353.
- Sager, R. 1989. Tumor suppressor genes: The puzzle and the promise. *Science*, 246:1406-1412.
- Saunders, J. R. 1984. Antibiotic resistance in bacteria. *Brit. Med. Bull.*, 40:54-60.
- Schaeffel, F., A. Glasser, and H. C. Howland. 1988. Accommodation, refractive error, and eye growth in chickens. *Vision Res.*, 28:639-657.
- Scriver, C. R. 1984. An evolutionary view of disease in man. *Proc. R. Soc. Lond. B*, 220:273-298.
- Shore, R. E., E. Woodard, N. Hildreth, P. Dvoretzky, L. Hempelman, and B. Pasternak. 1985. Thyroid tumors following thyroid irradiation. *J. Natl. Cancer Inst.*, 74:1177-1184.
- Stellman, S. D., and L. Garfinkel. 1986. Artificial sweetener use and one-year weight change among women. *Prev. Med.*, 15:195-202.
- Teikari, J. M., J. Kaprio, M. K. Koskenveno, and A. Vannas. 1988. Heritability estimate for refractive errors—a population based sample of adult twins. *Genet. Epidemiol.*, 5:171-181.
- Thornhill, R., and N. W. Thornhill. 1989. The evolution of psychological pain. In R. Bell (ed.), *Sociobiology and the Social Sciences*, pp. 73-103. Texas Tech. Univ. Press, Lubbock.
- Trevathan, W. R. 1987. *Human Birth: An Evolutionary Perspective*. Aldine de Gruyter, New York.
- Usanga, E. A., and L. Luzzatto. 1985. Adaptation of *Plasmodium falciparum* to glucose 6-phosphate dehydrogenase-deficient host red cells by production of parasite-encoded enzyme. *Nature*, 313:793-795.
- Vander, A., J. H. Sherman, and D. S. Luciano. 1990. *Human Physiology: The Mechanisms of Body Function*, 4th ed. McGraw-Hill, New York.
- Voland, E., and R. Voland. 1989. Evolutionary biology and psychiatry: The case of anorexia nervosa. *Ethol. Sociobiol.*, 10:223-240.
- Wallace, B. 1989. Can stepping stones be bridges? *Am. Nat.*, 132:578-579.
- Wallman, J., M. D. Gottlieb, and V. Rajaram. 1987. Local retinal regions control local eye growth and myopia. *Science*, 237:73-77.

- Wasser, S. K., and D. P. Barash. 1983. Reproductive suppression among female mammals: Implications for biomedicine and sexual selection theory. *Q. Rev. Biol.*, 58:513-538.
- Weinberg, E. D. 1984. Iron withholding: A defense against infection and neoplasia. *Physiol. Rev.*, 64:65-102.
- . 1989. Cellular regulation of iron assimilation. *Q. Rev. Biol.*, 64:261-290.
- Weindruch, R., and R. L. Walford. 1988. *The Retardation of Aging and Disease by Dietary Restriction*. C C Thomas, Springfield.
- Wenegrat, B. 1984. *Sociobiology and Mental Disorder: A New View*. Addison-Wesley, Menlo Park.
- Williams G. C. 1957. Pleiotropy, natural selection, and the evolution of senescence. *Evolution*, 11:398-411.
- . 1966. *Adaptation and Natural Selection*. Princeton Univ. Press, Princeton.
- Wilson, D. S. 1987. Altruism in Mendelian populations derived from sibling groups: The haystack model revisited. *Evolution*, 41:1059-1070.
- Winer, H. 1977. *Psychobiology and Human Disease*. Elsevier, New York.
- Wissing, H., H. A. Braum, and K. Schafer. 1988. Dynamic response characteristic of the ampullae of Lorenzini to thermal and electrical stimuli. *Prog. Brain Res.*, 74:99-107.
- Wolf, S., C. M. Deom, R. N. Beachy, and W. J. Lucas. 1989. Movement protein of tobacco mosaic virus modifies plasmodesmatal size exclusion limit. *Science*, 246:377-379.
- Young, F. A., G. A. Leary, W. R. Baldwin, D. C. West, R. A. Box, E. Harris, and C. Johnson. 1969. The transmission of refractive errors within Eskimo families. *Am. J. Optom.*, 46:676-685.