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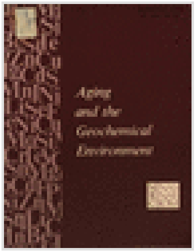

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Aging and the Geochemical Environment

PANEL ON AGING AND THE GEOCHEMICAL ENVIRONMENT
Subcommittee on the Geochemical Environment in Relation to Health and Disease
U.S. National Committee for Geochemistry

Assembly of Mathematical and Physical Sciences
National Research Council

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PREFACE

This report describes and assesses the aging process and related environmental aspects that may provide useful insights toward postponing some of the inevitable effects of aging. Although the Panel on Aging and the Geochemical Environment is convinced that the geochemical environment is associated with aging, it of course recognizes that other factors may also be significant or, perhaps, more important. Accordingly, the report is intended to enhance the awareness of biomedical and geochemical research scientists, decision makers in related areas, and the lay public interested in an understanding of the relation of the geochemical environment to senescence.

As the human lifespan is gradually extended, and more people live longer, interest in adding meaning and purpose to these years is likewise on the increase. The formation in 1974 of the National Institute on Aging (NIA) within the National Institutes of Health is an important milestone in this trend. Before NIA was formed, federal research on aging was centered in the Gerontology Research Center at Baltimore City Hospitals, which was under the National Institute of Child Health and Human Development (NICHHD).

The Subcommittee on the Geochemical Environment in Relation to Health and Disease (GERHD), which was formed in 1969 under the U.S. National Committee for Geochemistry, Assembly of Mathematical and Physical Sciences (AMPS), National Research Council (NRC), recognized that, statistically, people from portions of the upper midwest and the high plains of the United States live longer than those from the southeastern Coastal Plain; GERHD strongly suspected that the geochemical environment might be contributing to this difference. Accordingly, it established the Panel on Aging and the Geochemical Environment (PAGE) with the following objectives--all in the context of causal relationships to human aging:

- To investigate, assess, and extend what is known about the distribution of elements in the environment and their availability to plants and animals, including man, and about the effects of excesses or deficiencies of these elements in living organisms, especially man.
- To consider methodology related to data collection and analysis, including computer storage/retrieval and manipulation of the

collected data, to achieve comparability of data across disciplinary lines.

- To consider also experimental design from the standpoint of achieving comparability of research results among the disciplines involved, allowing construction of more effective probability models.
- To establish avenues of communication among the various disciplinary groups concerned with these problems.
- To promote interdisciplinary and international education, research, and exchanges of knowledge and expertise concerning the geochemical environment and its relation to health and disease.
- To be responsive to the specific needs of the sponsoring organizations.

The Panel was formed with knowledgeable biomedical, environmental, and earth scientists from agencies and universities that have available the needed pathological, epidemiological, geochemical, soil-science, and hydrological expertise.

The geochemical portion of this report, in counterpart to that on health and aging, reflects the properties of earth materials (rocks, minerals, soils, fluids) that produce or condition the geochemical environment that may affect aging. Readers not immediately familiar with the earth sciences will find it helpful to review the differences between <u>mineral</u> and <u>chemical</u> compositions of rocks and soils because these two entities are <u>not</u> interchangeable--especially in the context of interaction with the bioenvironment. Several examples will illustrate this.

The inorganic constituents of soils and rocks are minerals. Minerals typically are naturally occurring, inorganic substances that possess characteristic crystal structures and whose compositions may be expressed by chemical formulas. They cannot be adequately characterized by a chemical formula alone. Moreover, a given composition may occur in more than one mineral form, each of which has radically different physical and/or reactive properties within the environment. For example, carbon occurs as the hard, abrasive mineral, diamond, but also as the mineral, graphite, in which the carbon is soft and lubricative; further, carbon is the major constituent of anthracite coal, in which mineral form it is dissimilar to both diamond and graphite. To consider another example, mercur<u>ous</u> chloride is calomel, a mineral known from antiquity for its medicinal qualities; on the other hand, mercur<u>ic</u> chloride or "bichloride of mercury" is a corrosive sublimate, a deadly poison with no mineral name because, except for one questionable occurrence in the Atacama Desert, it probably does not occur in nature. Thus, <u>minerals</u> have greater significance and are more specific than their <u>chemical</u> formulations would indicate.

More common to the geochemical environment that affects health are minerals containing, and supplying, essential macroelements and microelements, particularly cations. Sodium (which is related to hypertension), calcium and magnesium (both of which are related to mortality from arteriosclerotic heart disease) are examples of important macroelements. In the mineral halite, sodium chloride, or table salt, the sodium is highly soluble. Likewise in the mineral calcite, $CaCO_3$, and dolomite, $CaMg(CO_3)_2$, the calcium (with magnesium) is relatively soluble in typical groundwater. On the other hand, sodium and calcium in plagioclase feldspar, NaCaAl silicate--also a common mineral--are so insoluble that rocks containing feldspar are used as building stones or monuments. The chemical composition of this feldspar determined by chemical analysis using destructive fusion, acid, or electric arc methods shows dominant sodium and calcium, but the bioenvironment in association with it may never interact with those elements--in contradistinction to rock (rock salt) containing halite, and limestone containing calcite and dolomite. Similarly, boron when in borax mineral is exceedingly soluble, whereas in the mineral tourmaline, the boron is locked within an exceedingly refractory structure, making it biologically unavailable.

Thus it is evident that studies relating the geochemical environment to human aging must consider the minerals in, as well as the chemical compositions of, the soils and rocks.

Another incongruency in terminology used by geochemical and biomedical groups is referring to unspecified combinations of chemical elements as minerals when given as nutritional supplements or medicine. When "calcium" is ingested, is it as calcium carbonate, phosphate (and which phosphate), lactate, or other? Turning to microelements, iron, which is well known for its essential contribution to the hemoglobin molecule, may be ingested as a relatively soluble ferrous compound or as a low-solubility ferric compound, depending on which mineral is the environmental source. Thus researchers and writers using merely the names of chemical elements in describing deficiencies or toxicities in the bioenvironment and geoenvironment need to sharpen the resolution of their terminology to avoid misleading their scientific colleagues as well as the public.

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1

INTRODUCTION

Howard C. Hopps, Chairman

The Panel on Aging and the Geochemical Environment has sought to identify those geochemical factors that are associated with longevity coupled with health, with the view that if cause and effect relationships can be established, the information could be exploited to increase longevity and health throughout the United States and beyond. The Panel has concentrated on regions of increased longevity and decreased longevity in the United States but, in its search for clues, has also looked at characteristics of several other geographic regions that are renowned because of a reportedly high proportion of healthy old people, e.g., Vilcabamba, Ecuador; Hunza, Pakistan; and the Georgian SSR and Azerbaijan SSR, USSR.

Much care has been taken in identifying the two geographic areas in the United States selected for study (Figure 1). Emphasis was on regions in which factors suspected to affect longevity either positively or negatively did not seem to be exerting major effects. These included unusual levels of stress related to urban environment, industrial pollution, or mining activity; obvious genetic factors--admittedly a difficult problem to deal with (one approach is to identify ethnic groups, and also, when appropriate, the country of ancestral origin); and, of course, unusual patterns of migration (e.g., as in Florida or Alaska) that would confuse the issue of geochemical association. Such an approach has allowed us to focus upon the so-called unexplained residual, i.e., populations in which there is less chance for the effects of geochemical environment to be masked by more-powerful factors.

As implied above, the primary objective of the studies described in this monograph is to determine whether the geochemical environment significantly affects the development and course of advanced aging, i.e., senescence in humans who live in the United States. Because of the complexities of senescence, however, it is necessary to do more than merely associate appropriate epidemiologic and geochemical data; it is also necessary to explore mechanisms by which geochemical environment could be affecting senescence. It is in this context that the report includes, for example, considerations of cellular and tissue changes that occur with senescence, theories of aging, and pathologic and physiologic aspects of aging.

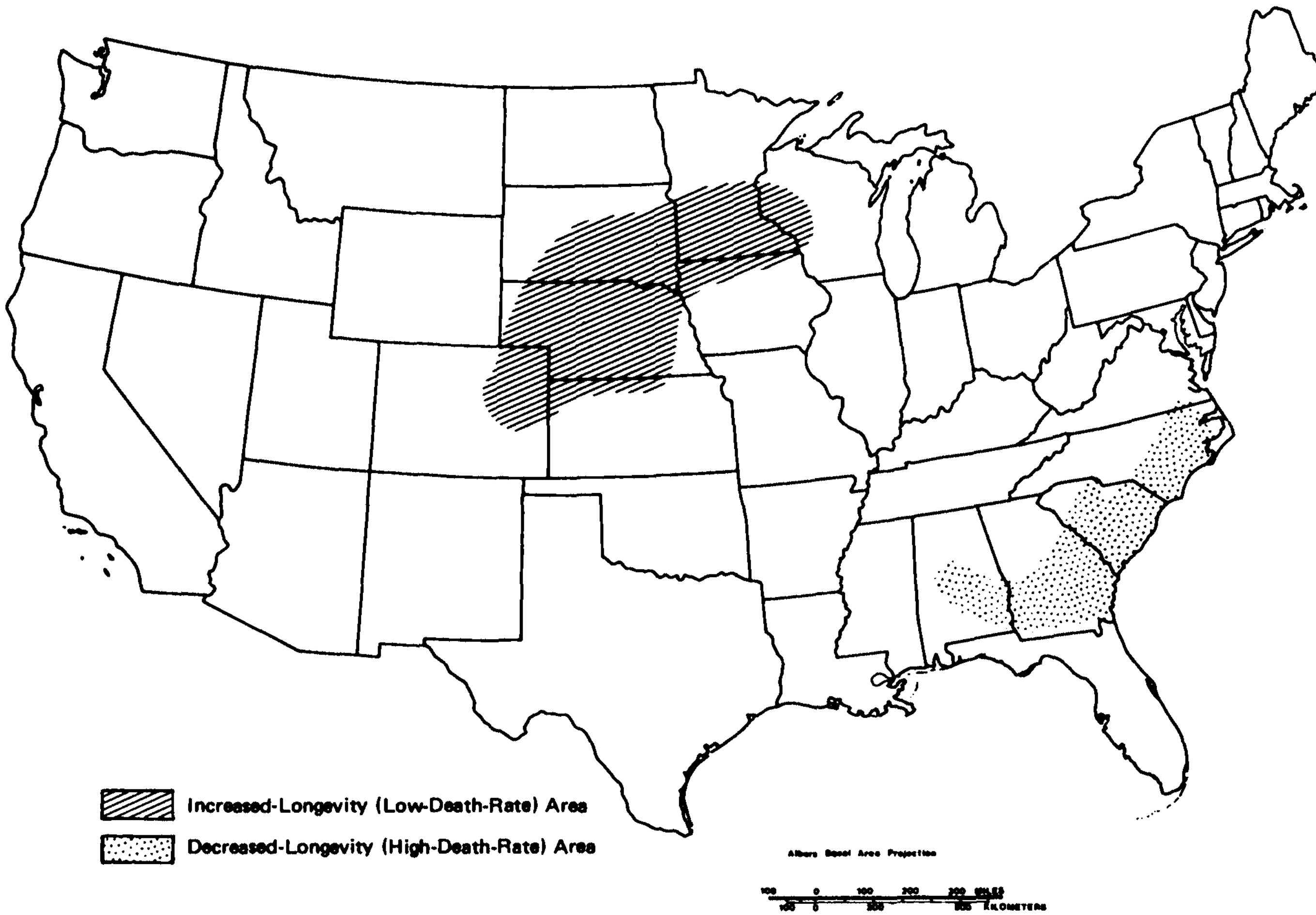

FIGURE 1 The two areas studied.

Studies of tissue cultures indicate that lifespan is determined by intracellular mechanisms, which limit the total number of cellular divisions that will occur. This is analogous to the limiting effects of the amount of gasoline in the fuel tank on the number of miles the car can travel. But there are many factors that affect how many miles the car will go per gallon of gas! And, continuing this analogy, it is the miles-per-gallon aspect that we are primarily concerned about in our studies of aging. It is unlikely that biomedical scientists will be any more successful than Ponce de Leon in finding the Fountain of Youth. The evidence does clearly indicate, however, that most humans do not achieve the effective longevity (quantity/quality of life) that is possible for them. The studies presented here consider these matters, focusing on the contributions that a highly favorable geochemical environment may make toward realizing the individual's longevity potential.

Our concern is not merely for longevity in the sense of survival but a retardation of senescence to give a longer productive life, i.e., quality coupled with quantity. In this sense, we strongly support the motto of the Gerontological Society, "to add years to life and life to years."

This general area is of great importance, and enormously complicated, and it is not reasonable to anticipate quick, easy answers to many questions.

This report represents a multidisciplinary effort that goes well beyond the obvious aggregation of sections by different authors. Each section reflects the broadened perspective and background knowledge derived from the close interrelationship that the panel members achieved during their work together in its preparation.

2

AGING AND SENESCENCE--GENERAL CONSIDERATIONS

Howard C. Hopps

In his Foreword to The Geriatric Patient, Reichel (1978), expressed some of the reasons for our concern about aging. "The numbers in themselves are instructive. There are 22 million Americans aged 65 or older, 10% of the U.S. population. By the year 2000, assuming fertility at a replacement rate, there will be approximately 30.6 million persons aged 65 or older, 15.5% of the total population. By 2030, there will be 50 million Americans over 65 years of age." The "very old" are also increasing in proportion and number. In 1970, fewer than 1 in 5 were 80 years old or older; projections indicate that in 1990 the proportion will be 1 in 4.

In addition to the obvious humanitarian reasons for concern about the aged, there are pressing economic reasons. Old age is a time of numerous medical problems, many of which are either recurring or chronic. The cost of health care among the aged is great, and rapidly increasing.

Yet another important basis for interest is because further insight into the nature of the aging process should help us to understand many pathologic disorders that affect both the young and the old--disorders involving growth and development, e.g., cancer; degenerative diseases, e.g., atherosclerosis; and immunopathologic disorders, e.g., abnormal susceptibility to infections and autoimmune diseases.

THE GENERAL PROBLEM

How Does One Define Aging?

Aging is a continuous process and obviously beneficial during the period of growth and development to maturity. The term aged implies postmaturity--the period of progressive deterioration associated with old age, terminating in death. It is this stage of the aging process that we are primarily interested in, and this stage is best termed senescence.

Another way of characterizing aging is in terms of the second law of thermodynamics. Senescence reflects the breakdown of integrative mechanisms; progressively decreasing efficiency of the total system complex leads to progressively increasing entropy.

Senescence, a state of postmaturity, is as difficult to define as "immaturity." Certainly the extent of deterioration associated with age cannot be measured by elapsed time; some persons 80 years of age are less aged functionally than others who are 65. This is a major reason why more and more research is being directed to the aging process--to separate the normal from the pathologic and to see whether the former (physiologic) process can be slowed.

The commonly accepted figure of 65 years as the beginning of old age is an arbitrary number attributed to Chancellor Bismarck, who, on being asked what age railway employers should begin paying retirement benefits, chose 65 years because he could not recall any employees who were yet that old. Certainly this is an unsatisfactory basis for defining the beginning of old age. If becoming old is to be defined as the time that various degenerative diseases seriously interfere with performance, there will, of course, be enormous variations among individuals. If it is to be defined on the basis of declining physiologic functions, which ones should be measured, and how? Obviously no one has yet devised a satisfactory means of resolving this problem--perhaps there is no satisfactory means. Actually, in evaluating the U.S. aged, there are three categories to consider. First, there are those 65 to 75 years of age, who, for the most part, are vigorous and continue to play an active role in their social milieu. Second are those 80+, who, in the main, are relatively inactive and whose place in the social structure has markedly changed. Moreover, many of this group are too poor to maintain their customary living standards, and thus are subject to a variety of environmental stresses, e.g., malnutrition and exposure to excess cold or heat, along with inadequate medical attention to problems that seem, initially at any rate, to be minor. Third is a subgroup aged 80+ years, who represent a small, elite class, so distinguished by past performance that they are still highly respected. Many of them are at least intermittently productive. A high proportion is sufficiently affluent to be well cared for, which includes protection from many environmental stresses, also prompt medical attention to the early signs and symptoms of disease. The group 75 to 80 years of age has not been forgotten; it is a borderline group about which it is difficult to make generalizations.

What is the Relationship between Aging and Longevity, and How Do Physiologic and Pathologic Aspects Interact?

There are distinctive chemical, functional and morphologic physiologic changes evident in the aged (see Chapters 5 and 6). Some of the most important of these act by interfering with homeostatic mechanisms that normally (in the mature) play such an important role in preventing serious disease or, if disease does occur, in effecting an adequate response. In an infectious disease such as lobar pneumonia, for example, response among the aged is characteristically too little and too late with respect to fever, leukocyte response, and antibody formation. And if the aged patient does recover, convalescence is prolonged and often fraught with complications.

Senescence and longevity are closely related, but somewhat indirectly. The ultimate limit to lifespan may reflect a built-in cellular control mechanism, but there is good reason to doubt that anyone has ever died of old age, as such. It appears rather that, in the manner described above, the relentlessly deteriorating physiologic processes of aging progressively increase the aged person's vulnerability to pathologic processes, and he dies of disease or injury before reaching his "ultimate limit" (see Chapter 7). In support of this view, the considerable increase in U.S. life expectancy, which, contrary to many reports, is significant at a base age of 45 years, has occurred not because of any demonstrable increase in ultimate lifespan but because of decreased (or deferred) mortality from many diseases that occur primarily during the middle or later years. This has allowed more individuals to come closer to achieving their maximal lifespan. Major decreases in mortality from cardiovascular diseases, including stroke, and infections have contributed heavily to the gain in longevity of those 45 years old and older.

Only a few of the environmental factors that affect mortality among the aged have been adequately studied; cigarette smoking is one of these. According to Mathews (1977), "On average, non-smokers live up to 7 years longer than smokers," and this effect of smoking cigarettes is supported by many observations. In the Bell and Rose (1975) study of 500 "recently deceased males from the Boston area" some 69 variables were evaluated to determine which were the best predictors of "age-at-death below 70, and 70 and above." In order of importance, not smoking cigarettes was number one. There has been relatively little study on effects of nutrition among those of middle age and early old age on longevity, and virtually none on the effects of the geochemical environment. Nevertheless, the influence of environmental factors on longevity, most of which are unidentified, much less understood, is evident from the marked, persistent geographic differences in risk of dying, i.e., mortality, among the older populations observed among and within various countries. Studies in the United States at the level of counties and state economic areas show that highest-rate counties have rates more than twice those of lowest-rate counties (Sauer and Donnell, 1970; Sauer and Brand, 1971). Evaluation of health among those who have survived beyond "middle age" (based largely on estimates of disease prevalence, i.e., morbidity) is much more difficult than assessing longevity. There are some data to suggest that the aged in some portions of the United States are healthier than in other portions, however.

How Does One Differentiate between Causally Related Geochemical Factors and Those That Are Merely Spatially Associated?

To determine possible effects of associated geochemical factors on the aging process, one must look carefully at the nature of the aging process and its mechanisms of action in order to determine a sound theoretical basis for geochemical effects. The results of these observations will be described later.

To be considered as possibly causal, geochemical factors associated with regions of longevity should first meet the test of theoretical feasibility, then be examined by other methods. The ideal, of course, would be controlled laboratory experiments. A second, epidemiologic, approach would be to identify geochemical environments presumed to favor longevity and then examine the population of the region. Another valuable approach--and one that we have employed--is to compare common denominators of those geochemical environments associated with increased longevity with those associated with decreased longevity. This approach is discussed in detail in Chapters 8, 9, and 10.

THE APPROACH

One way of looking at old age is to view it as the inevitable consequence of escaping death by accident or disease, as has been mentioned. This is an inadequate approach from our standpoint, however, because it does not consider the aging process, per se, nor its effects on the quality of life. Our concern is principally with the "normal" aging process and the (geochemical) environmental factors that affect it. There is good evidence that many environmental factors can act to accelerate the aging process, as we have mentioned, and obviously these factors should be identified and controlled if possible. But are there environmental factors that retard the aging process? And if so, can we control them so as to increase the quantity and quality of life?

As with many problems of this sort, there are at least two fundamental ways of attack.

One, by observing experiments of nature--using epidemiologic methods to identify groups of people living in specific geographic areas who have a longer (or shorter) lifespan than usual and, having identified them, examining the environmental factors that they share.

Two, by examining the cellular, tissue, and organismal events that characterize aging, trying to determine the basis for these events, then searching for ways to control them.

A great deal of research is concentrated on the second approach, so far without spectacular results. One of the reasons for this is the difficulty in developing a suitable experimental model. The experimental approach has a great advantage because it allows precise analyses to be carried out under tightly controlled laboratory conditions. Its limitations come because both the organisms studied and their environments are quite different from the human organisms and their environments, which are of primary concern.

The epidemiologic approach has the great advantage in that conditions and events are observed as they occur in nature, not as designed and implemented in the laboratory. The disadvantage comes from the imprecise measurements and lack of tight controls inherent in the methods that must be used.

The ideal approach is a combination of one and two, as we have implied. First, identify likely environmental factors from studies carried out in real-life situations. Then explore these leads under controlled laboratory conditions. The studies reported here are based mainly on the epidemiological approach.

How Does One Identify and Study Geographic Areas of Increased and Decreased Longevity?

There are three complex and difficult problems in studying the geochemical environment related to aging, in addition to those problems associated with evaluating effects of geochemical environment, that must be resolved before one can begin to determine spatially associated geochemical factors. The first, is to identify relatively large geographic regions where people have significantly increased longevity, and also their converse, i.e., areas with decreased longevity. One way to do this is to determine the proportion of the aged population at the geographic level of relatively small, well-defined areas such as counties or state economic areas, then group contiguous counties or regions to produce a region sufficiently large for study. This would, however, assume that birth rates are uniform and that any migration, in or out, would not affect the age distribution of the population within the specified counties or areas. Unfortunately, the data available do not allow this approach.

Another method would be to determine the distribution of centenarians, but recent experiences of the U.S. Bureau of the Census clearly indicate the unreliability of this method. Siegel and Passel (1976) have concluded that "...about 95 percent of the 106,000 reported centenarians in the 1970 census are in fact less than 100 years old," this error resulting principally from age misstatements by respondents. They comment: "A tendency to overreport age among the extreme aged is apparently characteristic of populations in general." And this tendency is not limited to the United States. There are many reports to the effect that numbers of the very aged are greatly exaggerated in the Caucasus, Ecuador, and other regions renowned for their high proportion of healthy old people (see Chapter 4). In discussing the problem, Felstein (1973) said the "...apparently high incidence of centenarians in the Georgian communities...[teaches] us a useful 'skeptic's rule.' The more isolated an area of population remains in an otherwise advancing country, the greater its claim for a high percentage of centenarians and very senior citizens."

The most feasible way of determining the areas of increased and decreased longevity, with acceptable accuracy, is by measuring the end point of age, i.e., death. This is because mortality statistics are quite complete, relatively accurate, and readily accessible in a form suitable for computer manipulation. These mortality data must be used carefully, however, because deaths are not necessarily the result of senescence. Moreover, the place in which a person dies may not be the place where he has lived most of his life. There are several ways to minimize these constraints. One of the most important is to use age-specific rather than age-adjusted mortality rates. Because age-specific death rates are used to calculate life expectancy, this method, used with appropriate safeguards, gives a good, indirect measure of longevity. As Mathews (1977) stated: "Longevity usefully measures many aspects of the aging process."

In selecting the geographic regions of increased longevity and decreased longevity for this study, we were careful to assure that (1) the populations would be sufficiently large to provide statistically reliable data; (2) the areas did not include high levels of environmental factors recognized as having adverse effects on aging (e.g., metropolitan areas with serious pollution problems); and (3) the areas did not reflect a large in-migration of either older or younger persons, as occurs in the Tampa-St. Petersburg area of Florida or much of Alaska, for example.

The second problem is to separate the pathologic from the purely physiologic aspects of aging, because it is the latter in which we are primarily interested. (See Chapter 6 for a detailed discussion.) Obviously problem areas one and two overlap considerably because serious pathologic processes, even though not directly related to aging, such as those seen during an epidemic of influenza, can markedly increase mortality rates in the age groups of interest.

The third problem arises when we attempt to evaluate the quality of life among the aged. Problems two and three are less amenable to solution with the data currently available but, as discussed later by Sauer (see Chapter 3), they are not totally insoluble.

Details of the methods used to identify areas of increased longevity and decreased longevity and the basis for selecting the areas for this study are described by Sauer (Chapter 3). Characterization of the geochemical environment of these areas is described by Keller (Chapter 8), Feder (Chapter 9), and Beeson (Chapter 10).

REFERENCES

Bell, B., and C. L. Rose. 1975. The interdisciplinary study of life span. In Understanding Aging: A Multidisciplinary Approach. Marian G. Spencer and Carolne J. Dorr, eds. Appleton-Century-Crofts, New York, pp. 40-66.

Felstein, I. 1973. Living to be a Hundred: A Study of Old Age. Hippocrene Books, Inc., New York. 200 p.

Mathews, J. D. 1977. Genetic and environmental determinants of longevity--an epidemiological approach. In Multidisciplinary Gerontology: A Structure for Research in a Developed Country. I. R. Mackay, ed. S. Karger, Basel, pp. 81-87.

Reichel, W. 1978. Foreword. In The Geriatric Patient. HP Publishing Co., Inc., New York, 233 pp.

Sauer, H. I., and F. R. Brand. 1971. Geographic patterns in the risk of dying. In Memoir 123, Geological Society of America, Inc. Boulder, Colo. pp. 131-150.

Sauer, H. I., and H. D. Donnell, Jr. 1970. Age and geographic differences in death rates. J. Gerontol. 25:83-86.

Siegel, J. S., and J. S. Passel. 1976. New estimates of the number of centenarians in the United States, Am. Stat. Assoc. 71(355):559-566.

3

THE DEFINITION AND DEMOGRAPHIC CHARACTERIZATION OF AN INCREASED LONGEVITY AREA AND A DECREASED LONGEVITY AREA IN THE UNITED STATES

Herbert I. Sauer

The general question being considered is: What is the effect of the geochemical environment on aging, which includes longevity in the physiologic sense, also the risk of dying prematurely from a pathologic process? Demographic questions that arise from this question include the following:

In the United States, what area of substantial size is most conducive to increased longevity, and what area to decreased longevity? More specifically, what area has the lowest risk of death for adults before the age of 75? In what area is the risk greatest?

The measure used is the risk of death per calendar year for adults of specific ages. Death rates have been calculated for several different groups of years, to provide a basis for inferring the relative average annual risk of death.

For this purpose, age-, sex-, and race-specific death rates have been calculated from the death detail tapes obtained from the National Center for Health Statistics and population-at-risk tapes by the Bureau of the Census, obtained both directly and through the Institute for Behavioral Research, University of Georgia, for each county of the United States and for groups of counties (U.S. Bureau of the Census, 1971). Rates have been calculated for all diseases combined, often called "natural causes," International Classification of Diseases, Adapted (ICDA) Codes 000-796 (National Center for Health Statistics, 1967). External causes, that is, accidents, suicide, and homicide, are not included in order to focus on diseases that may be affected by the environment. Thus it is not feasible to calculate life expectancy in the conventional way. Further, by concentrating on age-specific death rates, which are the basic building blocks from which life expectancies are calculated, we avoid the problem of making assumptions about death rates for age 85 and over. To measure the impact of the serious diseases of midlife on survival, rates have been calculated for ages 35-74 (age-adjusted by the direct method by 10-year age groups in the U.S. 1950 population, per Linder and Grove, 1943). This method tends to produce maximum differences in death rates between different groups, consistent with minimizing standard error or chance fluctuation.

Rates used are for white males, because of the high risk for this group as compared with white females. While rates have been calculated for black groups, our resources are currently inadequate for handling properly some of the demographic problems involved in their sound use.

The areas of increased longevity and lowest risk during the 1973-1976 period are clearly concentrated in the Middle West or Great Plains area, extending roughly from west central Wisconsin to the high plains of eastern Colorado (Figure 2). The groups of counties or areas are State Economic Areas, as defined by the U.S. Bureau of the Census (1972b); there are 207 metropolitan State Economic Areas (SEA) and 303 nonmetropolitan areas, the latter usually consisting of 4 to 20 counties with relatively similar occupations and other economic activity (U.S. Bureau of the Census, 1972b). The areas of decreased longevity and highest risk are concentrated in the southeastern Coastal Plain and nearby areas.

The delineation of low- and high-rate areas is similar for earlier time periods: 1968-1972, 1965-1967, and 1959-1961.

To identify the low- and high-rate areas with greater specificity, the 5 percent of the counties with the lowest rates have been identified along with the 5 percent with the highest rates for 1968-1972 (Figure 3). From the concentration of counties from central Wisconsin to eastern Colorado, a low-rate area has been delineated, similar to that from SEA rates. The heavy somewhat irregular line in the north central United States (Figure 3) encloses the largest area of low death rates, which is therefore designated as the major area of increased longevity. Of the 3082 U.S. counties, or equivalent areas, slightly more than three fourths of those within this low-rate area are in the lowest quartile of death rates for the United States.

A high-rate area has been similarly identified, extending along the Coastal Plain from Alabama to North Carolina. The heavy similarly irregular line in the southeastern United States (Figure 3) delineates the largest area of high death rates, which is thus the major area of decreased longevity. Within this area, the other counties that are also in the highest quartile of death rates are shown, and clearly more than three fourths of the counties in this area meet this high-rate definition.

Figures 20 and 21 of Chapter 8 show the increased-longevity and decreased longevity regions in larger-scale maps, with identification of counties.

Obviously there is a degree of arbitrariness in drawing the lines to identify the areas of extreme rates. However, rates for other time periods--1973-1976, 1965-1967, and 1959-1961--produce similar definitions of areas. Further, alternate definitions of extreme rate have been used with similar results; specifically, a map of lowest 3 percent and highest 3 percent and also a map of lowest 10 percent and highest 10 percent demarcated similar areas. Therefore, a variety of definitions might be used and still identify these areas.

There are other low-rate counties scattered in the western half of the United States but with some concentration in Utah; evidence indicates that Mormon lifestyle contributes substantially toward these low rates. While some of the scattered high-rate counties are considered geologically as part of the Coastal Plain [including counties near (within 50 miles of) the junction of the Ohio River and

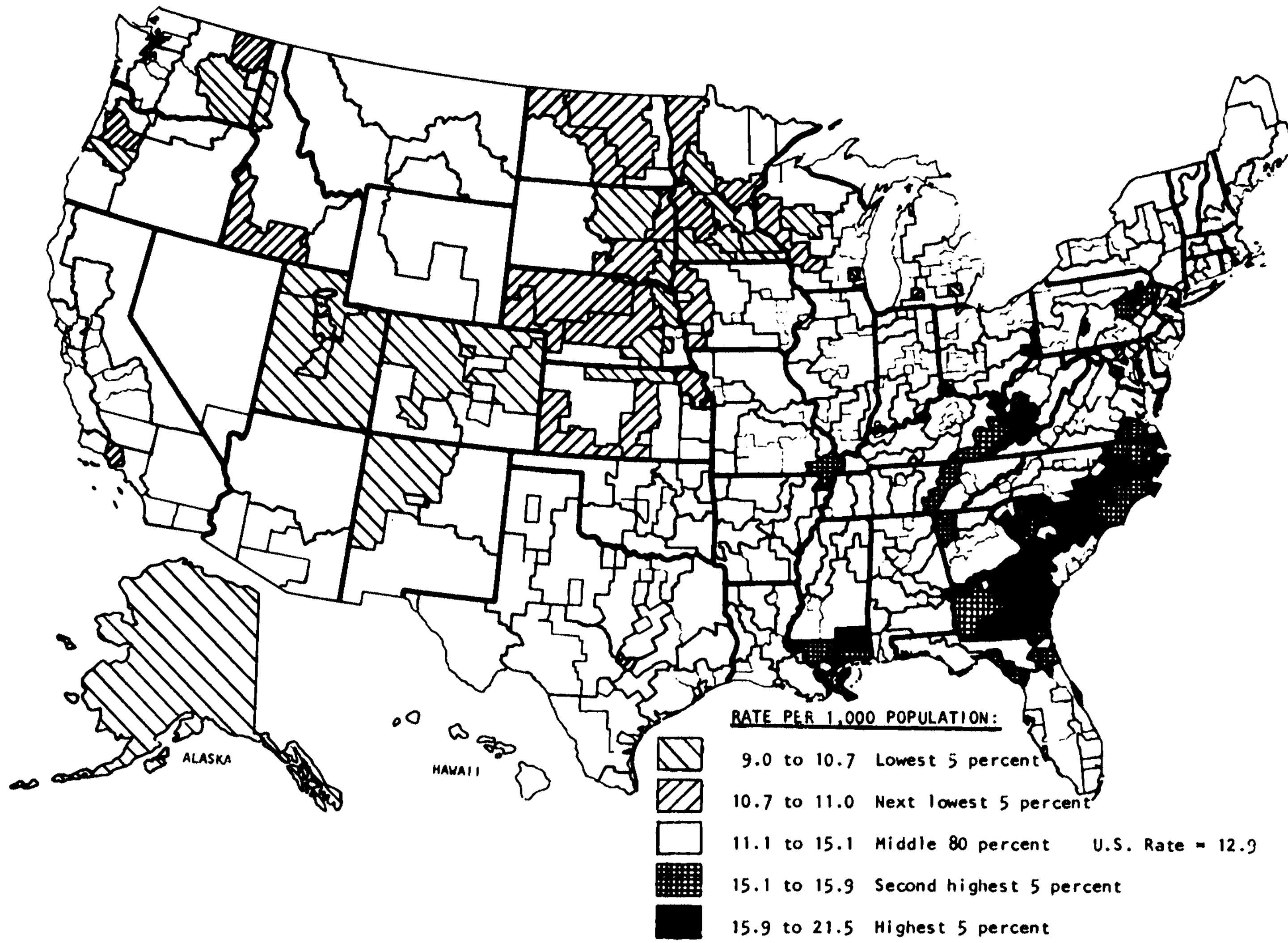

FIGURE 2 Death rates for natural causes, white males 35-74 (age-adjusted), 50 lowest- and 50 highest-rate state economic areas, 1973-1976.

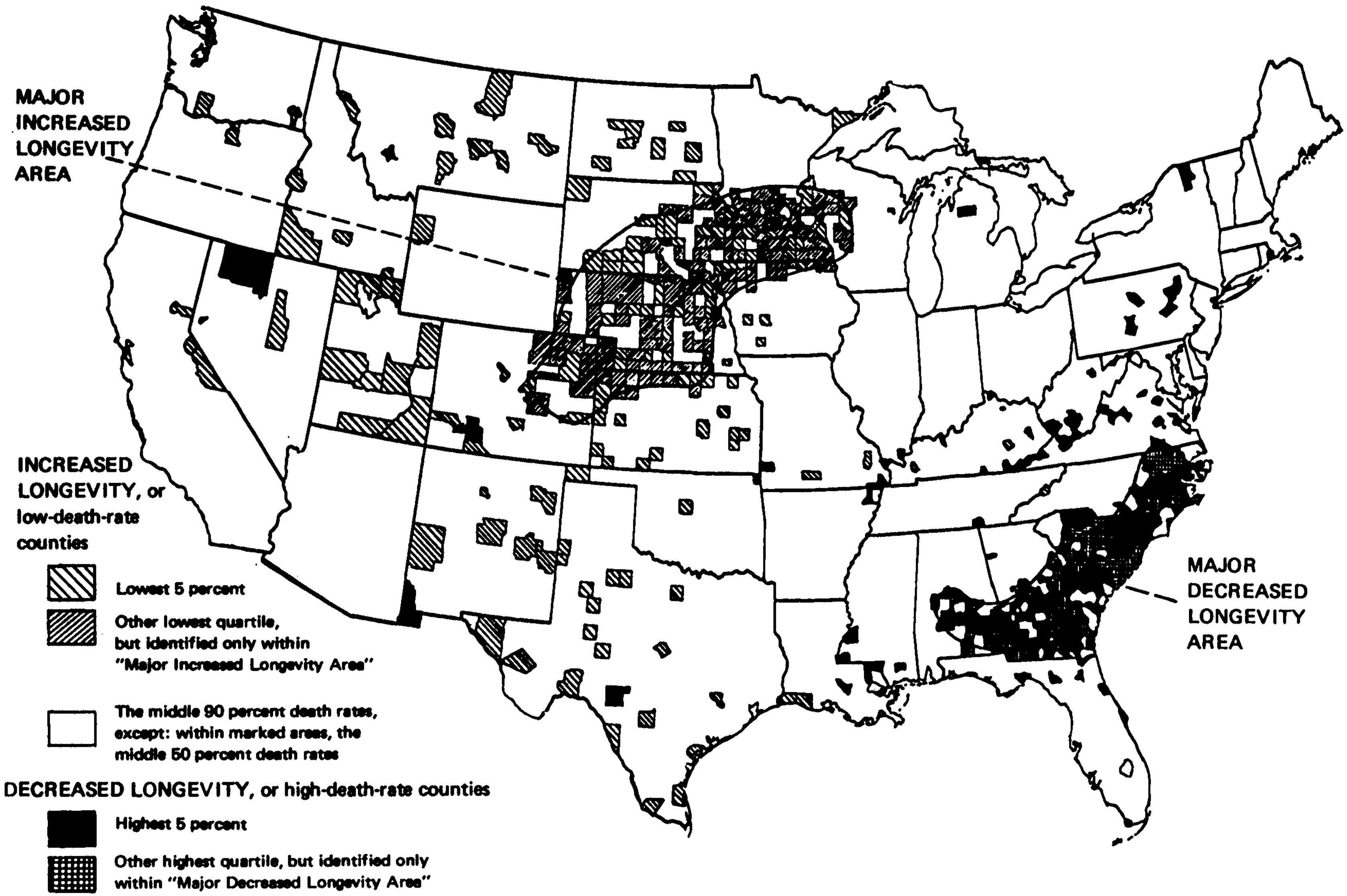

FIGURE 3 Areas of increased and decreased longevity as measured by death rates for natural causes, white males age 35-74 (age-adjusted), 1968-1972.

the Mississippi River], most of them are mining counties ("coal or metal mining and/or history of mining"), which have already been considered (Sauer et al., 1978). However, each of these two groups of extreme-rate counties is considerably smaller than the two already identified.

The low-rate areas are those in which each major disease, or group of diseases, occurs less often compared with the U.S. rate. Even external causes, as a group, are slightly below the U.S. rate. Thus, as yet, no specific causes have been identified as being responsible for the low rates (Sauer and Stearley, 1980). In the high-rate areas, the rates for cardiovascular diseases are especially high, but the group of malignant neoplasms other than respiratory are not high, as compared with the U.S. rates.

In view of the limited knowledge now available regarding the underlying causes of most chronic diseases, the underlying factors responsible for a low risk of various chronic diseases in the increased-longevity area and of a high risk in the decreased-longevity area are not currently known and are not easy to determine. It therefore seems inappropriate to assume that the residents of the increased-longevity area are receiving either the optimum dosage of beneficial factors or a minimum feasible dosage of deleterious factors. Nor should the assumption be made that the decreased-longevity area residents are receiving maximum dosage of harmful factors or minimum dosage of beneficial factors. Therefore, there may well be the potential in both of these areas for longevity to either increase or decrease.

Generally, the annual risk of dying increases rapidly with age, but this does not imply that chronological age is the sole index of "aging." Rather, chronological age is an index of exposure to various risk factors, including currently unrecognized factors as well as obvious factors, such as cigarette smoking (Sauer, 1980). General limitations in present knowledge have been widely recognized (e.g., Ostfeld and Gibson, 1975).

All deaths have been classified according to county of usual residence. There has been a substantial out-migration of adults, including retirees, from some of the low-rate areas. However, those who have moved to other states, generally to states with higher death rates, still have rates lower than U.S. rates and similar to those who have moved into the low-rate states (Sauer, 1962; 1967). However, the lowest rates are for those who were born in their state of usual residence. While older adults moving to Florida tend to have low rates (as compared with U.S. rates for adults of the same age), presumably because of selective migration, none of the Florida counties fell into the low-rate category for 35-74 age group (age-adjusted). Likewise, present evidence suggests that the high-rate areas are not the result of special migration patterns.

Various alternative approaches may be considered for identifying areas of greatest and least longevity. A popular method is to consider the number and/or characteristics of centenarians. This approach may also have substantial potential for further study, provided that several factors are considered critically, such as:

• Centenarians are atypical individuals. In recent years individuals reported as centenarians accounted for about 1 death in 500 in the United States. In the 1970 U.S. population, less than 1 person in every 40,000 was a centenarian (calculated from data of Siegel and Passel, 1976).

• In the 1970 census, there was a marked overcount of centenarians, apparently resulting from an occasional entry by individuals of various ages as "born 1870 or earlier" when they meant to enter "born in Jan., Feb., or March." [Obviously, anyone "born 1870 or earlier," and not born April to December 1870, would properly be classified as age 100+ in the 1970 census. The published 1970 census counts of centenarians are more than 20 times as high as the count in the revised computer tape (U.S. Bureau of the Census, 1972a).]

• Individuals in some areas, especially those with limited education and with limited attention to record-keeping, achieve considerable recognition for their apparent longevity. In some areas the elders of a community are given recognition for their widsom, which provides an incentive biasing their estimate of age. Then as they achieve recognition for their superlongevity from outsiders, there is further incentive for biasing their estimates. One extreme reported instance involved a man in Vilcabamba, in the mountains of Ecuador, who claimed to have been born in a year calculated to be five years before the birth of his mother (Mazess and Forman, 1979).

Mazess and Forman (1979) also state that "None of the 23 'centenarians' investigated had in fact survived to 100 years. Similarly none of the 15 'nonagenarians' investigated had in fact reached 90 years."

Substantial evidence has also been presented that seriously challenges the accuracy of age of centenarians in the Caucasus, USSR (Medvedev, 1974). One analytical approach by Mazess and Forman (1979) "suggested that the population [of Vilcabamba, Ecuador] was not especially long-lived." Until more definitive studies are completed, it therefore seems appropriate to suspend judgment regarding whether these are areas of "superlongevity" (Hayflick, 1974).

QUALITY OF LIFE

General concern about aging is in regard to both duration and quality of life. Many indices may be devised to measure "quality of life" or the general health of individuals, but much work using data that are already available or readily collectible needs to be done to develop and validate such an index. The use of patient-care resources does not necessarily measure either quality of life or general health; specifically a large number of visits to physicians or a large number of days hospitalized per 1000 population in some instances is obviously evidence of poor health and in other instances evidence of prompt patient care when needed, resulting in better health.

In areas with low death rates, the proportion of the population surviving to older ages is obviously greater than in areas with high death rates, resulting in a higher proportion of the population age 65 and over. (Exceptions may be caused by high birth rates, by out-migration of older individuals to "retirement areas," and/or in-migration of young adults and their children.)

In the low-rate areas, do those surviving to age 65 and over have a better "quality of life"? Or more specifically, is their health status equal to or better than those in the high-rate areas? At present, data are not available to answer this question with precision. However, men age 65 and over who are still in the labor force may be inferred to be, as a group, in better health than those who are not. Men, age 65 and over, do show a slight tendency to have a higher percentage in the labor force in the low-rate areas than in the high-rate areas, suggesting the possibility that, as a group, those age 65+ in the low-rate areas may be in slightly better health than those in the high-rate areas.

REFERENCES

Hayflick, L. 1974. The strategy of senescence. The Gerontologist 14:37-45.

Linder, F.E., and R.D. Grove. 1943. Vital Statistics Rates in the United States, 1900-1940. U.S. Bureau of the Census. U.S. Government Printing Office, Washington, D.C.

Mazess, R. B., and S. H. Forman. 1979. Longevity and age exaggeration in Vilcabamba, Ecuador. J. Gerontol. 34(1):94-98.

Medvedev, Z. A. 1974. Caucasus and Altay longevity: A biological or social problem? The Gerontologist 14:381-387.

National Center for Health Statistics. 1967. International Classification of Diseases, Adapted. Eighth Revision. PHS Pub. No. 1693. U.S. Government Printing Office, Washington, D.C.

Ostfeld, A. M., and D. C. Gibson, eds. 1975. Epidemiology of aging (Summary rport of a conference June 1972). DHEW Publication No. (NIH)73-711. U.S. Government Printing Office, Washington, D.C.

Sauer, H. I. 1962. Epidemiology of cardiovascular mortality--geographic and ethnic. Am. J. Public Health 52(1):94-105.

Sauer, H. I. 1967. Migration and the risk of dying. Proceedings, Social Statistics Section, American Statistical Association. Dec. 27-30, 1967, pp. 399-407.

Sauer, H. I. 1980. Geographic patterns in the risk of dying and associated factors, age 35-74 years, United States, 1968-72. National Center for Health Statistics: Vital and Health Statistics Series 3, no. 18 DHHS pub. (PHS)80-1402. U.S. Government Printing Office, Washington, D.C.

Sauer, H.I., and R.F. Stearley. 1980. Potential for further decline in U.S. mortality rates. Presented at the Annual meeting of the Population Association of America, Denver, April 11.

Sauer, H.I., L.E. Reed, and R.W. White. 1978. Minerals and the risk of chronic diseases. In Proceedings of the Twelfth Annual Conference on Trace Substances in Environmental Health, June 5-8, 1978, D.D. Hemphill, ed. University of Missouri, Columbia, pp. 62-71.

Siegel, J.S., and J. S. Passel. 1976. New estimates of the number of centenarians in the United States. J. Am. Stat. Assoc. 71:559-566.

U.S. Bureau of the Census. 1971. Second Count Summary Tapes from the 1970 Census of Population and Housing. Computer Tape Series CT-3 (Rev.). Central User's Service. U.S. Bureau of the Census, Washington.

U.S. Bureau of the Census. 1972a. Census of population: 1970 General population characteristics, Final Report PC(1)-B1 United States Summary. U.S. Government Printing Office, Washington, D.C.

U.S. Bureau of the Census. 1972b. Census of population: 1970 State Economic Areas. Final Report PC(2)-010B. U.S. Government Printing Office, Washington, D.C.

4

CENTENARIANS

Charles H. Barrows, Jr.

Recent reports (Leaf, 1975) have indicated at least three areas that have a markedly higher percentage of centenarians than is found throughout the world. These areas are Vilcabamba in Ecuador, the Eastern Shore of the Black Sea in the Caucasus Mountains (the Georgian and Azebaijan SSRs), and the Pakistan-Chinese border. Unfortunately, the ages of these people are very much in doubt. Soviet scientists only began to study their centenarians in about 1960. They have little documentary evidence to work with because these people have no birth certificates. Thus, they have to rely almost entirely on biological evidence, which at best is scanty, and hearsay. In general, they must cross check the claims of the centenarians against the knowledge and evidence of the centenarians' relatives and the other old people in the community.

The most critical evidence of the age in Ecuador is the baptismal certificates. However, the investigators have indicated that they had to cross-check and double check from the centenarians' own accounts and that of their friends and relatives as well as connecting the dates of various events. Unfortunately, the reports of this particular group of people give no evidence as to the numbers of people that can be verified by the baptismal certificate.

Nevertheless, it is of interest to compare the environmental factors that may be common to these three groups of people. Among these factors is altitude. All three areas are in valleys at a height of about 1700 to 1900 m. All have a particularly low rainfall, generally they are dry and dusty (see Appendix). The Ecuadorians have a habit of drinking large amounts of various locally produced alcoholic beverages, usually four to six cups daily. The Abkhasians of Russia and Hunzas of Pakistan also consume considerable amounts of alcohol. In general, it has been found that the oldest people in these areas, those alleged to be over 110, are males. This, of course, is in contrast to what is generally found throughout the world. For example, females outlive males by as much as 8 years in the United States. Diet has been the only environmental factor that has been shown consistently to increase the life span of animal model systems. In these studies, the life span of animals has been increased by reducing the dietary intake of a nutritionally adequate diet or by reducing the dietary protein intake. Therefore, it is critical to consider the diet of these centenarians. Unfortunately, there are no data to substantiate the quantity or quality of food consumed by these peoples. However, they are vegetarians and consume little, if any, meat during the course of their lives.

REFERENCE

Leaf, A. 1975. Youth in Old Age. McGraw-Hill Book Co., New York, 233 pp.

5

THE EFFECT OF AGE ON PHYSIOLOGICAL FUNCTIONS

Charles H. Barrows, Jr.

In addition to an increased frequency of diseases with age, there is evidence that aging is associated with decrements in specific physiological functions. For example, there are discernible age changes in human subjects who have been carefully screened for the absence of specific diseases. The data presented here have been obtained at the Gerontology Research Center of the National Institute on Aging. The subjects were community-dwelling volunteers ranging in age from 17 through 96 years. They spent two and one-half days in the Gerontology Research Center at 12- and 18-month intervals undergoing a battery of clinical, physiological, and psychological tests. Subjects were generally of middle and upper socioeconomic status and involved in sedentary work. All participants in the longitudinal study were self-recruited. Social and demographic characteristics of the study population have been described in detail elsewhere (Stone and Norris, 1966). Among the age changes noted have been decreases in certain renal functions. In the study by Rowe *et al*. (1976), 884 subjects were examined clinically for indications of renal diseases and other clinical conditions known to effect renal function. Of the total, 548 subjects were considered normal, and creatinine clearances were determined. The results of this cross-sectional study in which men of different ages are compared are shown in Figure 4. These data indicate that between the third and eighth decade approximately 30 percent of the renal function is lost in men. Similarly, the effect of age on the time required to metabolize glucose was estimated in men between the ages of 21 and 95 (Pozefsky *et al*., 1965). Known diabetics were excluded, as well as subjects taking drugs known to alter carbohydrate metabolism. In addition, men were excluded because of a distant or uncertain relationship to a known diabetic. The test employed was the cortisone-glucose tolerance test (Fajans and Conn, 1954), which is capable of detecting mild carbohydrate intolerance unrecognized by the standard glucose tolerance test. The results of this experiment are shown in Figure 5. The data clearly indicate that old subjects take longer to metabolize a given amount of glucose than do young subjects.

Age decrements in lung functions have been described in nonsmokers as well as subjects free of clinical evidence of pulmonary disorders (J. Tobin, Gerontology Research Center, personal communication). In Figure 6 is shown the effect of age on the forced expiratory volume,

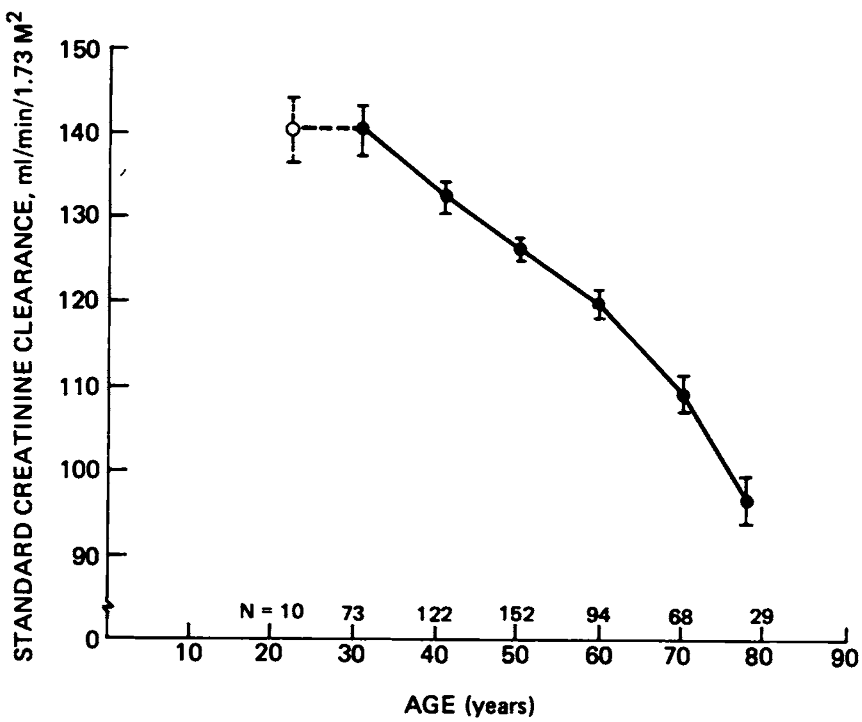

FIGURE 4 Standard creatinine clearance plotted against age. The number of subjects in each age group in this cross-sectional study is indicated above the abscissa. Values plotted indicate mean ±S.E.M. (standard error of the mean) (Rowe et al., 1976).

which is an accepted pulmonary function test. The data indicate a 35 percent reduction in pulmonary function between the ages of 30 and 80 years.

Studies of the type previously described, generally referred to as cross-sectional studies, have been criticized on the basis of selected mortality and cohort differences. Therefore, longitudinal studies have been carried out in which individuals have been studied over periods of 10-15 years. Comparisons of the cross-sectional age differences in the longitudinal age changes in creatinine clearances may be made by comparing the data in Figure 7 with those represented in Figure 4. Because the longitudinal changes approximate cross-sectional differences, there does not appear to be any significant effect of selected mortality or of differences among cohorts in the cross-sectional results. Taken as a whole, these data demonstrate that age markedly effects various physiological functions.

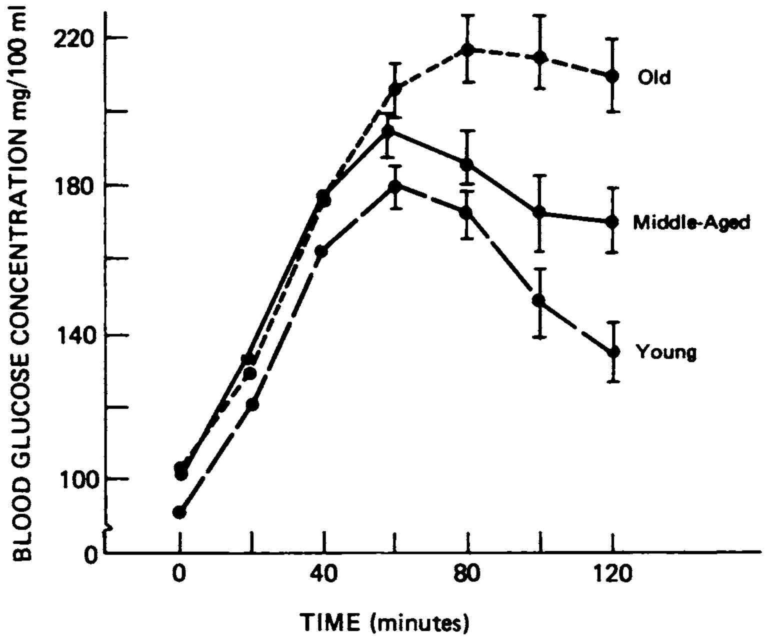

FIGURE 5 Mean cortisone-glucose tolerance test curves for three age groups of men having no family history of diabetes. The standard error of the mean for each time period after 40 minutes is also shown. The young subjects were aged 21 to 44 years; the middle-aged subjects were aged 45 to 64 years; the old subjects were aged 65 to 95 years (Pozefsky et al., 1965).

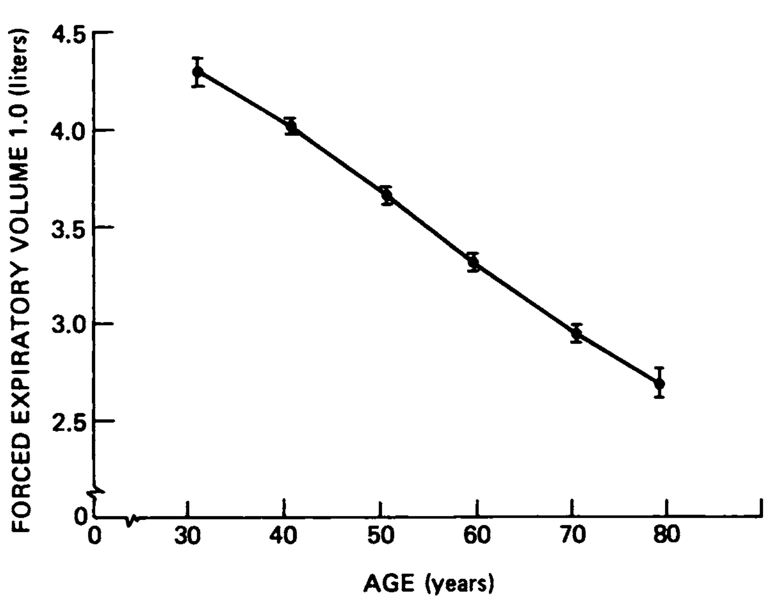

FIGURE 6 The effect of age on the forced expiratory volume. Values plotted indicate mean ±S.E.M. (standard error of the mean) (J. Tobin, Gerontology Research Center, personal communication, 1979).

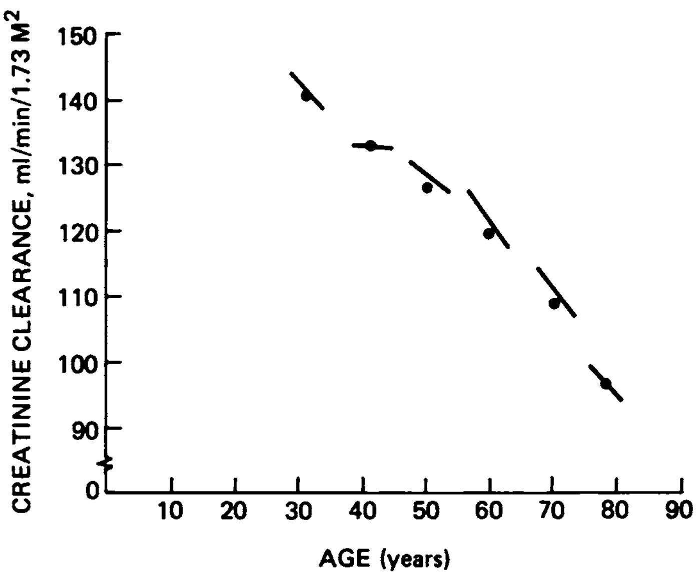

FIGURE 7 Longitudinal age changes in creatinine clearance. The dots represent the mean values for each age decade obtained from cross-sectional data (Figure 4). Longitudinal results are represented by line segments that indicate the mean slope of changes in creatinine clearance for each age decade (Rowe et al., 1976).

REFERENCES

Fajans, S. S., and J. W. Conn. 1954. An approach to the predictions of diabetes mellitus by modification of the glucose tolerance test with cortisone. Diabetes 3:296-304.

Pozefsky, T., J. L. Colker, H. M. Langs, and R. Andres. 1965. The cortisone-glucose tolerance test: The influence of age on performance. Ann. Intern. Med. 63:988-1000.

Rowe, J. W., R. Andres, J. D. Tobin, A. H. Norris, and N. W. Shock. 1976. The effect of age on creatinine clearance in men: A cross-sectional and longitudinal study. J. Gerontol. 31:155-163.

Stone J. L., and A. H. Norris. 1966. Activities and attitudes of participants in the Baltimore longitudinal study. J. Gerontol. 21:575-580.

6

PATHOLOGIC VERSUS NONPATHOLOGIC ASPECTS OF SENESCENCE

Howard C. Hopps

Most workers in the field of aging consider it to be a normal, i.e., physiological process, rather than a pathologic one, albeit there are particular diseases associated with old age--just as there are particular diseases associated with youth. With this view, the aged condition is a normal continuation of the process that includes growth and development, culminating in the plateau we call maturity. Then comes the gradual decline in bodily structures and functions that represents postmaturity, perhaps best termed senescence. Many physiological functions decline at a rate that averages about 0.8 to 0.9 percent per year as compared with activity at age 30 (Hayflick, 1977). Different functions decline at different rates, however, as shown in Figure 8.

At the outset, two major difficulties beset those who attempt to study senescence. First, aging is not a direct function of time in the sense that all persons 80 years old are at the same stage of senescence. Second, a variety of pathologic disorders are so intertwined with old age that it is difficult to determine which, if any, are actually a part of the aging process (e.g., cataracts?) and which are superimposed (e.g., atherosclerosis?). The problem of separating the physiological from the pathologic aspects of aging is intimately related to the problem of separating causes from consequences.

But regardless of cause/effect relationships, a person cannot attain old age unless he escapes "premature" death. For this reason alone, it is important to look carefully at those diseases that are apt to terminate life, especially during the late years, seeking ways to prevent the pathologic events, or at least to temper their effects. Another reason, as we have mentioned, is that a better understanding of the aging process should give valuable insight into the etiology and pathogenesis of many degenerative diseases and cancer.

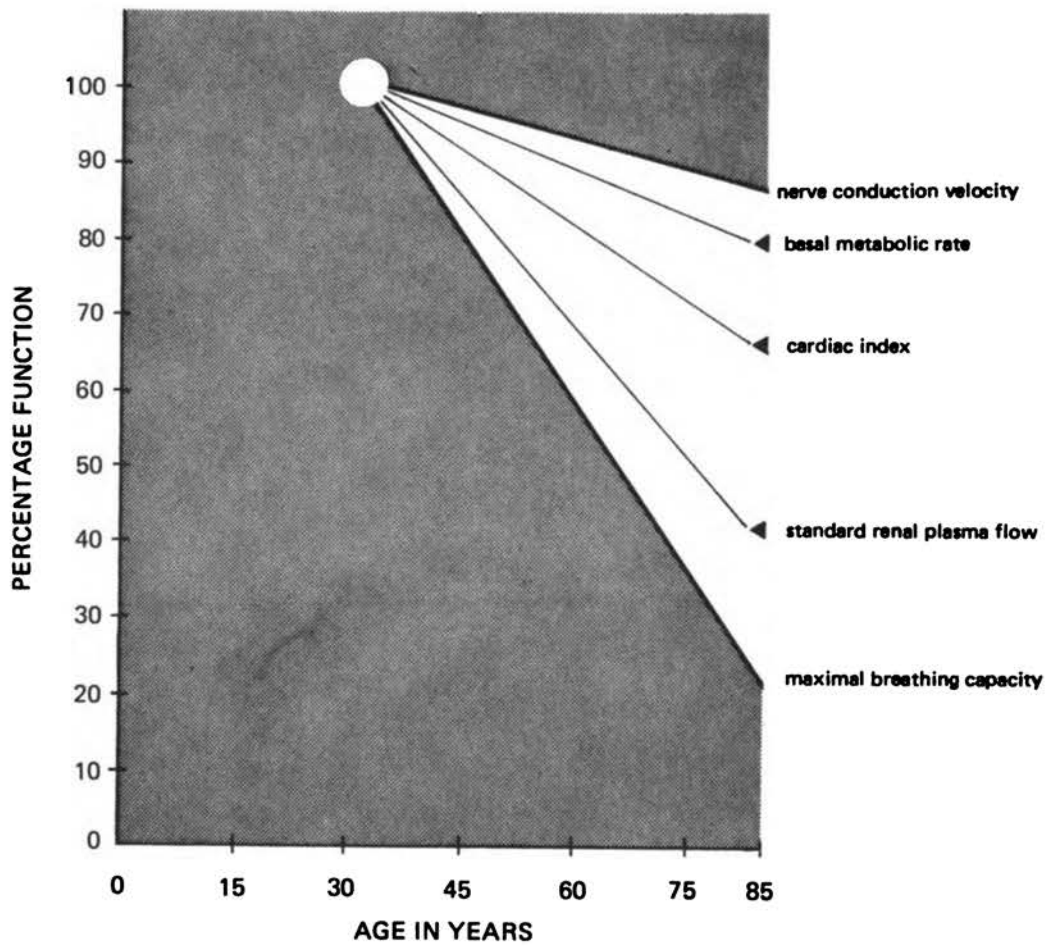

FIGURE 8 The range of reduction in a variety of physiological functions related to age, based on data by Shock (1960).

SENESCENT CHANGES AT THE LEVEL OF THE CELL, THE TISSUE, AND THE ORGAN

Senescent Changes in Cells

The physiological aspects of aging are often related to gross changes, e.g., graying of the hair and wrinkling of the skin, but many important changes have also been observed at the cellular level. The following account of some of these is taken largely from Frolkis (1975). With senescence there are changes involving all stages of energy transformation, against a background of decreasing tissue respiration (much of which reflects the decreased cellular population). Although glycolytic activity is increased, this intensified use of reserve anaerobic pathways of energy generation in the cell cannot make up for the energy deficit of decreased oxidative phosphorylation. Some tissues, e.g., brain and skeletal and cardiac muscle, are more affected than others, e.g., liver and kidneys. The reduction in "cell energetics" is particularly evident during response to (physical) stress and restricts an organism's capacity for adaptation.

Another category of important changes is a consequence of reduction in the concentration of active nucleic acids, particularly deoxyribonucleic acid (DNA) (Flickinger et al., 1979; R. W. Oxenhandler, University of Missouri, personal communication, 1981). The proportion of inactive DNA increases with the age of the cell. This is evident structurally as well as functionally. Electron microscopy reveals an increased proportion of heterochromatin (coiled, relatively inactive DNA) as compared with euchromatin, which is the active, or at least available, DNA. Preparations from the tissues of old animals show DNA to contain many more covalent cross-links, and with increasing age the bonding of DNA to protein molecules in the deoxyribonucleoprotein (DNP) complex becomes more stable. These changes bring about marked alterations in protein metabolism, leading to an irregular pattern of change in the cellular content and activity of various enzymes. The overall effect is not merely a decrease in total enzyme activity but an associated distortion of the enzyme-producing systems, with greater loss of their potential capacity than decrease alone would indicate. The effects of such changes are much more important in some tissues than in others. The control systems are affected most, particularly as they involve the neurohumoral regulation of metabolism and function. This is because information feedback, with prompt response, is critical for the effective adaptation necessary to preserve homeostasis.

Senescent Changes in Organs and Tissues

The importance of integrated structure and function is apparent when we look at an organ, such as the heart, to see what structures (other than cardiac muscle fibers) are necessary for normal cardiac function. Effective contraction of the muscle fibers depends on adequate supplies of oxygen and nutrients, not only in terms of blood delivered by the coronary arteries but also in terms of the interstitium, the immediate cellular milieu through which these nutrient materials must diffuse in order to reach the muscle cells. In addition, the interstitial tissues are quite complex, contributing metabolic functions as well as providing physical support. They include supporting collagen and elastic fibers, a variety of mesenchymal cells (with important functions in their own right), also proteoglycans and structural glycoproteins, the latter comprising the so-called ground substance. In addition, there are the cardiac nerve centers that provide the impulses required for integrated contraction and the fibers that conduct these impulses. All of these components are critically important.

Although senescence affects every cell, it begins at different times and develop at different rates. This variation causes a functional imbalance of tissue components, which produces much more serious effects than would be assumed from evaluating any one of the cellular constituents alone. In the case of the heart, for example, vascular changes that produce ischemia will seriously affect the performance of the heart as a whole, and this is a common disorder. Disturbances of the nerve centers or conducting fibers--also a common disorder--frequently lead to serious cardiac arrhythmias, which can produce congestive heart failure and, sometimes, sudden death.

The connective tissues, the immune system, the brain and endocrine system, and the liver are considered in Chapter 7. The effects of aging on other organs have been discussed in Chapter 5.

Senescent Changes in the Whole Person

Of course, there is great variation among the aged. In many cases however, the characteristic changes are quite familiar and include a coarse, dry, wrinkled skin with splotchy tan pigmentation; sparse, graying hair; a stooped posture; loss of teeth; flabby, atrophied skeletal muscles; a tremor; gnarled hands and other evidence of worn joints, an increased opacity of the lens and an opaque grayish ring in the peripheral part of the iris (arcus senilis). The aged person is usually shorter than he once was by as much as an inch or two because of increased curvature of the spine, atrophy of the intervertebral disks, and flattening of the plantar arches. The dorsal spine is particularly affected, and this alters the shape of the thoracic cage, increasing its size and also, at the same time, decreasing its flexibility. As a result, vital capacity is reduced although the volume of the lungs is actually increased. Most organs show a slight to moderate decrease in weight, which does not reveal the total decrease in parenchymal tissues, however, because with organ atrophy there is an increase in the proportion of supporting elements, particularly fibrous tissue--so-called condensation fibrosis. Although these are primarily gross morphologic changes, they do give clues to cause and mechanisms of action (see p. 59), as well as describing some of the consequences of aging.

More important in our consideration of the "total system," i.e., the whole person, is our ability to understand the serious effects from malfunction of an organ or subsystem in a way that would never be apparent from looking at DNA, or cellular organelles, or even whole cells, because the whole is much more than the sum of its parts. Age changes are demonstrably greater in total animal (or organ) performance than in intracellular biochemical processes.

The sequence of changes that result from a gradually occurring chain of events is most dramatic when so-called "control" systems are involved, e.g., the neuroendocrine system or the immune system (as discussed in detail beginning p. 59). But the effects of aging on vital support systems are obviously important too. As with cells and tissues, these often occur earlier and progress more rapidly in one system than another. Such functionally significant senescent changes as occur in the circulatory system, the respiratory system, the gastrointestinal system (which includes the liver and pancreas), and the genitourinary system, can affect every tissue and cell. Moreover, senescent changes in less-important systems (in terms of life support), such as those that enable seeing, hearing, and physical balance, can also have profound effects on the total system, as illustrated in the case described on page 36.

PATHOLOGIC CHANGES OFTEN ASSOCIATED WITH SENESCENCE

A major difficulty is to determine where the normal changes of senescence end and the pathologic changes begin. In this context, Blumenthal (1975) presents an interesting consideration of "the pathology of normalcy," pointing out that we modify "normal" according to the age in many of our evaluations. He states that "...if we apply the same diagnostic criteria for diabetes mellitus to a population over age 65 as we do to a population under age 30, then a very large percentage of the old people would have diabetes (according to Andreas). Since most investigators find such a conclusion unacceptable, they consider the manifestations of diabetes in many of the aged to represent normal senescence." Similar inconsistencies are seen in evaluating other systems, too. For example, the disproportionate rise in systolic as compared with diastolic blood pressure among the elderly is well recognized. There has been a general tendency, however, to consider this as normal for the aged and to discount the likelihood of deleterious effects so long as the diastolic pressure is not significantly increased. But Kannel (1976) considers the systolic pressure to be as important as the diastolic in its contribution to cardiovascular disease.

From these comments it is apparent that a broad separation exists between the physiological and the pathologic, rather than a sharp line.

A person can only reach his longevity potential by escaping death from injury or disease earlier in life, as we have said. Thus we need to look carefully at diseases with high mortality, particularly those notorious for causing death among those 65+ years of age. These are shown in Table 1. Clearly, diseases of the cardiovascular system (numbers 1, 3, and 5) far outnumber those of any other system, accounting for nearly two thirds (61.8 percent) of the total deaths.

TABLE 1 Death Rates for the Eight Leading Causes of Death, for Ages 65 and Over, by Age, 1973[a]

Rank	Cause of Death	65 Years and Over	65 to 74 Years	75 to 84 Years	85 Years and Over
	All causes	5,874.4	3,440.0	7,932.1	17,439.4
1	Diseases of heart	2,643.2	1,461.6	3,609.2	8,382.1
2	Malignant neoplasms	946.7	768.1	1,187.9	1,435.3
3	Cerebrovascular diseases	839.3	355.1	1,233.5	3,197.9
4	Influenza and pneumonia	210.3	82.1	295.6	910.4
5	Arteriosclerosis	146.0	32.4	190.6	890.2
6	Accidents	127.7	77.5	160.6	401.2
	Motor vehicle	33.2	29.4	40.7	34.7
	All other	94.5	48.1	119.8	369.5
7	Diabetes mellitus	126.3	85.4	179.7	245.9
8	Bronchitis, emphysema, and asthma	97.7	79.4	126.2	133.2

[a]Source: Siegel (1976). Prepared on basis of data from U.S. Public Health Service, National Center for Health Statistics, *Vital Statistics of the United States, Mortality, Part A, 1973.*

Atherosclerosis

Among the cardiovascular diseases, atherosclerosis is the dominant primary condition. It is a slowly progressive process, thus its effects increase with age. Almost surely it is a pathologic process rather than a normal consequence of aging. Evidence for this includes, but is not limited to, the fact that in many parts of the world this condition is rarely a serious problem, even among the aged.

Because atherosclerosis is such an important age-related disease, a brief discussion of its general nature is appropriate here. Atherosclerosis is a particular kind of arteriosclerosis. Since it is the major type, the term arteriosclerosis is sometimes substituted for atherosclerosis when the context of the discussion justifies it--as is commonly done in the case of "arteriosclerotic heart disease." Atherosclerosis affects primarily the aorta and the arteries that come directly from the aorta, including the coronary arteries. The arteries of the brain are also markedly affected. The well-developed lesion of atherosclerosis is a yellowish plaque that rises above the intimal surface (lining) of the affected artery. The plaque contains proliferative tissue (muscle and fibrous elements), but its most striking content is a mixture of cholesterol, cholesterol esters, fatty acids, and necrotic debris, which presents a mushy appearance--and which is responsible for the name atherosclerosis.

The plaque can be sufficiently large to virtually block the lumen of small blood vessels such as those of the heart and of the brain. Moreover, because the plaque disturbs the normal intimal surface of the vessel, it may stimulate the process of blood coagulation, leading to the production of a thrombus, which may quickly build up to the point of completely obstructing the vessel lumen.

In addition to its effects on the inner part of the artery, atherosclerosis produces structural damage to the major part of the wall (the media), which, if sufficient, can lead to a marked bulging of the artery, i.e., an aneurysm (which, when it occurs, usually involves the aorta). It is beyond the scope of this discussion to provide details about the etiology and pathogenesis of atherosclerosis, but it is important to recognize that there are three primary factors: one is concerned with metabolism of cholesterol; another is related to the proliferation of cells (primarily smooth muscle cells) within the intimal layer of the aorta, which have a proclivity for ingesting and storing the cholesterol that "leaks" into the artery wall; the third is the integrity of the endothelial lining of the arteries. The onset and progress of atherosclerosis is greatly accelerated by hypertensive disease, also by diabetes mellitus. Except in rare instances, atherosclerosis does not <u>cause</u> hypertension or diabetes mellitus.

Important categories of cardiovascular diseases include <u>arteriosclerotic heart disease</u>, which frequently terminates life abruptly by sudden coronary occlusion (a "heart attack") but often causes chronic congestive heart failure; also <u>arteriosclerotic brain disease</u>, which often terminates life suddenly by "stroke" but more commonly leads to chronic dysfunction of the central nervous system, causing or contributing to senility.

Some comments about stroke (apoplexy) are pertinent at this point. Stroke is not a disease in itself; it is a component of a larger complex of vascular disorders of the heart, the brain, and the arterial system. Hypertensive disease and, to a lesser extent, diabetes mellitus, are important risk factors. There are two quite different causes of stroke: hemorrhage and infarction. Of these two, brain hemorrhage (from a ruptured artery) is usually causally related to hypertensive disease and atherosclerosis. It is much more likely to cause death than infarction is. Infarction of the brain occurs because an artery is suddenly occluded, shutting off the supply of blood to a portion of the brain. If the vessel is large, a large portion of the brain is destroyed (infarcted), often causing death. If the occluded vessel is small, the infarct will be small and usually compatible with continued life, depending on the size and location of the tissue destruction, although there may be residual effects such as paralysis and defective speech. There are two causes of brain infarction. The first of these, thrombosis of an artery of the brain, is usually directly related to atherosclerosis in that the thrombus forms over the atherosclerotic lesion. The second cause, which is more common, is embolic occlusion; a "foreign body," usually a portion of blood clot (thrombus), becomes dislodged from the heart or one of the large arteries in the neck, and is carried by the bloodstream to lodge in and obstruct an artery of the brain. As atherosclerosis is an important cause of thrombus formation in the heart and large arteries of the neck, it is often indirectly responsible for embolic occlusion of arteries in the brain. Other important changes in the brain (aside from stroke) are not necessarily related to atherosclerosis. Of these, the most serious is senile dementia, which, in itself, is a major cause of death among the aged, though not reflected as such in mortality statistics (see p. 61).

Less commonly with atherosclerosis there are the following:

- Massive involvement of the aorta--causing formation of an aneurysm;
- Massive involvement of iliac arteries (primarily)--causing gangrene of a leg;
- Massive involvement of celiac and mesenteric arteries--resulting in gangrene of a large segment of intestine or severe malabsorption;
- Massive involvement of renal arteries--causing renal failure or, rarely, hypertension.

Malignant Neoplasms

Malignant neoplasms, i.e., cancers, are actually a group of diseases that vary enormously in behavior. The incidence of most kinds of cancer increases directly with increasing age, and approximately half of all cancers occur in the 65+ year old group (Peterson and Kennedy, 1979). The commonest cancer among the aged is carcinoma of the exposed skin, particularly the face and back of the hands, related to excessive exposure to the sun. As this type of cancer is not ordinarily fatal, the number of cancers that occur in old people is actually much greater than the rate of mortality in Figure 9 suggests. Our emphasis will be on cancer as a disease of the aged, however, rather than on the characteristics of specific types of cancer.

Cancer is a cellular disease, and cancer cells have two essential characteristics that normal cells do not have: a virtually uncontrolled capacity for mitotic division--which allows progressive, unrestricted growth--and a virtual unresponsiveness to those control mechanisms responsible for keeping cells in their proper place--which allows invasive, destructive extension locally and distant spread to other parts of the body by lymphatic and blood vascular dissemination, i.e., metastasis.

We have suggested that understanding aging may help in understanding diseases of senescence, and the converse is also true; diseases that occur much more frequently among the aged may give clues as to the nature of the aging process--and cancer is a case in point. Cells with decreased capacity for DNA repair appear to be much more susceptible to cancerous transformation. The most dramatic example is the rare condition, xeroderma pigmentosum (also Fanconi's anemia and Down's syndrome). Senescence is also characterized by a progressive decrease in capacity for DNA repair, and, as we have said, senescence is also associated with increased frequency of malignancy. According to Ringborg _et al_. (1977),

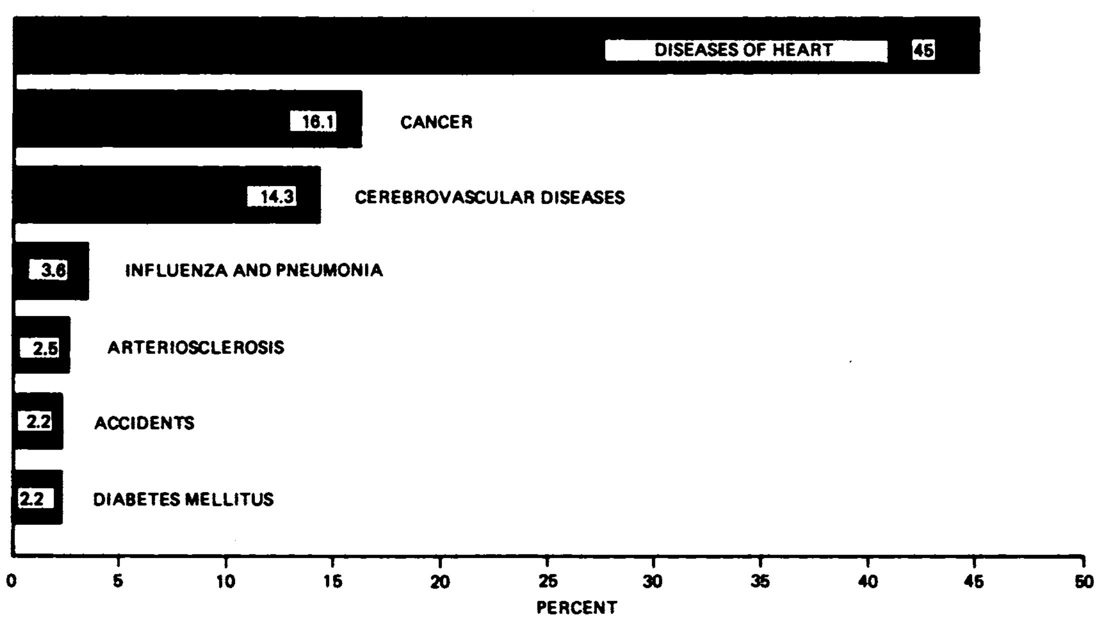

FIGURE 9 Major causes of mortality in the population group 65+ years of age (based on data from Siegel, 1976).

> The DNA repair synthesis was significantly lower in individuals 60-94 years old when compared to that in individuals 13-54 years old. About a 30 percent decrease in the repair synthesis was observed between 20-90 years of age.

The mechanisms by which molecular information is altered to produce cancer may be quite similar to the mechanisms that cause cellular senescence, and a great deal of research is being done in this area.

An entirely different approach to the cancer problem also points to causal connections between senescence and cancer. Many researchers believe that the kind of faulty cellular replication that produces cancer cells commonly occurs in each of us, but that in the great majority of cases our immune system recognizes these altered cells as "strangers" and destroys them before they can become well established. With increasing age there is decreased immune responsiveness. A major hypothesis as to the cause of clinical, i.e., overt, cancer is ineffective immunologic surveillance--and it is known that immune mechanisms become less effective in senescence. This is discussed in more detail in Chapter 7.

The direct relationship between cancer incidence and age may be explained in several ways, reflecting different views of carcinogenesis:

- The right sort of spontaneous mutation can cause cancer--and the number of mutations, spontaneous as well as those induced by mutagens, increases with age.
- The right sort of chromosomal injury, coupled with faulty repair, can cause cancer--and the chances of this occurring increase progressively with age.
- When carcinogens (initiators and promoters) reach a critical level and duration of action, cancer results--and the amount of carcinogens in the body, also time for their action, increases with age.
- Immunologic surveillance may provide one of the most important mechanisms for protection against the occurrence of clinical cancer--and the effectiveness of immunologic surveillance decreases progressively with increasing (old) age.

Infection

Increased susceptibility to infection among the aged, another important cause of death, has many contributing causes: less attention to sanitation and body cleanliness; proneness to accidents and the increased prevalence of skin and mouth lesions (which provide portals for infection); and inefficient mechanical "cleansing" mechanisms in the respiratory tract (e.g., emphysema, mucous plugs in bronchi) and urogenital tract (e.g., because of hyperplasia of the prostate). Inefficient immunologic defense mechanisms are also a major factor.

Lack of sanitation, particularly in food handling, is much more important than is generally recognized. Many bouts of gastroenteritis among the aged have their origin in bacterially contaminated food. The gastrointestinal infection that results can lead to fluid and electrolyte imbalance, and frequently converts borderline to manifest malnutrition. The chain of events can lead to death from pneumonia and/or heart failure.

The infectious diseases most likely to cause death include those that affect the respiratory, urinary, and gastrointestinal tracts. Respiratory infections can seriously aggravate subclinical or clinical heart failure; urinary tract infections can lead to renal failure with serious disturbances of fluids and electrolytes; gastrointestinal infections can seriously interfere with nutrition and can also produce fluid and electrolyte imbalance. Although pneumonia is the most common infection listed as a cause of death among the aged, it is probably overreported because it is often a secondary effect of heart failure and fluid imbalance.

Old men are particularly vulnerable to urinary-tract infections because of obstruction to the outflow of urine from the bladder, a common sequel of prostatic enlargement. If the infection extends up the ureters and reaches the kidneys it causes pyelonephritis, which may terminate in uremia.

Instability, poor vision, and hearing loss among the aged all predispose to accidents. Moreover, the injury is likely to be more severe because reflexes are slowed and protective action is delayed during the fall. Also the bones are more fragile and often less protected by their covering of muscle and adipose tissue. Finally, recovery is delayed and frequently complicated by infection. In addition, the depressed homeostatic mechanisms make serious fluid and electrolyte imbalance much more likely. Many seriously injured patients die of such complications as hypostatic pneumonia or pulmonary thromboembolism. For this reason, accidents as a primary cause of death are considerably underreported on death certificates, and the figure given in Table 1 is considerably less than it should be.

Diabetes Mellitus

Diabetes mellitus, another important cause of mortality, is a disease that, particularly among the aged, merges imperceptibly with variations in carbohydrate metabolism considered to be within "normal" limits, as discussed in Chapter 5. Its prevalence certainly increases with age, however, and it is reported to be more than twice as prevalent at age 70 as at age 50 (Hazzard and Bierman, 1978); its true prevalence is not known for the reason mentioned. With current medical treatment, the most serious effects of diabetes are not directly related to carbohydrate metabolism, however, but result from other conditions that diabetes is known to cause or accelerate: atherosclerosis, renal disease (diabetic nephropathy), disturbances of the body's microcirculation (through its effects on very small arteries and capillaries--an entirely different process from atherosclerosis), decreased vision (from cataracts and retinopathy), increased susceptibility to infection, and heightened susceptibility to severe fluid and electrolyte imbalance.

Morbidity

We have talked about diseases that cause mortality, but this is only part of the story. Table 1 does not give a true indication of morbidity (sickness) among the aged because many of the age-associated diseases seldom cause death, even though they produce great incapacity--osteoarthritis, for example. Valid data as to the incidence of these diseases and their severity are virtually impossible to obtain for the United States at the level of counties or state economic areas. This is doubly unfortunate because, first, we are interested in environmental causes of diseases, and second, such information would provide a basis for evaluating levels of health in different parts of the country, thus helping us to estimate quality of life among the aged.

Major causes of morbidity in old people include visual and auditory difficulties, skin rashes, varicose veins, constipation, insomnia, urinary retention (secondary to prostatic hypertrophy), and urinary incontinence (in the female). These may appear trivial; they are not. More disabling diseases include osteoarthritis, congestive heart failure, chronic bronchitis, emphysema, and diabetes mellitus. Pathologic changes in the central nervous system are also a major cause of disease and disability, including tremor and a variety of mental disorders, which cover the range from forgetfulness to disorientation, aphasia, and paralysis.

Although not nearly so common as the other diseases mentioned, the prevalence of so-called <u>autoimmune diseases</u> increases strikingly with senescence and includes such serious conditions as pernicious anemia, Addison's disease, and chronic thyroiditis. The reasons for this are discussed further in Chapter 7.

General Characteristics

Diseases that are age-related have certain general characteristics:

- They are usually multiple and often causally interrelated. Moreover, they are much more likely to be complicated by adverse reaction to drugs because the presence of multiple diseases often leads to the prescription of multiple drugs. Moreover, the altered metabolism of drugs by the aged often leads to abnormal breakdown products or slowed excretion, further increasing the risk of "drug reactions."
- Signs and symptoms of disease are frequently delayed and diminished so that the disease is recognized late. In addition, the signs and symptoms are apt to be atypical, increasing the likelihood of incorrect diagnoses.
- The body's normal defense mechanisms, including the healing processes, are deficient, so that complications are frequent.

A typical example of multiple disorders reinforcing one another is illustrated by the following case (from the author's case files):

A 78-year old malnourished, arteriosclerotic man had considerable difficulty in describing his problems because of cerebral changes (at least in part due to ischemia). Apparently he fell off his front porch because of instability (in balance) and, probably, decreased vision because of cataracts. His left lower leg was severely lacerated. Improper care of the wound led to progressive, extensive infection before he sought medical care. His impaired immunologic mechanisms (physiologic), coupled with a diminished blood supply to the lower leg (because of atheroscloerosis), contributed markedly to the severity of the infection. Moreover, he forgot to take his antibiotic pills regularly, did not apply hot packs, as instructed, and procrastinated with respect to return visits to his doctor because of forgetfulness, difficulties in getting transportation, and concern about the cost of his treatments. The lower leg became gangrenous, requiring amputation. During the patient's hospital stay he was uncooperative with respect to exercise, and developed a thrombus in his leg vein which released thrombotic emboli, causing several infarcts in the lungs which, in turn, precipitated overt heart failure. This was complicated by hypostatic pneumonia--the precipitating cause of death.

This case obviously involved central nervous system disorders--"senile dementia" (physiological?), aggravated by ischemia from atherosclerosis--plus a depressed immune system (physiological) plus ischemia of the leg, from atherosclerosis, plus decreased adaptability in maintaining homeostatic control of fluid and electrolytes (physiological) all contributed in a major way to the terminal disease complex. An autopsy revealed, in addition to these five most serious conditions mentioned in the patient's history, the following pathologic conditions:

1. A small atherosclerotic aneurysm of the abdominal aorta.
2. Small "softenings" in the cerebral cortex, evidence of past infarcts.
3. Severe atherosclerosis of the celiac artery, markedly limiting the flow of blood to much of the intestinal tract.
4. Cholelithiasis, associated with 5.
5. Subacute cholecystitis.
6. Marked hyperplasia of the prostate with high-grade obstruction, causally related to 7.
7. Cystitis and bilateral chronic pyelonephritis.
8. Foci of prostatic adenocarcinoma, confined to the gland.
9. Osteoporosis, moderate.
10. Old, healed caseocalcific tuberculosis, left lung.
11. Extensive fibrous pleural adhesions in the left pleural space with focal areas of atelectisis and emphysema.
12. Focal adhesive pericarditis.
13. Atrophic gastritis, moderate.
14. Diverticulosis of the colon.

CAUSAL CONNECTIONS BETWEEN SENESCENCE AND DISEASE

As has been stated, there is good reason to believe that few people have ever died of old age, as such. But the physiological processes of aging are intimately related to the pathologic disorders that terminate life. With advancing age there is progressive limitation of adaptive capacities. The reactions are not merely delayed, i.e., inadequate at the time of need, but often overreactive in terms of ultimate response, causing distorted adaptations characterized by great compensatory swings that, in themselves, help to "break" homeostasis (see Figure 10). Because of the disturbed homeostatic mechanisms, serious reaction occurs from an injury (used in its broadest sense) that would be trivial for a healthy young person. Moreover, injuries are much more likely to occur during old age. There is no proof that any disease is an inherent part of senescence, but there are several types of disease that appear to be the direct effect of aging.

The first category has been termed wear and tear syndromes. A major group of these reflects decreased elasticity of elastic and stretching of collagen and reticular fibers, which lead to wrinkling of the skin, ptosis of abdominal organs, and dilation of the aorta and major arteries (ectasia). The effects on blood vessels can be quite important, as we have said. Characteristically, there is increased systolic blood pressure with normal or even decreased diastolic pressure, e.g., 160/70. The increased pulse pressure (90 mm of Hg--approximately twice normal) increases physical stress on much of the arterial system (see Figure 11). Some of the harder tissues are particularly vulnerable to wear and tear, e.g., the teeth and the articular surfaces of bones. Osteoarthritis (degenerative arthritis) may be an almost inevitable consequence of aging in the United States and is often a serious problem causing much pain and disability.

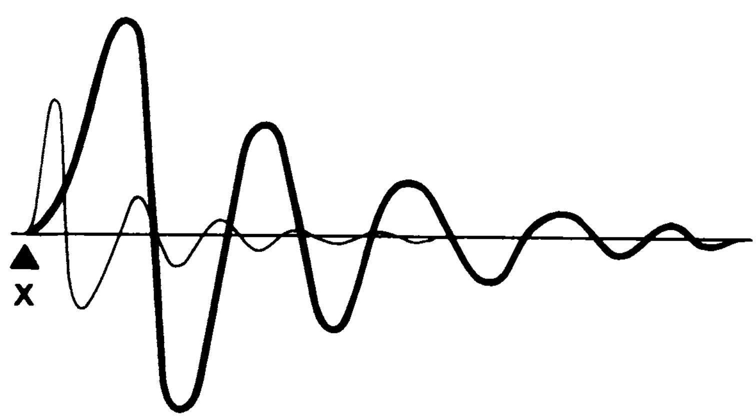

FIGURE 10 The two curves show the differences in counteraction to a hypothetical stress (X) that disturbs homeostasis, as related to age. The delayed, prolonged, overreactive response (heavy line), characteristic of senescence, contrasts strikingly with the much more effective homeostatic control mechanism of a normal young, mature person (fine line).

Although there is a component of wear and tear, the etiology and pathogenesis is very complex and incompletely understood at this time.

Another change in the skeletal system that ordinarily occurs with advancing age (but that can also occur in younger persons from certain metabolic disorders) is loss of bone density, as has been mentioned. Sometimes this progresses to a pathologic state, osteoporosis (rarefaction of osseous tissue), which can so reduce structural integrity that weight-bearing bones--especially those of the vertebral column--collapse, producing so-called compression fractures (see Figure 12).

The second category includes autoimmune diseases and (probably) cancer--direct consequences of a senescent immune system, as noted earlier.

The third category of conditions reflects a senescent neuroendocrine system. Prostatic hyperplasia is a dramatic example, but there is increasing evidence that some types of diabetes and other less-obvious but no-less-important endocrine disorders are direct effects of the aging process.

In a more general sense, the decline in function/structure of various tissues resulting from senescence predisposes to a variety of diseases and disorders. For example:

Decreased sight and hearing increase the likelihood of accidents.

Decreased sensory perception and response at the CNS level causes both relative instability and insensitivity, leading to accidents.

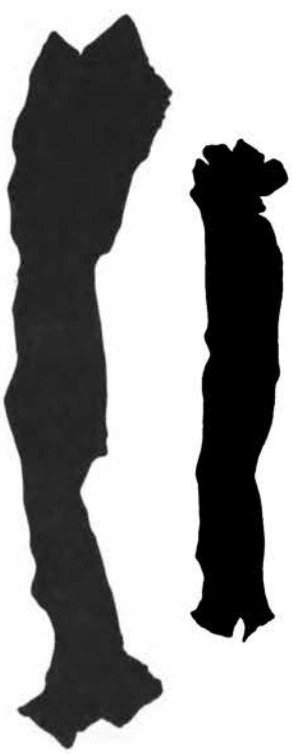

FIGURE 11 An outline of the opened aorta from an aged person (left) compared with that of a young, mature person. The dilitation and lengthening of the aged aorta reflect primarily deterioration of elastic fibers. Performance of materials such as collagen and elastin have a time-dependent, stress-strain behavior, i.e., the amount of strain (deformation) resulting from stress depends not only on the amount but also the rate of stress. These relationships are particularly important in blood vessels subject to marked pulsatile pressure, such as the aorta and its major branches.

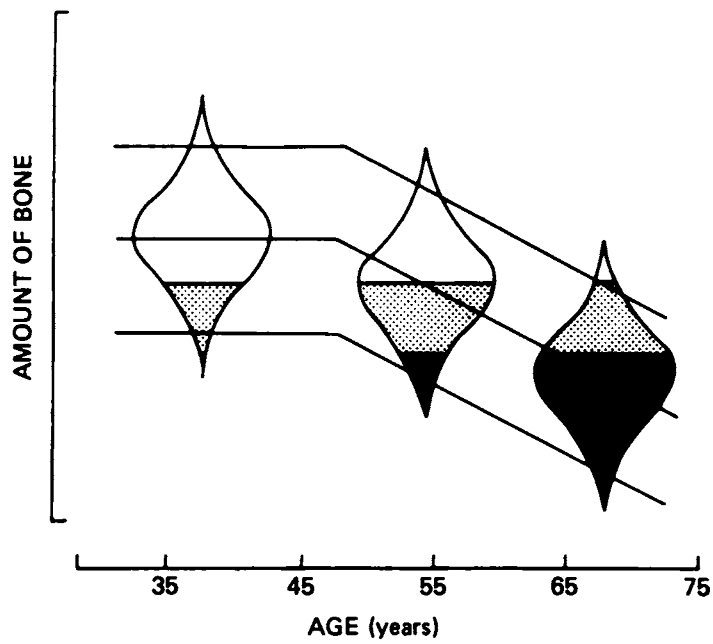

FIGURE 12 This graph illustrates the rate at which an aging population appears to lose bone structure. The shape of the top-like areas shows that values for the amount of bone at different ages have a normal distribution. The stippled area plus the black area indicates -1 SD (standard deviations), and the black area alone -2.5 SD from the mean at age 30-40 years (Newton-John and Morgan, 1970). Used by permission of J. B. Lippincott.

Decreased homeostatic control of blood pressure predisposes to postural hypotension, increasing the chances of falling, thus traumatic injury.

Increased fragility of bone greatly predisposes to bone fractures from traumatic injury, also such serious complications as fat embolism (which is more likely to occur as a result of accidents that involve fractured bones) (see Figures 12 and 13).

Wound healing and regeneration in general are delayed and often inadequate, predisposing to wound infection and to incomplete recovery following injury of parenchymal tissues, e.g., renal or hepatic.

Decreased homeostatic control of fluid and electrolyte balance predisposes to shock, dehydration, acidosis or alkalosis, too much or too little potassium or other cations/anions, increasing the likelihood of serious complications from physical injury (including surgical procedures), infections, and the like.

Decreased homeostatic control of body temperature increases vulnerability to both hypothermia and hyperthermia.

Decreased responsiveness of the immune system increases the likelihood and severity of infectious disease, also autoimmune diseases, also (probably) cancer.

Decreasing elasticity of the walls of large blood vessels causes an increase in systolic blood pressure, which probably contributes to vascular damage and disease, particularly atherosclerosis.

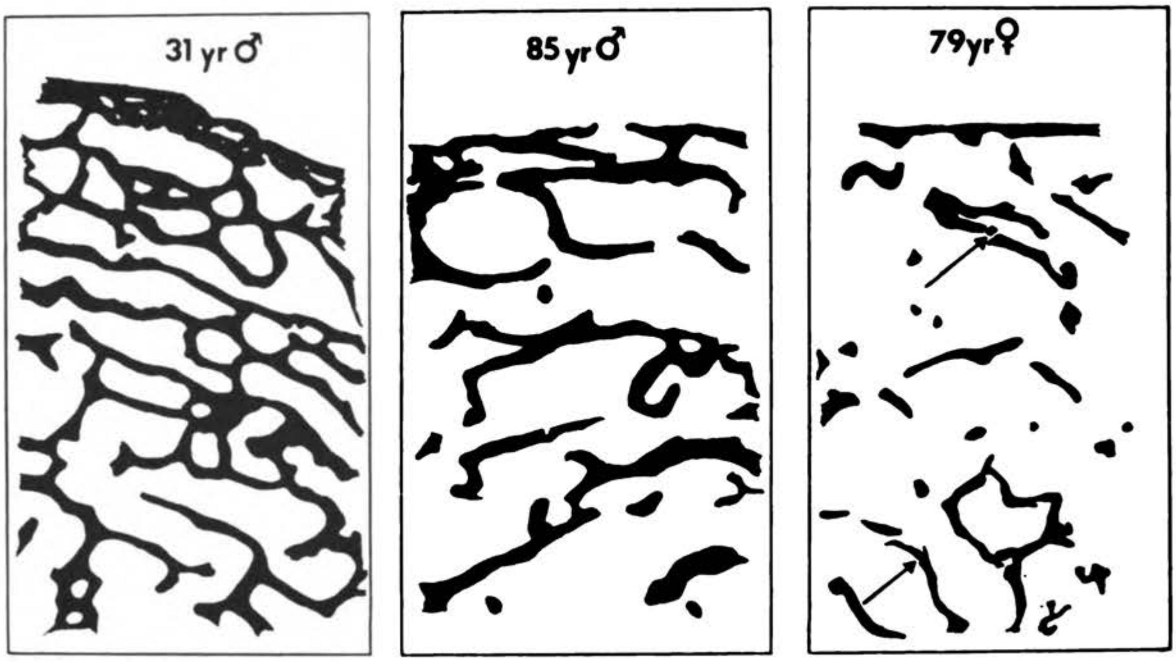

FIGURE 13 These outline drawings show changes in trabecular density of iliac crest bone with age. The arrows indicate possible regions of microfractures (Aaron, 1976). Reproduced with permission of Churchill Livingstone, publishers.

Decreased functions of the liver, kidneys, and reticuloendothelial system reduce the ability of the individual to detoxify chemical substances, including drugs.

Decreased smell (taste) leads to decreased appetite and malnutrition. It also increases the risk of eating bacterially contaminated food.

Atrophy and other degenerative changes in the gastrointestinal mucosa alter absorption of nutrients, contributing to malnutrition.

All these serious physiological/pathologic handicaps make the aging individual increasingly dependent on others at the same time that internal "forces" are working to cause his withdrawal from society. The psychological problems that result are of major importance, often producing a destructive cycle involving a sense of unimportance, resentment, anger, a disturbed sleep pattern,* and depression--all of which can seriously accelerate the development and course of senile dementia and very significantly shorten life, to say nothing of its quality. Underscoring the importance of these psychosocial disorders is the fact that self destruction, i.e., suicide, is an important cause of death among the aged--again, one that is underreported.

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*Perhaps disturbed sleep patterns affect synchronization of physiological processes that have a 24-hour circadian rhythm, further jeopardizing homeostasis.

REFERENCES

Aaron, J. 1976. Histology and micro-anatomy of bone. In Calcium, Phosphate, and Magnesium Metabolism: Clinical Physiology and Diagnostic Procedures, B. E. C. Norton, ed. Churchill Livingstone, Edinburgh, pp. 302-356.

Blumenthal, H. T. 1975. Athero-arteriosclerosis as an aging phenomenon. In The Physiology and Pathology of Human Aging, R. Goldman and M. Rockstein, eds. Academic Press, New York, pp. 123-147.

Flickinger, C. J., J. C. Brown, H. C. Kutchai, and J. W. Ogilvie. 1979. Chromatin. In The Interphase Nucleus, pp. 156-161 of Medical Cell Biology. W. B. Saunders Co., Philadelphia, 566 pp.

Frolkis, V. V. 1975. Physiological aspects of aging. In Practical Geriatrics: Guidelines for General Practice, H. P. von Hahn, ed. S. Karger, Basel, pp. 1-20.

Hayflick, L. 1977. The biology of aging. National History 86(7) Aug-Sept: 22, 26-27, 30.

Hazzard, W. R., and E. L. Bierman. 1978. Old age. In The Biologic Ages of Man: From Conception through Old age. D. W. Smith, E. L. Bierman, and N. M. Robinson, eds. W.B. Saunders, Philadelphia., pp. 229-254.

Kannel, W. B. 1976. Blood pressure and the development of cardiovascular disease in the aged, In Cardiology in Old Age, F. I. Caird, J. L. C. Dall, and R.D. Kennedy, eds. Plenum Press, New York, pp. 143-175.

Newton-John, H.F., and D.B. Morgan. 1970. The loss of bone with age, osteoporosis and fractures. Clin. Orthop. Relat. Res. 71:229-252.

Peterson, B. A., and B. J. Kennedy. 1979. Aging and cancer management. Part I: Clinical observations, CA-A CANCER J. Clin. 29(6):322-332, Nov.-Dec. 1979.

Ringborg, U., B. Lambert, and G. Swanbeck. 1977. DNA repair in conditions associated with malignancy: Aging and actinic keratosis. In Prevention and Detection of Cancer, Part I (Prevention), Volume I (Etiology), H. E. Nieburgs, ed. Marcel Dekker, New York, pp. 39-45.

Siegel, J. S. 1976. Demographic aspects of aging and the older population in the United States. Current Population Reports, Special Studies Series P-23, No. 59. U.S. Department of Commerce, Bureau of the Census, Washington, D.C.

Shock, N. W. 1960. Discussion on mortality and measurement. In The Biology of Aging, B. L. Strehler, J. D. Ebert, H. B. Glass, and N. W. Shock, eds. Symposium of the American Institute of Biological Sciences, Gatlinburg, Tennessee, May 1-3, 1957. AIBS Pub. No. 6. American Institute of Biological Sciences, Washington, D.C. pp. 22-23.

7

WHAT CAUSES SENESCENCE?

Howard C. Hopps

In discussing mechanisms of the aging process, the critical question is whether senescence is a period of life that normally follows growth and development, i.e., a programmed event that causes the machinery to run down, or an abnormal process resulting from the cumulative effects of error or injury that causes the machinery to break down or wear out.

The cause or, more likely, causes of senescence are unknown, but a number of hypotheses have been developed, each of which can explain at least some of the known facts, none of which is completely satisfactory. These fall under three major categories: A and B relate directly to the cell; C relates to key tissues, organs, and systems.

A. Intrinsic Defects in the Intracellular Molecular Information System Affects Formation of:

1. New cells
2. Parts required for normal cellular maintenance and repair

B. Extrinsic Injury to Cells Involves:

1. DNA/RNA
2. Structures other than those of the molecular information system--special cases include:

B' Harmful Effects from Intracellular Accumulation of Indigestible Materials, particularly:

1. Mechanical effects
2. Damage to lysosomes

B" Harmful Effects from Viral Infections

C. Adverse Effects on the Organism as a Whole Result from Failure of Essential Integrative or Control Mechanisms Provided by Multicellular Tissues and Organs, specifically:

1. Interstitial connective tissue
2. The neuroendocrine system
3. The immune system
4. The liver

Before discussing these hypotheses in more detail, it will be useful to give a brief overview.

With respect to A.1, new cells, it has been postulated that parenchymal cell populations* are not maintained because mitosis stops or is delayed. There are four major mechanisms that can explain this, and these are not mutually exclusive:

(a) Programmed within each cell is a mitotic "off switch," which, after a certain number of mitotic events, is activated.

(b) The cell runs out of the program information required to replicate itself.

(c) Previously repressed deleterious programs within the cell are activated, in essence providing a time-related, self-destruct mechanism.

(d) The mitotic cycle is retarded, so that it cannot keep pace with requirements for cellular replacement.

Considering A.2, parts required for normal cellular maintenance and repair, it has been postulated that cumulative (spontaneous) errors affect DNA and/or RNA to the point that the structure and function of organelles become progressively disturbed, thus synthetic mechanisms become less and less effective.

The principal difference between B and A category hypotheses is that the B group represents effects of injury to any of the cellular components, not merely intrinsic defects of DNA or RNA. In Category B, specific cellular structures and mechanisms (including those of the intracellular information system) are changed to cause the following:

(a) Decreased or distorted intracellular functions, including synthesis.

(b) Loss or dysfunction of plasma membrane receptors, altering the cell's response to normal bodily control mechanisms.

(c) Altered antigenic characteristics, marking the cell for immune injury or destruction.

In addition to injury from the usual types of physical and chemical injury, there are two special causal mechanisms to consider, as indicated by the subheadings B' and B", which will be discussed shortly.

Obviously, the mechanisms described in hypotheses B and A can interact. For example, any of the B group could accentuate the effects of all Category A mechanisms by increasing demands for cellular replacement, and any of the A group could affect any Category B mechanism.

Category C recognizes that the functions of an organized, integrated complex of tissues is a great deal more than the sum of its cellular parts, also that, in terms of their overall contributions, some tissues, organs, and systems are much more important than others. As Dayan (1972) put it:

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*Those cells of the tissue that are responsible for its major function in contrast to the supporting elements.

> ...a defect in the organisation and co-ordination of metabolic processes might be just as important as the actual processes themselves. It also means that a basic deficit at one point in a sequence or chain of biochemical processes could well result in a lesion detectable with present day techniques at a critical point in a far distant step, even in a physically remote tissue or organ.

Continuing our general comments, there are some that apply particularly to the hypotheses listed under A and B, which deal with the cell itself. Genetic information is "programmed" in the nuclear DNA, and this information program is analogous to a detailed blueprint for every structure in the body. With the exception of germ cells, however, only a very small part of the total information is used to produce and maintain specialized cells. This means that much of the information is unused, which requires highly selective suppression of the inappropriate portions. The appropriate part of the information (which varies according to the tissue) is transcribed into RNA code (messenger RNA), which is transported to the cytoplasm in this form. The appropriate portion of the information is then translated into explicit instructions by mechanisms that involve ribosomes and transfer RNA (tRNA). In this way all complex synthesis (normally) is an orderly and precise process, under tight genetic control. From this highly condensed, very simplified account, it is evident that defective cells, or their parts, or their functions can occur because of:

(a) Errors in the DNA program, as such
(b) Faulty repression--allowing inappropriate information to be used or, conversely, restricting necessary information,
(c) Errors in transcription (mRNA)
(d) Errors in synthesis (involving ribosomes and tRNA)

Many of the defects that occur in DNA are reparable, but some are more difficult to repair than others. These so-called error-prone processes are particularly susceptible to environmental factors.

Approximately 1 to 2 percent of the body's cells ordinarily die each day and are normally replaced by mitotic division of those cells that remain. Maintenance of (some) cellular populations in this way is an important homeostatic mechanism and the basis for a major theory of senescence, which postulates that, as aging advances, there is an ever-increasing deficit in cellular replacement. As a result, the tissues gradually lose their functional capacity, ultimately causing death of the individual. This is not quite so simple as it at first appears, however, because tissues fall under three general categories, based on their cellular replicative capabilities:

Type-one tissues are essentially nonrenewable after birth or early infancy. These are highly differentiated "postmitotic" cells such as nerve cells (neurons) and cells of cardiac and skeletal muscle. Renewal, in the sense of replication, does not occur in the adult. When cells of this type are lost they are not replaced.

Type-two tissues ordinarily have a slow rate of cell turnover (loss and replacement) but are capable of much regenerative repair when portions are destroyed by disease or traumatic injury. Liver cells and kidney tubular cells are examples.

Type-three tissues normally have a high rate of cell loss and replacement. Epithelial cells of the skin and mucous membranes and cells found in circulating blood are examples. The turnover rates of type-three tissues vary considerably. Among the most short-lived, mucosal cells of the duodenum live approximately 2 days, and the most common white blood cell (polymorphonuclear leukocyte) lives less than 24 hours once it enters the bloodstream. Human red blood cells, on the other hand, live approximately 120 days.

Continual replacement of effete cells by new ones is essential to maintain type-three tissues, which deteriorate quickly if the number of cells that can reproduce is decreased or if the time required for reproduction is increased. Similarly, type-two tissues will quickly deteriorate if, as the result of disease or injury, there is increased need for new cells without a compensatory increase in cellular production. Since type-one tissues do not reproduce, depletion is dependent entirely on the rate of their loss.

Under normal conditions, the mitotic index, i.e., the numbers of cells undergoing mitosis per 1000 cells counted, gives a quantitative perspective to the continuous replacement of dying cells required to maintain the cell populations of many human tissues under conditions of health. This has been observed as 28 in duodenal mucosa, 9 in the bone marrow, 5 in the gingiva, and 0.5 in the abdominal skin. Of course, the mitotic index is greatly increased following destructive injury of type-two and -three tissues.

Now let us consider the individual hypotheses listed under categories A, B, and C.

CATEGORY A HYPOTHESES OF AGING

A.1 New Cells

A major stimulus for the programmed theory of aging came when Hayflick (1965) observed that human fibroblasts grown in tissue culture were limited in the number of times they could divide, after which the tissue culture died. Moreover, fibroblasts taken from embryos or children were shown to have a potential for more cellular division than fibroblasts derived from older persons. These observations have been confirmed many times, and under "optimal conditions," embryonic fibroblasts of tissue culture will divide only 50 $\pm$ 10 times, even though periodically transferred to new culture flasks. The so-called Hayflick limit has been proved valid for many different kinds of human cells, also for a variety of cells from many other mammalian species. In addition, it has been shown that embryonic cells grown in tissue culture proliferate rapidly for a while, then, toward the end of their reproductive life, decrease their rate of replication. Elaborate studies to determine which part of the cells is responsible for this limit to reproduction include experiments in which the nuclei of young cells were exchanged with old nuclei, and vice versa. These experiments suggest that the "off switch" is contained in the nucleus (Hayflick, 1979).

To view the Hayflick theory in proper perspective, it is necessary to consider how the cells of different kinds of tissues are renewed. Those tissues with a large potential for replication have a population of two (parenchymal) cell types. One type, a relatively undifferentiated cell, retains its ability to divide again. The other type loses its ability to reproduce as a consequence of becoming differentiated, during which process it escapes from the mitotic cycle to become a "postmitotic" cell. By maintaining a balance of these two cell types, the tissue preserves its renewal capability, yet maintains its capacity for highly specialized function.

Two types of cells are exempt from the Hayflick limit: germ cells and cancer cells. The reasons for this have stimulated much investigation. It appears that a major factor in the germ cell is its unique characteristic of exchanging chromosomes between the sperm and the egg during the fertilization process, thus, in some way, renewing its replicative capacity. Why cancer cells are "immortal" in tissue culture is unknown.

A.1(a): The Hayflick mechanism has been described as a biological clock, and has been concisely characterized by Burnet (1970) as one "...that, being set to give sexual maturity at time $\underline{X}$, will ensure that average lifespan will be $\underline{X}^1 + \underline{Y}$." Because different tissues and organs wear out at different rates, it has been suggested that the causative mechanism is failure of a key integrative or control system, such as the thymus and parts of the neuroendocrine system or, alternatively, that the changes occurring in the cells of specific tissues have an aggregative effect that seriously disturbs critical interrelationships within or among major systems. The failure of key mechanisms hypothesis is discussed in detail beginning on page 55.

There have been several criticisms of the Hayflick theory. For one thing, not all vital tissues are maintained by cellular renewal--the brain, for example. Another point at issue is whether the nutritional environment provided by current tissue culture methods is truly optimal. Could there be a trace element deficiency that becomes incompatible with life only after the dilution resulting from 50± cell divisions? Franks et al. (1970) have pointed out that the use of proteolytic enzymes and of chelating agents in the preparation of cell suspensions for cell culture may damage the cells, perhaps by producing changes in the cell coat and secondary changes in cell organelles. More significant, they raise the question of interdependence of epithelial cells and supporting stroma and have demonstrated that (mechanically) separated human epithelial prostate cells cannot be maintained in tissue culture, although epithelial cells from explant cultures of undissociated prostatic tissue can be grown in vitro for many months. Finally, senescence of the organism is more than just the sum total of the aging changes of its cells. And this is the basis for the most important criticism of the programmed theory of aging based on the Hayflick phenomenon; a cell line grown in tissue culture is deprived of the regulating factors inherent in the intact organism. This includes not only the supporting stroma with its structural glycoproteins, which contributes directly to the tissue's metabolism as well as to its organization, but hormones and a variety of other "signals" from distant cells and tissues that contribute to the control of growth, metabolism, and function.

A.1(b): Running out a program would have essentially the same effect as an "off switch."

The cellular replicating process is not perfect; spontaneous errors occur. It has been estimated that the rate of error per base pair (DNA) is approximately 1×10^{-9} (Watson, 1965), a frequency that can be very significant for large populations of rapidly dividing cells. According to the running-out-of-program hypothesis, cumulative errors affect the DNA program to the point that it is no longer effective. So long as the damaged portion of the code can be replaced by duplicate material, so-called redundant DNA, the cell continues to function well and retains its capacity for replication. The reserves are limited, however, and there comes a time when they are exhausted, which, it is postulated, is the time that the cell becomes senescent and dies. Strehler (1974) agrees that deterioration of molecular information is an important factor in the aging process, but he believes that the major effects are distal to the nuclear DNA, involving errors in transcription and translation. Such changes certainly occur and have been demonstrated by several workers in terms of a decrease in specific enzyme activities isolated from aged cells, also in terms of the presence of abnormal forms of enzymes in aging cells.

A.1(c): As implied by the discussion above, some scientists think that the onset of senescence is a deliberately programmed event, analogous to a computer that is turned off by instructions given at the end of the program tape. An alternative view assumes that because of the complexity of the genetic program directing development, growth, and reproduction, associated deleterious phenomena occur, which are, in a sense, incidental by-products; they are not planned to be either beneficial or harmful. (A gene can have more than one function.) In keeping with the Darwinian theory that evolution is strongly influenced by survival of the fittest, it is likely that such secondary adverse effects of programs would become operative only after the primary functions of the program were no longer contributing to perpetuation of the species. This might occur in connection with programs that control the production of hormones related to reproduction, for example, and some observations support this idea. Associated with the complex hormonal changes that effect the menopause, there also occur changes in lipid metabolism (and, possibly, functional or structural alterations in the walls of major arteries) that cause the female to become much more susceptible to atherosclerosis than during the premenopausal period. This accounts for the fact that development of atherosclerosis in the female is delayed approximately 10-15 years over that in the male (in the United States and other affluent countries with similar dietary habits). Incidentally, this is a major reason why in the United States women, on the average, live significantly longer than men.

A.1(d): Two principal mechanisms could be responsible for retardation of mitotic activity. The first involves the differentiation pathway, which is irreversible. When a "reserve" cell divides, ordinarily one daughter cell develops only to reserve status, the other going on to differentiation, thus escaping from the mitotic cycle described above. If both daughter cells become differentiated, that particular cell line is finished. The more cells that develop this aberration, the more of the tissue's cellular replacement potential is lost. The second mechanism involves a delay in the process of mitosis itself. See Figure 14 for the normal mitotic cycle. There are three places in the cycle where mitoses can be delayed: G_1, G_2, and a sidetrack, so to speak, G_0. Of these, G_0 is potentially more important because it represents an "arrest" position in which the cell may remain for an indefinitely long period of time--until it receives a specific stimulus to re-enter the cycle. Obviously, if many mitotic cells were held in the G_0 position for a long time, this would disrupt normal maintenance of cell populations and the accelerated regeneration of tissue necessary for repair of injury. (Times required to complete a mitotic cycle vary with the kind of cell. These can be thought of as intrinsic rates. Several types of human cells have reproduction times of 20 to 30 hours.) An important extrinsic mechanism of controlling the rate of mitosis is discussed in connection with the neuroendocrine system (p. 59).

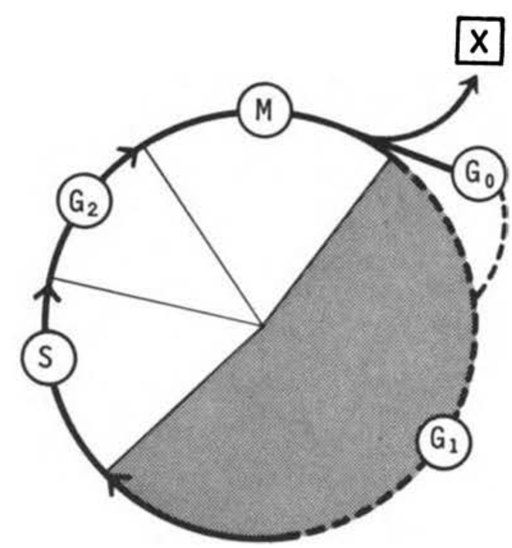

FIGURE 14 Phases of the mitotic cycle, including the escape route taken by differentiating cells X and the arrest stage provided by G_0. M indicates the phase of mitotic division: G_1, S, and G_2 are preparatory phases.

CATEGORY B HYPOTHESIS OF AGING

Solid support for the cumulative error theory of aging, hypothesis B, is the observation that a variety of continued, low-level injuries significantly shorten the lifespan and, in some instances, produce many of the changes characteristic of senescence. The most extensive experimental studies have used total body ionizing radiation as the injurious agent. Although this decreases longevity, and is associated with some of the changes of senescence, there are significant differences, indicating that the primary mechanisms of aging and of radiation injury are not identical. The bases for this conclusion are complex differences in Gompertz diagrams for mortality when the accelerated mortality following ionizing irradiation is compared with that characterizing normal aging. These data are reviewed and discussed by Sacher (1977). A large number and variety of other agents have also been studied. For example, Forbes and Gentleman (1973) have demonstrated and evaluated "smoking-induced life shortening" and compared this with natural aging. They conclude that the mortality curve for the smoking population is displaced in a way that suggests accelerated aging rather than increased mortality from any specific group of diseases.

Decreased or distorted intracellular functions resulting from injury can affect any part of the cell. We have spoken of errors in the molecular code from spontaneous mutation, but there is abundant evidence that injury can also cause mutations. Mutagenic effects of x rays and ultraviolet light have received most attention, but free radicals induced directly by chemical means can also damage DNA in ways that preclude effective repair. Such damage can disrupt the process of cell replication, and this is most dramatic when germ cells are involved.

Many studies have demonstrated that mutations increase over time, and a significant portion of these are probably the result of injury. In a careful study of 570 mothers with 2191 offspring, 607 of which were defective, Murphy (1954) found that

> ...the proportion of defective to normally developed children remained more or less constant for births occurring between maternal ages of 15 and 29 years. Beginning at the age of 30, or even a little earlier, however, the proportion of defective children increased [progressively for each succeeding five-year period]....When birth took place between 45 to 49 years of maternal age, the proportion of defective to normal children was approximately three times as great as that observed when the mothers were under 30 years of age.

Effects of mutation are more likely to involve somatic cells, however, causing a decrease in or distortion of some specific function such as contraction or enzyme production. The injury can also cause errors in the mechanisms responsible for internal maintenance, damaging the cell directly or increasing its susceptibility to injury. As a consequence of either of these latter two effects, the cell's lifespan is significantly shortened.

Sinex (1975), in his consideration of the biochemistry of aging, gives an excellent general discussion of the possible role of injury to DNA, including aspects of repair, in which he points out:

> The rate of accumulation of aging injury to DNA within the cell would be a function of the rate at which aging injury was being produced and the rate that it was being removed. The rate of repair is therefore as important as the rate of injury....Unfortunately, we know more about what inhibits repair than about what stimulates it.

He states the general problem succinctly in a later publication (Sinex, 1977):

> Aging may well be the result of coding error or point mutation in DNA. Assuming this is the case, it is important to know if aging is the result of intrinsic mutagenesis, dependent on generational number, or as a result of mutation in postmitotic cells, dependent upon the passage of time. In either case, differences in the apparent rates of aging in different tissues must be explained.

He suggests as an alternative mechanism that:

> Changes in aging tissues may reflect altered control rather than altered DNA. Spontaneous hydrolysis of amide nitrogen in protein is possible with the passage of time. The repair of altered states of differentiation may be as significant as the repair of DNA.

Most cellular enzymes that have been studied become progressively, adversely modified during the aging process (Gershon et al., 1979). This is important in terms of ordinary function and in decreasing the reserve capacity of the cell so that it cannot react to stress by an adaptive enzyme response. As a result, homeostatic mechanisms are restricted and susceptibility to injury is increased. Orgel (1963) suggested that certain types of errors, particularly those involving "templates" for the production of critical enzymes, would be self-perpetuating, thus causing rapidly cumulative injury culminating in cell death. He termed this "error catastrophe" and pointed out its special significance for nonreplicating tissues such as those of the brain. In 1973, he revised his hypothesis (Orgel, 1973), concluding that the type of error he had described was, to some extent at least, reversible, thus it would not necessarily increase exponentially.

Injuries to DNA/RNA that cause abnormalities in synthesis of proteins, including enzymes, have received most attention mainly because there is more interest in proteins and we understand them better. Synthesis of lipids and polysaccharides is also important, however. Cellular membranes are predominately lipid and are responsible both for compartmentalizing the nucleus and the cytoplasmic organelles and for integrity of the cell itself by means of the plasma membrane. Although this outer membrane serves as a protective shell, and is very much concerned with intracellular metabolism, it is also dynamically involved in intercellular activities in that, through its highly specialized receptor sites, the membrane provides the means for communication among cells, without which there could be no integrated function. Polysaccharides are an integral part of the interstitial connective tissues and will be discussed under Category C hypotheses.

An enormous number of chemical and physical agents can injure cells to produce the effects considered under Category B. A highly productive way of identifying these agents has been to look first at the chemical changes that characterize senescence, then identify and examine the injurious agents that are likely to produce these effects. One important chemical change related to senescence, which has stimulated much interest, is cross-linkage. Its effects on fibrous tissues such as collagen and elastin have been emphasized, but cross-linkage can also seriously damage other proteins, also DNA.

Cross-linkage results when two molecules (or two parts of one molecule) are joined together by a chemical bond, and this can be produced in many ways. In the context of aging, however, we are most interested in cross-linkages produced by highly reactive chemical agents that are endogenous (metabolic products) or derived from the external environment. Cross-linkage is a normal mechanism in many biological reactions--stabilization of collagen and of fibrin, for example--but abnormal cross-links can cause great damage. In fact, maximal injury from minimal chemical reaction occurs when a small molecule or free radical reacts simultaneously with two macromolecules, cross-linking them in such a way that the function of each is destroyed.

Bjorksten (1968), in reviewing the cross-linkage theory of aging that he proposed in 1944, presents some of the basic aspects of his theory in these terms:

> Crosslinking is damaging to the tissues and involves loss of elasticity, reduced swelling capacity, increased resistance to hydrolases and probably enzymes generally, and thus an increase in molecular weight and a tendency toward embrittlement....Inherent in the crosslinkage theory is the postulate that crosslinkage is a primary reaction underlying age-dependent changes. The numerous crosslinking agents known to be normally available in the organism will, by random uncontrolled action, slowly immobilize the large molecules in all cells and tissues by crosslinkages. Most of these will be removed in the metabolic processes, but such renewal is not 100% effective....Of all known reactions involving proteins or nucleic acids, none even comes near the crosslinking reactions in sensitivity to small quantities of causative reactants.

Bjorksten (1968) speaks of slow-acting cross-linking agents that accumulate in tissues, listing compounds of polyvalent metals such as aluminum, lead, and cadmium; polycarboxylic acids such as citric acid and its esters; and probably silicon compounds. Among fast-acting cross-linking agents he mentions several aldehydes that are normal tissue metabolic products, including formaldehyde and acetaldehyde, also derivatives of lipid oxidation--peroxides and epoxides, as well as aldehydes. Another category of powerful cross-linking agents is the orthoquinones, which can be produced by the biological oxidation of adrenalin. Regarding possible effects of the geochemical environment on aging, these statements by Bjorksten (1968) are of special interest:

> All polyvalent metals are potential crosslinkers. Living organisms are equipped to handle certain of these efficiently: iron, zinc, magnesium, manganese, cobalt, copper, and possibly chromium and calcium with some reservations. But aside from these, polyvalent metals are capable of accumulating with age, particularly in the circulatory system. Even the essential metals show some such tendency....Most detrimental are probably those metals which are present in traces small enough so that the individual can proliferate before being severely damaged, yet large enough to attain serious proportions over a lifetime. Among these particularly suspect metals are cadmium--which accumulates in arterial tissues...--aluminum, silicon, lead, tin and titanium.

The free radical (one with a single unpaired electron in its outer orbital) has a large amount of "free energy" that allows it to attack and oxidize neighboring molecules. These highly reactive entities are among the most powerful causes of cross-linkage. They act directly, but many times their indirect effects, through the generation of chain reactions that produce additional strong oxidizing agents, are even more important. Thus they produce cross-linking plus other types of damage.

Free radicals are required in many normal metabolic processes, but they are usually highly controlled and spatially restricted, as within mitochondria. It is when free radicals are uncontrolled and diffuse throughout the cell that they cause serious injury.

Free radicals can certainly injure DNA as well as other cellular structures. Their effects on DNA have been carefully studied in connection with ionizing irradiation because free radicals have been considered responsible, at least in part, for the mutagenic effects of such irradiation. This is of particular interest because total body ionizing irradiation at appropriate levels will shorten the lifespan of experimental animals and produce some of the changes associated with aging, as mentioned earlier. There are, of course many other sources of free radicals.

In Sinex's (1977) excellent discussion of the molecular genetics of aging, he states: "One of the more probable sources of an endogenous mutagen is superoxide $\cdot O_2^-$." He reviews the products formed by the addition of electrons to oxygen as follows:

$$O_2 + \underline{e} = \cdot O_2^-$$
$$O_2 + 2\underline{e} + 2H^+ = H_2O_2$$
$$O_2 + 3\underline{e} + 3H^+ = H_2O + \cdot OH$$
$$O_2 + 4\underline{e} + 4H^+ = 2H_2O$$

Superoxide is formed by the addition of one electron to oxygen. The addition of two electrons gives peroxide. The addition of three gives water and hydroxy-free radical, and four, two molecules of water...[and concludes that] The real danger inherent in the production of both superoxide and peroxide in cells is the reaction between these two reduction products to form hydroxyl ion, hydroxy radical, and oxygen.

$$\cdot O_2^- + H_2O_2 \rightarrow OH^- + \cdot OH + O_2$$

There are many other free radicals important in cross-linkage, including:

$\cdot CO_3^-$, which is particularly apt to attack unsaturated lipids of membranes (Hayaishi and Asada, 1977)
$\cdot CCl_3$
$\cdot Cl$

As noted earlier, metals can play an important role in the production of free radicals. For example, hydroperoxides can be formed by molecular-induced homolysis catalyzed by metals such as copper: $\underline{R}\text{-}H + O_2 \rightarrow \cdot\underline{R} + \cdot HOO$. Redox reactions of the peroxides also produce free radicals, transition metals acting to catalyze their decomposition: $Fe^{2+} + \underline{RO}OH \rightarrow Fe^{3+} + \cdot\underline{R}O + HO^-$ (Cutler, 1976).

In discussing the multiplicity of free radical pathogens, Demopoulos (1973) states:

Air pollutants form a long list that includes NO_2, SO_2, aldehydes, and particulate iron, to mention but a few. Other environmental pollutants, such as DDT and human habits like ethanol consumption and cigarette smoking, add up to a situation of repetitive exposure to multiple free radical pathogens.

Free radicals can initiate lipid peroxidation, causing chain reactions that lead to extensive damage, often to the point of molecular disruption. Most susceptible to this type of injury are the polyunsaturated lipids in cellular membranes--the plasma membrane as well as the inner membranes, including those of organelles such as lysosomes and mitochondria. Injury to lysosomal membranes is particularly important because it allows powerful hydrolytic enzymes to escape into the cytoplasm, which, depending on the rate and extent of release, may destroy the cell quickly or impair its function. If mitochondrial membranes are seriously injured, the intracellular processes dependent on energy input are jeopardized. In addition, the peroxidation chain reaction can involve a relatively large proportion of adjacent molecules, causing much more extensive damage. For example, if the free radical hits a labile amino acid in an enzyme, the amino acid is oxidized and a new product is formed, resulting in complete loss of enzyme activity.

Although free radicals initiate lipid peroxidation, they do not maintain it. Peroxide and oxygen are particularly effective in this latter respect (Sinex, 1977), which is quite important in any consideration of how to control the process.

One of the lines of experimental evidence that connects lipid peroxidation with senescence is the accumulation of lipofuscin pigments as a function of age. Histochemical analysis reveals these pigment masses to be complexes of lipid-protein, with characteristics suggesting that they are the end product of lipid peroxidation of polyunsaturated lipids of cellular membranes. The amount of this material can be measured rather easily because it has a characteristic fluorescence spectrum--a maximum at 470 nm when excited at 365 nm (Tappel et al., 1973).

Quite a different sort of cellular injury results from the intracellular accumulation of indigestible materials, i.e., "clinkers,"--Category B' hypothesis (see page 42). These indigestible materials may interfere with cellular metabolism in at least two ways: (a) by their sheer bulk and (b) by a very slow release of toxic substances. Lipofuscin is such a material, and, as discussed above, its age-related accumulation is so predictable, especially in the heart and brain, that it is considered a valid marker for aging. In cardiac muscle it accumulates at a rate of approximately 0.67 percent of myocardial volume per decade (Martin, 1977). [As an aside, lipofuscin accumulates in dog myocardium at a rate of approximately 5.5 times greater than it does in humans--and the dog lives about 1/5.5 times as long.] Two characteristics of lipofuscin are of special interest with respect to aging: first, it accumulates particularly in neuronal and cardiac muscle cells--two of the major nonrenewable tissues--and second, its chemical composition is consistent with the view that it is an end product of lipid peroxidation. There are other ideas as to the chemical formation of lipofuscin, however. For example, Gershon et al. (1979) suggest that the accumulation of lipofuscin may result from incomplete degradation of proteins, an effect of the modified activity of enzymes that occurs with aging.

A second mechanism of injury from accumulated materials focuses on lysosomes--B',2 hypothesis. Lysosomes are enzyme-rich cellular organelles responsible for disposing of phagocytosed particulate matter and cellular debris of endogenous origin (Ericsson and Brunk, 1975). Ordinarily the incorporated materials are dissolved and eliminated, but not always. Among the indigestible materials that accumulate in lysosomes are various metals, e.g., copper, iron, and aluminum, also relatively insoluble inorganic compounds such as silica. It is well known that the solubility products of silica damage the lysosomal membrane, allowing enzymes to leak into the cytoplasm, causing cellular damage, often cellular destruction.

It has also been demonstrated experimentally that high concentrations of iron or copper can also cause leakage of enzymes from lysosomes. This has been shown to occur in humans suffering from hemochromatosis (Fe) and Wilson's disease (Cu). The extent to which this phenomenon occurs in humans under ordinary conditions is not known, however, nor is it known how much of this reaction is a result of lipid peroxidation (Ghadially, 1975).

The Category B" hypothesis considers that aging is an ultimate consequence of infection by viruses, which become so well adapted, i.e., they are such effective parasites, that they cause minimal if any acute manifestations of disease in most instances. There is a critically important immediate effect, however; the viral nucleic acid genome is incorporated with and becomes an inherent part of the molecular information of the infected cells. Adler (1974) has summarized the essential features of this theory very well:

> With repeated viral infections, starting possibly at conception, the individual acquires a "library" of viral genetic information. Concurrently, the cell-mediated immune system undergoes a decline in activity. Viral infected tissue that cannot be policed by the lymphocytes is attacked by anti-viral antibody, or anti-tissue antibody and the phenomena of auto-antibody becomes manifest. Viruses plus antibody result in immune complex disease, but not in a rejection of the diseased tissue. The infections continue causing normal tissue disease and the induction of tumours. In the absence of effective cellular immune functions the tumours are allowed to grow, maybe even encouraged to progress by anti-tumour antibody. The results of infections, decreased immune function, immune complex disease, and carcinogenesis are all included as part of the contribution of this autoimmune theory to the aging process.

Two other important types of cellular injury that are thought to contribute directly to senescence involve plasma membrane receptors and altered cellular antigenicity, respectively. These are discussed under the Category C hypothesis, because they are so intimately concerned with functions of the neuroendocrine and immune systems.

CATEGORY C HYPOTHESIS OF AGING

The Category C Hypothesis of Aging is related to key integrative systems: In terms of their overall contributions, some tissues, organs, and systems are much more important than others. Malfunction of one of the important ones, by any of the mechanisms described above, would have more profound consequences for the individual than a similar degree of malfunction affecting less-important structures. With this perspective, our Category C hypothesis of aging focuses on the effects of dysfunction by those specific multicellular components of the body that have a major integrative role. The connective tissues, the neuroendocrine system, and the immune system are the ones ordinarily considered in this context. The liver should also be included, for reasons that follow.

Interstitial Connective Tissues (Hypothesis C.1): Connective tissue is a comprehensive term that includes not only the intercellular ground substance but also the fibrous elements, bone, cartilage, and, according to some classifications, adipose tissue. We have briefly discussed in Chapter 6 collagen and elastic fibers in connection with senescence and age-associated diseases. In this chapter, our emphasis is on the interstitial connective tissues, principally the structural glycoproteins.

There is no question that the intercellular matrix has a regulatory effect on the metabolic activity of the cells that "live" in this environment. In the words of Balazs (1977):

> ...the matrix is responsible for the solid structure of the body of multicellular organisms, and without the matrix the specific compartmentalization of cells with different functions would be impossible and the body in effect would be a random distribution of cells packaged in an epithelial bag.

Robert and Robert (1973) point out that

> The intercellular matrix starts with the cell membrane itself, which is intimately involved in the secretion and orientation of the macromolecules

These macromolecules refer to the two principal categories:

(1) Proteoglycans, i.e., fibrous macromolecules that include the distinct morphologic entities, collagen, elastin and reticulin; and (2) Structural glycoproteins, a complex of materials that make up the so-called ground substance (see Figure 15).

We have already referred to the role of the interstitial matrix, i.e., the supporting stroma, in Chapter 6. An extreme example of the important interdependence of parenchymal cells and supporting stroma is seen in cartilage, which, incidentally, is pertinent with respect to osteoarthritis, an important disease of the aged. Quoting from Sokoloff (1974):

> One ordinarily thinks of cells as the source and regulator of the extracellular components of tissues. Hyalin articular cartilage, however, is avascular and the chondrocytes are entirely dependent on a copious matrix for their metabolic exchanges. The matrix of cartilage is a composite material in which the fibrous component is collagen, and the filler is the proteoglycan ground substance.

From this it is evident that the senescence of articular cartilage with its associated (or resulting?) osteoarthritis could result from a loss of the cell-replicating capacity of chondrocytes--but it could also result from the physiochemical changes in the matrix that occur independently of cell function. Most probably the mechanism involves both, i.e., interaction of cells and matrix.

Even tissues that are not avascular, however, are not directly connected to their blood supply. The interchange of metabolites and

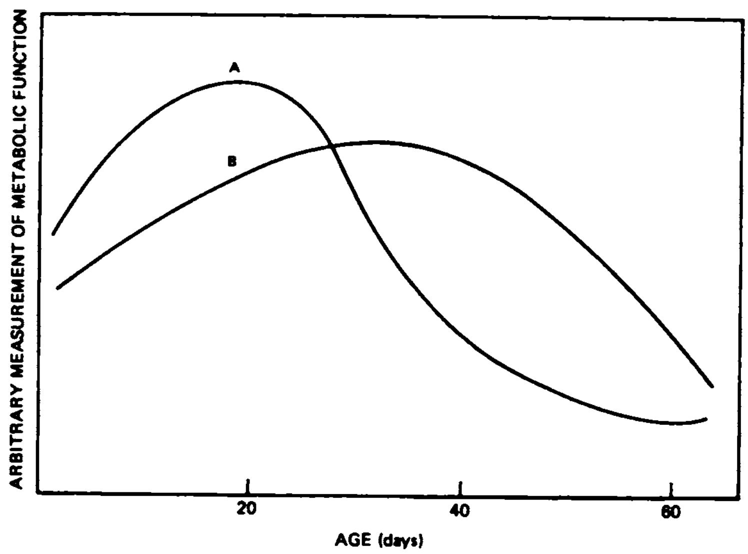

FIGURE 15 This figure illustrates changes in the "metabolic function" of granulomas during 60 days following the implantation of the initiating substance into young (A) and old (B) animals. The term "metabolic function" covers such factors as the synthesis of collagen and noncollageneous proteins, oxygen consumption, and the activity of glycolytic enzymes (after Heikkinen, 1973). Source: Hall (1976) with permission of Academic Press, Inc.

signal materials, e.g., hormones, occurs at the interface of the cell's plasma membrane and the intercellular matrix. In this connection it is important to realize that the events occurring in the intercellular milieu are not limited to transfer of substances controlled by the laws governing diffusion; the ground substance itself (structural glycoproteins) contributes important metabolic functions, and helps to modulate cellular activity. A wide variety of physical and biochemical changes occur in the ground substances during senescence (Fleischmajer et al., 1973; Schofield and Weightman, 1978). Although the precise mechanisms are not clear, it is hypothesized that these contribute in a major way to loss of important integrative functions involving all tissues and organs, by interfering with the functions that we have discussed.

Another important level at which connective tissues affect regulative mechanisms involves the minute blood vessels that provide the microcirculation. This vascular bed is made up of vessels less than 300 μm in diameter--small arterioles, venules, and the capillaries themselves. It is at this level where control mechanisms regulate the amount of blood delivered to the various tissues at different times and where the principal exchange of metabolites and signal substances occurs. The smallest of these vessels (capillaries) develop, in a predictable manner, age-associated changes involving glycoproteins that alter the rate of diffusion of essential materials (see Figures 16 and 17). This has been referred to as the hypoxia

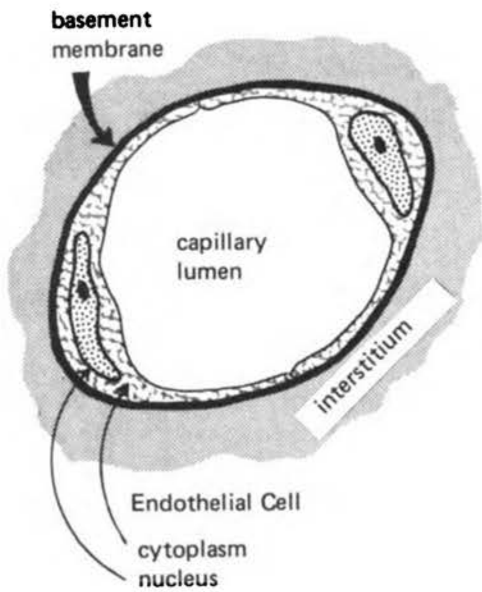

FIGURE 16 A typical capillary from a young adult, showing relationships of the basement membrane to the rest of the capillary and to the interstitium, which is shaded.

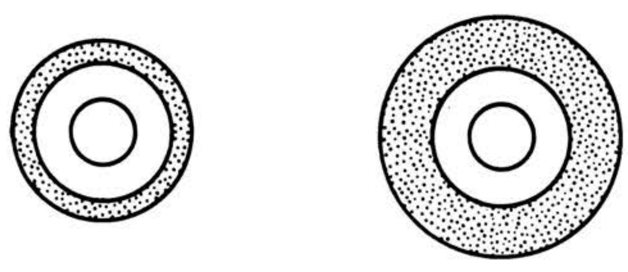

FIGURE 17 A schematic representation of capillaries to show the striking thickening of basement membrane (stippled layer) that occurs in old age (right) as compared with that of a young adult (left).

theory, but, obviously, many other important transport substances are involved. According to Kilo et al. (1972)

> Capillary BMW [basement membrane width] increases from approximately 650 Å at age 11 to 1,050 Å at age 70 in both sexes. This approximately 62 percent increase is highly significant statistically....

In addition to decreasing diffusion of highly soluble materials, Kohn (1977) has suggested that materials such as lipids and minerals would be trapped in the interstices, possibly injuring cells and stimulating a low-grade, chronic inflammatory reaction, which would contribute further damage to the interstitial connective tissue.

Although our principal concern in this chapter is with the structural glycoproteins, changes in some of the fibrous macromolecules warrant brief discussion.

Robert and Robert (1973) describe the chemical and biological changes that occur to produce senescence in elastic tissues as belonging to two distinct families. The first group, representing a continued differentiation-maturation process, is characterized by a continuous variation in the ratio of the macromolecules of the intercellular matrix. Changes in the matrix appear to develop first, followed by changes in the microfibrils. The second group of changes results from a gradual uptake of lipid by the elastic lamellae, leading to enzymatic fragmentation of the lamellae and, eventually, their solubilization. These changes--increasing catabolic activity, excessive cross-linking, lipid deposition, and calcification--occur independently of the first type and cause seriously impaired cell function and tissue lesions that contribute to such degenerative diseases as arteriosclerosis, osteoarthritis, and osteoporosis (see Figure 18).

Neuroendocrine (Hypothesis C.2): In searching for organs that exert important control mechanisms, the brain and the central nervous system (CNS) are particularly susceptible to damage by the aging process. First, neurons do not have the ability to reproduce, thus effects on the CNS from irreversible injury or death of individual cells are much greater than would be the case in systems made up of cells that have regenerative capability. Among the variety of important morphologic changes that occur in the brain, associated with senescence, there are:

1. A loss of neurons, particularly in certain regions of the brain (notably the locus ceruleus) that amounts to 30-40 percent in individuals 65 years of age and older (Martin 1977). Interestingly, the amount of DNA in brain tissue is not reduced significantly, but much of the DNA appears to be inactive.
2. A progressive age-related accumulation of (intracellular) lipofuscin pigment.
3. A significant decrease in the relative volume of the extracellular space of the brain (Bondareff, 1976).

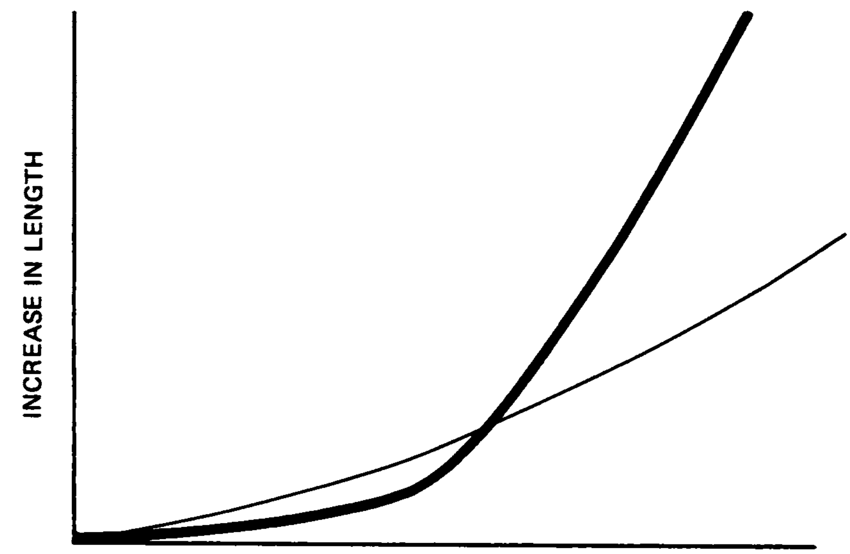

FIGURE 18 Graph showing the reaction of skin strips subjected to increasing stress over time. Note that the skin of the old animal (heavy line) is stiff and resistant to deformity during the period of light stress but soon reaches a breakpoint, following which it stretches rapidly. This is in striking contrast to the skin of the young animal in which reaction to similar stress reflects a high degree of elasticity (Viidic, 1973).

4. A progressive increase in glial (supportive) elements as compared with neurons--and it has been suggested that glial/neuron interactions play a critical role in the integrative capacity of the brain (Vernadakis, 1975).

5. At a tissue level, increasing numbers of neurofibrillary tangles and argyrophilic plaques, which reflect both degeneration and death of cells causing distorted reception and transfer of information (Terry and Wisniewski, 1977).

6. Less dendritic arborization in both aged human and animal brains.

> Not only is there a lessened length of dendrites per neuron, but many dendrites have fewer spines. Since spines are the receptor portions of the synaptic complex, this loss would result in a marked physiological deafferentation and could cause profound functional change (Terry and Wisniewski, 1977).

In addition, solid evidence of irreversible injury is seen in the age-dependent, functional alteration of important enzymes that occurs in the CNS (Iwangoff *et al.*, 1979).

Second, lipid-protein interactions are particularly important in nervous tissue, thus the brain would seem particularly susceptible to injury by lipid peroxidation of membranes. In aged humans lipofuscin masses comprise as much as 75 percent of the intracellular volume of large neurons in certain parts of the brain, e.g., the nucleus dentatus (Strehler, 1976). The striking age-related accumulation of lipofuscin in brain tissue implies that lipid peroxidation is a continuing process there. This view is supported by limited experimental evidence, both in vivo and in vitro, suggesting that dietary antioxidants (presumably through their protection against lipid peroxidation), have beneficial effects on the cellular membranes; they appear to decrease the formation of lipofuscin and increase the lifespan of experimental animals (Sun and Sun, 1978). On the other hand, accumulation of lipofuscin in cells of the CNS does not correlate with neuronal death. Portions of the medulla oblongata, in which cells acquire large amounts of lipofuscin, show virtually no decrease in cell population with age, whereas other regions of the brain, with little lipofuscin, show considerable cellular reduction. As Frolkis (1979) has emphasized, there are many unanswered questions about the formation and effects of lipofuscin, such as, why it accumulates in some neurons, but not in others, and why it occurs regularly and in large amounts in specific nuclei of some animal species, but not in other species (see p. 54).

We tend to think of the brain in terms of its skeletal motor activities, but a more vital function is performed by the autonomic portion of the CNS. The autonomic nerves modulate cellular and tissue activities so that they function in an integrative fashion to control circulation, respiration, and metabolism in general, by receiving and responding appropriately to stimuli that maintain homeostasis. The neuroendocrine aspect of autonomic function is so important in the context of aging as to warrant special attention.

In discussing hypothalamic control of aging and age-associated pathology, Dilman (1976) points out that

> ...age-associated disturbances of the internal environment of the organism naturally arise as a result of the intrinsic age-related elevation of the hypothalmic threshold to feedback suppression in the three main homeostatic systems of higher organisms: energy, reproduction, and adaptation systems.

The brain plays its unique role in effecting adaptation to the environment through reflexes, conditioning, and learning based on electrochemical codes; also through its control of endocrine organs that, in turn, integrate homeostatic feedback regulation of metabolism in response to environmental changes communicated by the release of hormones (Ordy, 1975).

Not to be overlooked in these important basic functions of the brain is its control of sleep patterns. The disturbed sleep that is so common among the aged may disturb circadian rhythms, in this way contributing further to the distorted mechanisms of adaptability that jeopardize homeostasis.

The hypothalamus and pituitary-peripheral endocrine system complex is critically important in governing those mechanisms that provide defense against the continual stresses provided by a hostile environment, but at the cost of accelerated aging. In this context, some of the adverse changes associated with these defensive reactions are the following:

1. A progressive decrease in glucose tolerance with age and, paradoxically, increased insulin production in response to the stress of glucose loading.
2. Decreased reserve adrenocortical secretory capacity in response to stress.
3. Reduction of thyroid function.
4. Decreased production of (pituitary) growth hormone (Everitt, 1976).

Moreover, since the neuroendocrine and thymus systems are closely linked, faulty interactions between the two contribute to dysfunction of the immunologic system (Fabris, 1977).

Adding insult to injury, as it were, there is a progressive loss of hormone-binding receptors with increasing age, so that the target cells are less responsive to messages from the endocrine system (Adelman, 1975).

A particularly interesting aspect of neuroendocrine activity is closely related to one of the hypotheses considered under Category A [A.1(d)], "retarded mitotic cycle." One form of cellular homeostasis, expressed by maintenance of cell populations in a tissue, is based on controlled mitosis--the production of new cells to balance the loss of old cells, as discussed in the context of molecular information contained in DNA and RNA. So far, however, we have said little about the factors that determine which cells shall undergo mitosis and when. The major regulating mechanism appears to be the cellular synthesis of chalones, messenger molecules that delay mitoses and that are specific for the tissue from which they originate. Bullough (1971) believes that chalones prolong the life of postmitotic cells by retarding mitoses of their undifferentiated counterpart, thus delaying cellular senescence and prolonging life of the individual. He postulates that because the adrenal gland, in its response to stress, elaborates substances that stimulate production of chalones, effective adrenal function is an important factor in delaying senescence.

Turning from the more general to a particular major component of the neuroendocrine system, there are three principal mechanisms that could explain the deterioration of the CNS, including its neuroendocrine function, which is so important in the pathogenesis of senescence:

(a) Signals are improperly received or interpreted.
(b) Signals are improperly sent in terms of quality, amplitude, or response time.
(c) Receptor sites on target cells are decreased or less effective.

Dilman (1971) suggests that the key process in aging is the progressive elevation in threshold sensitivity of the hypothalamus to feedback suppression; however, it is likely that all the mechanisms listed above are important.

Several important age-associated diseases of the brain were discussed in Chapter 6, including senile dementia. A particular kind of senile dementia deserves mention here--"senile dementia of the Alzheimer type" (SDAT), also called Alzheimer's disease--because of its general importance as well as certain etiologic aspects. This condition, which usually occurs among the aged, is responsible for approximately 50 percent of severe senile dementia and presents enormous economic problems. Terry (1978) estimated that nursing home care of elderly patients with senile dementia costs "...about 6 billion dollars per year." Perhaps the most interesting aspect of Alzheimer's disease in connection with geochemical environment is its association with high concentrations of aluminum in certain portions of the brain. Crapper et al. (1973) and others believe that the aluminum is causally related to the disease; others (Wisniewski et al., 1976) believe that the accumulation is age-related rather than an etiologic factor of the disease.

The Immune System (Hypothesis C.3): There are two major functional "arms" of the immune system, and although they are closely related and overlap to some extent, each is primarily dependent on a different kind of cell, and each operates in a different way. B-cells (B for bursa), derived from the bone marrow in humans, are members of the lymphocyte family. In response to antigenic stimulus they produce a variety of humoral antibodies that can act directly, once they are formed. These materials (gamma globulins) are highly specific in their reactions against exotoxins (such as those produced by the diphtheria bacillus) and most of the bacteria responsible for common infections, e.g., staphylococci and streptococci. They also react against allergens, such as ragweed pollen. The cell-mediated immune system, which is largely dependent on T-cells (T for thymus), also a type of lymphocyte, responds to a different type of antigenic stimulus to produce a different type of highly specific cellular reaction. It is the primary basis for defense against viruses, fungi, and certain other microorganisms such as the tubercle bacillus and the spirochete of syphilis. In addition, the "activated lymphocytes," which are mainly responsible for this type of immunity (macrophages are also involved), seek out and destroy cells identified as "nonself." These may be foreign cells, i.e., cells from another person or another species; graft rejection is an example of this type of reaction. The cells identified as nonself may arise from the individual himself or herself--so-called forbidden clones--and include cancer cells, and a variety of many abnormal types of noncancer cells that have significantly altered antigenic structure. Reaction to this latter type of cell is the basis for most autoimmune disease.

A major characteristic of senescence is the progressive decline in both B-cell and T-cell immunity. In this connection three major categories of immune reaction can be causally related to senescence and/or age-associated disease mortality:

1. Autoimmunity (reaction against self) can produce various types of effects on cells and tissues ranging from slowly developing, relatively slight injury (amyloid deposits, for example) to rapid cellular destruction by activated lymphocytes, often associated with violent inflammatory reaction. Autoimmunity can develop in two ways: first, the antigenic characteristics of the individual's own cells can change as a result of injury or inherent error, causing defective synthesis that results in abnormal proteins (or lipo-polysaccharide complexes) or because of viral infection (see p. 55); second, the immune mechanism itself may malfunction so that it is no longer reliable in its differentiation between self (its own normal cells) and nonself.

The incidence of autoimmune disease increases progressively with senescence.

2. It has been hypothesized that decreased immune function, both in amount and response time, is a major cause for the progressive increase in incidence of overt cancer with advancing age, thus contributing a major cause of mortality from age-associated disease (see p. 32).

3. Decreased immune functions, both in amount and response time, are unquestionably a major factor in the increased susceptibility of the aged to virtually all kinds of infectious disease--and infection is a major cause of death among the aged.

Burnet (1977), a champion of the immune theory of senescence, has provided this elegant description:

> In old age, the responsiveness of the immune system dwindles away and rather slow-moving diseases, like myeloma, chronic lymphatic leukaemia, and Waldenstrom's macroglobulinaemia, become relatively common. Minor autoimmune manifestations, like causal autoantibodies, round-cell infiltrations, and patches of amyloid, also become common. All of this can be readily interpreted in terms of progressive error interfering with the intricate web of cell to cell interactions. Probably more than anything else, it is this overall unresponsiveness that results in the increasing vulnerability to infection that provides the common occasion for death in the old.

An excellent general account of immunity and aging can be found in the chapter with that title by Makinodan (1977).

Liver (Hypothesis C.4): The liver is a complex organ that contains a major portion of the reticuloendothelial system in the form of the highly specialized Kupffer cells, which line its sinusoids. The liver is considered a key regulative organ because of the following major functions.

It has been named the great toxin remover because of its effectiveness in handling the following:

1. Ammonia, in part a product of metabolism, but derived mostly from the intestinal tract; ammonia content of the portal vein (from the intestines) is as much as 40 times that of blood within other vessels.
2. Purines, metabolic products related to nucleic acid metabolism
3. Metabolic products related to production and destruction of red blood cells.
4. Many other toxins of metabolic origin, also many of extrinsic origin; the liver is the major organ responsible for degradation of drugs, for example.

In addition, the liver is primarily responsible for "neutralizing" the considerable amounts of bacterial toxins that are continually being absorbed from the intestinal tract.

The liver has an important control function because it metabolically degrades many hormones and other signal substances, in this way allowing necessary flexibility for positive feedback mechanisms. Moreover, the liver itself produces at least seven transport proteins, some of which are necessary for the action of certain hormones.

The liver plays a major role in metabolism of proteins, carbohydrates, and fats in the following ways:

1. It produces a wide variety of proteins, including albumin, also fibrinogen and a group of "coagulation proteins"--the latter reflecting a critical control function.
2. It provides the body's primary rapid release storage for glucose and glycogen and is involved in conversion of one to the other. Through its ability to store and release glucose, it has a major effect in maintaining glucose homeostasis.
3. It takes up fatty acids from the blood and esterifies them.

Through its production and excretion of bile, the liver affects digestion and absorption of nutrients, and helps to control the intestinal microflora.

As a result of its reticuloendothelial functions, it contributes in a major way to defense against infectious disease.

With respect to senescent changes in human livers, Tauchi and Sato (1978), in their study of autopsy specimens, found that the number of hepatic cells begins to decrease in the sixth decade, continuing at a moderate rate through the eighth decade, then decreasing at a more rapid rate thereafter. They also observed that binucleate hepatic cells increased in number with advancing age, reaching a maximum in the seventh decade. Beyond this time, hepatic cell nuclei showed an increase in size that was quite variable. Mitochondria of the hepatic cells were decreased in number but increased in size. They conclude that the increased volume of hepatic cells was compensatory to a decrease in number but that this limited the reserve power of the remaining hepatic cells, thus increasing susceptibility to injury and further reducing their number--a vicious cycle.

A point of special interest concerns the reproduction of liver cells. In discussing the mitotic cycle (see p. 48), Baserga (1977) speaks of G_0 as a normal state, which hepatocytes enter (also several other types of cells), in which mitotic progression can be arrested for a long time. The concept of G_0 was first introduced by Lajtha in 1963, referring to quiescent cells that do not synthesize DNA or divide but that can be stimulated to do so by appropriate stimulus--a stimulus usually provided by tissue injury. Some have felt that G_0 is not an entity but simply reflects a very long G_1 period. In any event, experimental studies of recovery following partial hepatectomy in rats revealed a significant delay in new cell production among aged animals, although the original mass of the liver was eventually restored (Baserga, 1977).

Baserga (1977) concluded that

> . . . aging causes, in general, an increase in the length of the cell cycle and in the length of the prereplicative phase in stimulated G_0 cells. It also causes changes in the template activity of chromatin and in the synthesis and storage of nonhistone chromosomal proteins. The tentative conclusions are that aging cells are cells that go into deeper states of G_0 from which it becomes increasingly difficult to rescue them. This, in turn, could be due to changes in chromatin and in its components in aging cells.

Of course the Category C hypothesis is intimately related to A and B hypotheses because senescence, at the cellular level, is characterized by defective and/or diminished morphologic and chemical structures causing impaired function--and cellular dysfunction affects the function of tissues and organs. But the cellular changes are amplified at the systems level, resulting in a steady erosion of performance by the total organism, including decreased homeostatic control and increased vulnerability to environmental stress, which means increased susceptibility to cellular injury.

Connective tissue, the neuroendocrine and immune systems, and the liver are more important than most of the other tissues and organs because of their critical control and integrative functions, as has been noted. But one should not overlook the importance of other major systems--such as the renal-urinary, cardiovascular, respiratory, and gastrointestinal--which must have the potential for effective response, otherwise control and integrative mechanisms are useless.

SUMMARY

Just as disease is almost always multicausal, there is good reason to believe that senescence has multiple causes. Among the many contributing factors, there is substantial evidence that some of them operate at a molecular level, others at a cellular, or tissue, or organ level, and still others at the systems level. Moreover, it seems clear that some of these processes are intrinsic, i.e., built into the cell, whereas others are extrinsic, or environmental. The question: Why do we grow old? is closely related to: Why do we die? Sacher (1968), in

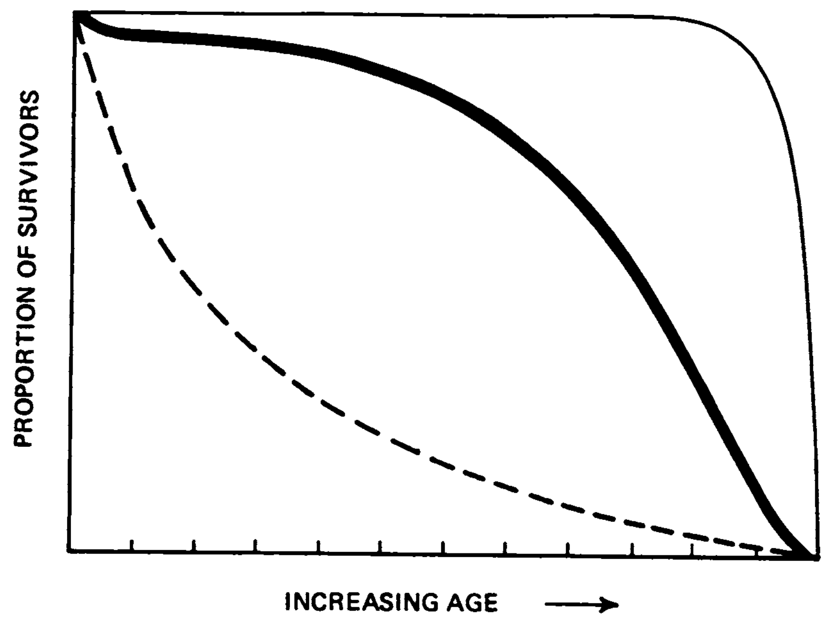

FIGURE 19 This figure gives the shape of survival curves in general terms under three quite different conditions. The heavy line indicates the survival rate related to age in the United States as it is today. The fine line (top) indicates the survival rate expected if deaths were an effect of senescence as such; the dashed line, if death were purely a random event.

discussing his stochastic theory, points out its compatibility with observations that a slow, steady decrement of physical performance can give rise to exponentially rising death rates, as described by the Gompertz equation. [Gompertz, an English actuary, reported in 1825 that the likelihood of dying doubles approximately each 8 years after the age of 30.] He further comments that this view helps us

> ...to understand why a human population (or a mouse population) dies out when its physiological performance falls to about half the prime value in the young adult.

See Figure 19.

There is a general view that man's life has an ultimate limit, probably in the range of 100-120 years, because of intrinsic factors. The best defined of these is sometimes referred to as the "Hayflick limit," based on the number of cellular divisions (50 ± 10) that will occur in human embryonic fibroblasts grown under what are considered to be optimal tissue culture conditions. It has been hypothesized that when this limit is reached the cells stop dividing, and, without continual cellular replacement, the tissue soon dies. But Hayflick (1977) himself has stated:

> The possibility that animals age because one or more important cell populations lose their proliferative capacity is unlikely. I would suggest instead that normal cells have a finite capacity for replication and that this finite limit is rarely if ever reached by cells *in vivo*....

Senescence of the individual is, obviously, much more complex than senescence of the cell, and there is abundant evidence that environmental factors may cause accelerated or distorted aging of one set of cells or a particular tissue to bring about a pathologic process that interrupts the life of the individual. One of the major problems in evaluating the aging process is separating the pathologic from the physiological aspects.

A fitting close to this discussion is the statement by Frolkis (1972):

> Gerontology has never been suffering from the lack of hypotheses. However the number of hypotheses is generally inversely proportional to the clarity of the problem.

REFERENCES

Adelman, R. C. 1975. Impaired hormonal regulation of enzyme activity during aging. Fed. Proc. 34(2):179-182.

Adler, W. H. 1974. An "autoimmune" theory of aging. In *Theoretical Aspects of Aging*. M. Rockstein, M. L. Sussman, and J. Chesky, eds., Academic Press, New York, pp. 33-42.

Balazs, E. A. 1977. Intercellular matrix of connective tissue. In *Handbook of the Biology of Aging*. C. E. Finch and L. Hayflick, eds. Van Nostrand and Reinhold, New York, pp. 222-240.

Baserga, R. L. 1977. Cell division and the cell cycle. In *Handbook of the Biology of Aging*. C. E. Finch and L. Hayflick, eds., Van Nostrand and Reinhold, New York, pp. 101-121.

Bjorksten, J. 1968. The crosslinkage theory of aging. J. Am. Geriatrics Soc. 15(4):408-427.

Bondareff, W. 1976. Extracellular space in the aging cerebrum. In *Neurobiology of Aging*, R. D. Terry and S. Gershon, eds., Raven Press, New York, pp. 167-175.

Bullough, W. S. 1971. Ageing of mammals. Nature 229(5287):7-32.

Burnet, F. M. 1970. *Immunology, Aging, and Cancer: Medical Aspects of Mutation and Selection*. W.H. Freeman, San Francisco, p. 83.

Burnet, F. M. 1977. Implications of a somatic mutational approach to ageing for gerontological research. In *Multidisciplinary Gerontology: A Structure for Research in Gerontology in a Developed Country*. I R. Mackay, ed., S. Karger, Basel, 116 p.

Crapper, D. R., S. S. Krishnan, and A. J. Dalton, 1973. Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration. Science 180:511-513.

Cutler, R. G. 1976. Cross-linkage hypothesis of aging: DNA adducts in chromatin as a primary aging process. In *Aging, Carcinogenesis and*

Radiation Biology: The Role of Nucleic Acid Addition Reactions, K. C. Smith, ed., Plenum Press, New York., pp. 443-492.

Dayan, A. D. 1972. The brain and theories of ageing. In Ageing of the Central Nervous System. H. M. Van Praag and A. F. Kalverboer, eds., De Erven F. Bohn N.V., Haarlem, Netherlands, p. 59.

Demopoulos, H. B. 1973. Control of free radicals in biologic systems. Fed. Proc. 32(8):1903-1908.

Dilman, V. M. 1971. Age-associated elevation of hypothalamic threshold to feedback control and its role in development, ageing and disease. Lancet 1:1211-1219.

Dilman, V. M. 1976. The hypothalamic control of aging and age-associated pathology. In Hypothalamus Pituitary and Aging. A. V. Everitt and J. A. Burgess, eds. Charles C Thomas, Springfield, Illinois, pp. 634-667.

Ericsson, J. L. E., and U. T. Brunk. 1975. Alterations in lysosomal membranes as related to disease processes. In Pathology of Cell Membranes, Volume 1. B. F. Trump and A. U. Arstila, eds., Academic Press, New York, pp. 217-253.

Everitt, A. V. 1976. Conclusion: Aging and its hypothalamic pituitary control. In Hypothalamus Pituitary and Aging. A. V. Everitt and J. A. Burgess, eds., Charles C Thomas, Springfield, Illinois, pp. 676-701.

Fabris, N. 1977. Hormones and aging. In Immunology and Aging. T. Makinodan and E. Yunis, eds., Plenum Medical Book Company, New York, pp. 73-89.

Fleischmajer, R., J. S. Perlish, and R. I. Bashey. 1973. Aging of human dermis. In Aging of Connective Tissues-Skin. L. Robert and B. Robert, eds., S. Karger, Basel, pp. 90-106.

Forbes, W. F., and J. F. Gentleman. 1973. A possible similar pathway between smoking-induced life shortening and natural aging. J. Gerontol. 28(3):302-311.

Franks, L. M., P. N. Riddle, A. W. Carbonell, and G. O. Gey. 1970. A comparative study of the ultrastructure and lack of growth capacity of adult human prostate epithelium mechanically separated from its stroma. J. Pathol. 100(2):113-119.

Frolkis, V. V. 1972. Regulation and adaptation processes in aging. In Leading Problems of Soviet Gerontology. Kiev, pp. 54-84.

Frolkis, V. V. 1979. Morphological changes of the brain. In Aging of the Central Nervous System. V. V. Frolkis and Vladislav V. Bezrukov, eds., S. Karger, Basel. pp. 2-15.

Gershon, D., A. Reznick, and U. Reiss. 1979. Characterization and possible effects of age-association alterations in enzymes and proteins. In Physiology and Cell Biology of Aging. A. Cherkin, C. E. Finch, N. Kharasch, T. Makinodan, F. L. Scott, and B. Strehler, eds., Raven Press, New York, pp. 21-26.

Ghadially, F. N. 1975. Ultrastructural Pathology of the Cell: A Text and Atlas of Physiological and Pathological Alterations in Cell Fine Structure. Butterworths, Boston, 543 p.

Hall, D. A. 1976. The Ageing of Connective Tissue. Academic Press, Inc., London. p. 146.

Hayaishi, O., and K. Asasa, eds. 1977. Biochemical and Medical Aspects of Active Oxygen. University Park Press, Baltimore. 313 p.
Hayflick, L. 1965. The limited in vitro lifetime of human diploid cell strains. Exp. Cell Res. 37:614-636.
Hayflick, L. 1977. The biology of aging. Natural History 86(7):22-30.
Hayflick, L. 1979. Cell aging. In Physiology and Cell Biology of Aging. A. Cherkin, C. E. Finch, N. Kharasch, T. Makinodan, F. L. Scott, and B. Strehler, eds., Raven Press, New York, pp. 3-19.
Iwangoff, P., K. Reichlmeir, A. Enz, and W. Meier-Ruge. 1979. Neurochemical findings in physiological aging of the brain. In CNS Aging and Its Neuropharmacology, W. Meier-Ruge, ed., S. Karger, Basel, pp. 13-33.
Kilo, C., N. Vogler, and J. R. Williamson. 1972. Muscle capillary basement membrane changes related to aging and to diabetes mellitus. Diabetes 21(8):881-905.
Kohn, R. R. 1977. Heart and cardiovascular system. In Handbook of the Biology of Aging. C. E. Finch and L. Hayflick, eds. Van Nostrand and Reinhold, New York, pp. 281-317.
Makinodan, T. 1977. Immunity and aging. In Handbook of the Biology of Aging. C. E. Finch and L. Hayflick, eds. Van Nostrand and Reinhold, New York, pp. 379-408.
Martin, G. M. 1977. Cellular aging--clonal senescence: A review. Am. J. Pathol. 89(2):484-530.
Murphy, D. P. 1954. The birth of congenitally malformed children in relation to maternal age: parental age and characteristics of the offspring. R.W. Miner, ed., Ann. N.Y. Acad. Sci. 57(5):503-506.
Ordy, J. M. 1975. Principles of mammalian aging. In Neurobiology of Aging: An Interdisciplinary Life-Span Approach. J. M Ordy and K. R. Brizzee, eds., Plenum Press, New York, pp. 1-22.
Orgel, L. E. 1963. The maintenance of the accuracy of protein synthesis and its relevance to aging. Biochemistry 49:517-521.
Orgel, L. E. 1973. Aging of clones of mammalian cells. Nature 243:441-444.
Robert, L., and B. Robert. 1973. Aging of connective tissues, general considerations. In Aging of Connective Tissue-Skin. L. Robert and B. Robert, eds., S. Karger, Basel, pp. 1-45.
Sacher, G. A. 1968. Molecular versus systemic theories on the genesis of ageing. Exp. Gerontol. 3:265-271.
Sacher, G. A. 1977. Life table modification and life prolongation. In Handbook of the Biology of Aging. C. E. Finch and L. Hayflick, eds., Van Nostrand and Reinhold, New York, pp. 587-597.
Schofield, J. D., and B. Weightman. 1978. New knowledge of connective tissue ageing. J. Clin. Pathol. 31, Supplement (Royal College of pathology), 12:174-190. Diseases of Connective Tissue, D. L. Gardner, ed., published for the Royal College of Patholoists by the J. Clin. Pathol, London, 241 pp.
Sinex, F. M. 1975. The biochemistry of aging. In Understanding Aging: A Multidisciplinary Approach. M. G. Spencer and C. J. Dorr, eds., Appleton-Century-Crofts, New York, pp. 21-39.
Sinex, F. M. 1977. The molecular genetics of aging. In Handbook of the Biology of Aging. C. E. Finch and L. Hayflick, eds. Van Nostrand and Reinhold, New York, pp. 37-62.

Sokoloff, L. 1974. The general pathology of osteoarthritis. In Proceedings of the Symposium, Normal and Osteoarthritic Articular Cartilage. S. Y. Ali, M. W. Elves, and D. H. Leaback, eds., Inst. of Orthopaedics, University of London, Stanmore, England., pp. 111-121.

Strehler, B. L. 1974. As cited by J. L. Marx. In Aging Research (1): Cellular theories of senescence. Science 186(4169):1105-1107.

Strehler, B. L. 1976. Introduction: aging and the human brain. In Neurobiology of Aging. R. D. Terry and S. Gershon, eds., Raven Press, New York, pp. 1-22.

Sun, A. Y., and G. Y. Sun. 1978. Effects of dietary vitamin E and other antioxidants on aging process in rat brain. In Pharmacological Intervention in the Aging Process. J. Roberts, R. C. Adelman, and V. J. Cristofalo, eds., Plenum Press, New York, pp. 285-290.

Tappel, A., B. Fletcher, and D. Deamer. 1973. Effect of antioxidants and nutrients on lipid peroxidation fluorescent products and aging parameters in the mouse. J. Gerontol. 28(4):415-424.

Tauchi, H., and T. Sato. 1978. Hepatic cells of the aged. In Liver and Aging--1978. K. Kitani, ed., Elsevier/North-Holland Biomedical Press, Amsterdam, pp. 3-19.

Terry, R. D. 1978. Senile dementia. Fed. Proc. 37(14):2837-2840.

Terry, R. D., and H. M. Wisniewski. 1977. Structural aspects of aging of the brain. In Cognitive and Emotional Disturbances in the Elderly: Clinical Issues. C. Eisdorfer, ed., Year Book Medical Publishers, Chicago, pp. 3-9.

Vernadakis, A. 1975. Neuronal-glial interactions during development and aging, Fed. Proc. 34(1):89-95.

Viidic, A. 1973. Rheology of the skin with special reference to age - related parameters and their possible correlation to structure. In Aging of Connective Tissues-Skin. L. Robert and B. Robert, eds. S. Karger, Basel, pp. 157-189.

Watson, J. D. 1965. The Molecular Biology of the Gene. 1st ed. W. A. Benjamin, New York, 494 pp.

Wisniewski, H. M., H. K. Narang, J. A. N. Corsellis, and R. D. Terry. 1976. Ultrastructural studies of the neuropil and neurofibrillary tangles in Alzheimer's disease and post-traumatic dementia. Abstract 136, 52nd Annual Meeting of the American Association of Neuropathology, June 11-13, San Francisco.

8

GEOCHEMISTRY OF SURFICIAL ROCKS AND CLIMATIC FACTORS IN THE INCREASED-LONGEVITY LOW-DEATH-RATE AND DECREASED-LONGEVITY HIGH-DEATH-RATE AREAS

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The purpose of this chapter is to compare and contrast the surficial rocks and to document such common denominators as may contribute to the geochemical environments relating to the aging process and/or increased longevity or decreased longevity, in the geographic regions identified by Sauer in Chapter 3. Inferences will then be drawn on how their properties may favorably or adversely affect the environment in relation to health and longevity.

Although solid rocks extend to subcrustal depths of the earth, those that directly affect the environment, and interact with the health and aging process of man, are the relatively thin surficial rocks and the near-surface aquifers from which we draw groundwater. These surficial rocks, contrary to the popular idea that all rocks are hard, strong, and compacted, may also be loosely consolidated and geologically young; such is the case in both areas of aging studies.

The two regions of increased and decreased longevity of major concern in Sauer's Chapter 3 (see Figure 3) are considered in greater detail in this and the two chapters that follow. Figures 20 and 21 provide higher resolution views of these regions that will be useful as we consider various aspects of their geochemical environment. Neither health and disease nor geochemistry relate well to political boundaries, but the two geographic regions shown include areas that concentrate counties with the highest and lowest percentile mortality, respectively. Most of the other counties included in the increased-longevity region are in the lowest quartile of mortality, and most of those in the decreased longevity region are in the highest quartile of mortality.

In the increased-longevity area, the predominating surface rocks are weakly consolidated gravel, sand, and clay deposits of alluvium (stream sediments), glacial drift deposited by overloaded and melting glaciers, and wind-blown loess deposits. In the decreased-longevity area, the surface rocks are Coastal Plain sand with minor clay and marl deposits and their weathering residues laid down in both landward and seaward directions from marine coastlines.

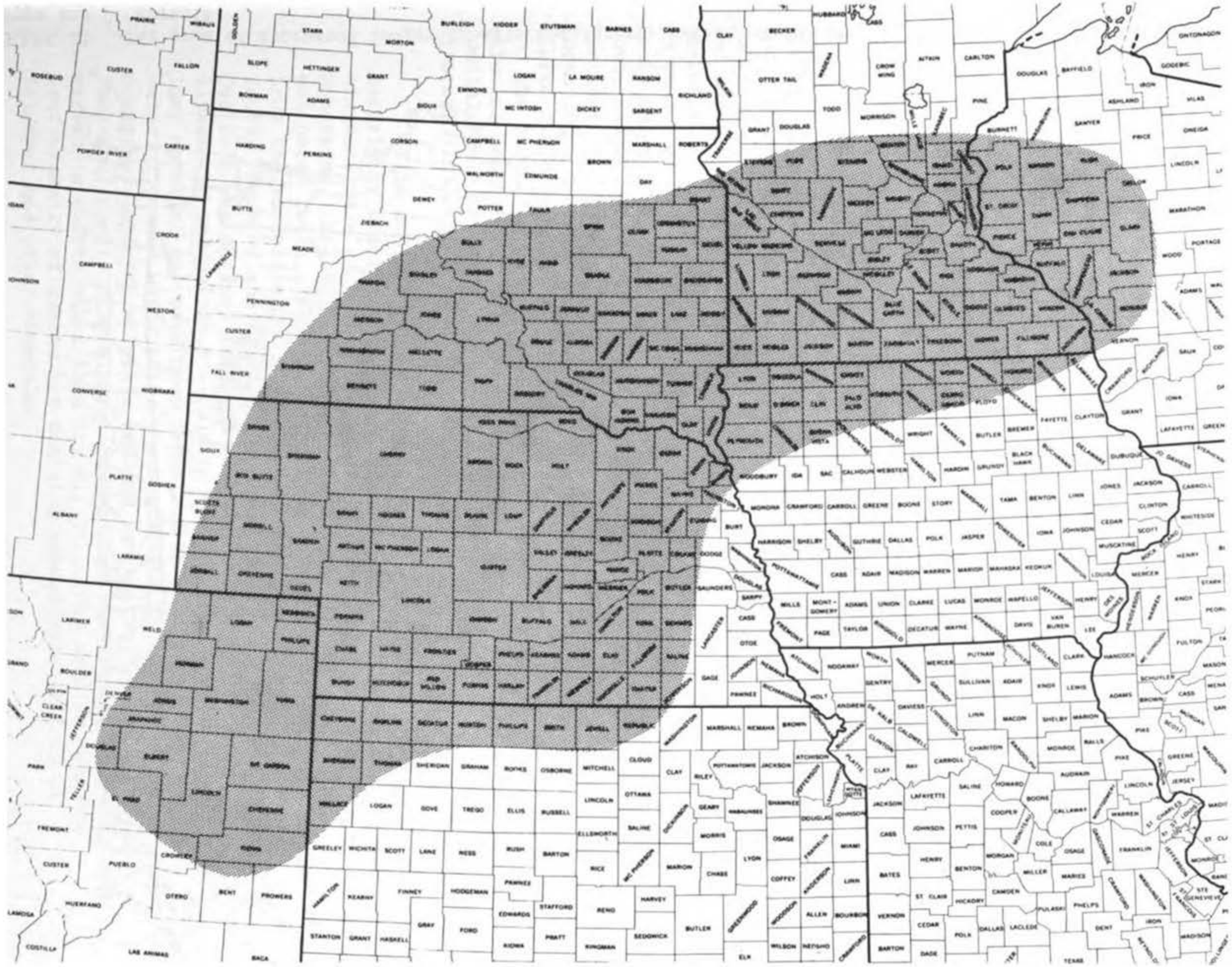

FIGURE 20   The area of increased longevity selected for evaluation of geochemical environment. Drafted by H. C. Hopps and C. Errante.

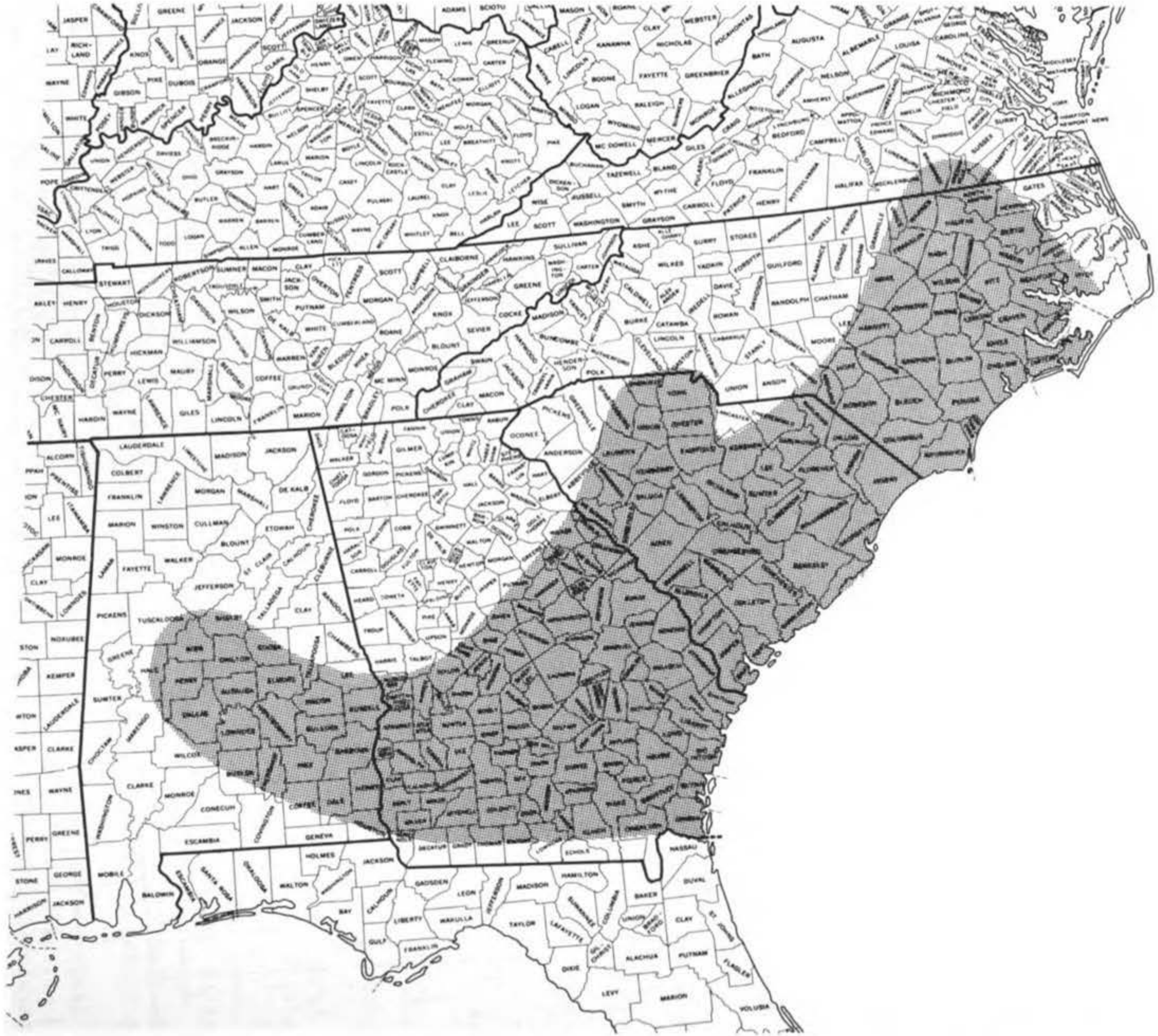

FIGURE 21 The area of decreased longevity selected for evaluation of geochemical environment. Drafted by H. C. Hopps and C. Errante.

SURFACE ROCKS AND CLIMATIC FACTORS IN THE INCREASED-LONGEVITY AREA

The distribution of younger less-indurated sedimentary rock types in the north central United States, which includes the increased-longevity area, may be readily seen on the generalized map (Figure 22). The stippled area is underlain by Tertiary alluvial deposits spread eastward by streams from the Rocky Mountains. The shaded area with vertical lines is underlain by Pleistocene glacial drift. The area marked with diagonal lines shows the more prominent mantle of windblown loess that covers the alluviated and glaciated regions, and other areas that are widely spread adjacent to the alluvial and glacial deposits. It is especially noteworthy that almost all of the increased longevity area is mantled by windblown material, the significance of which will be discussed later.

Alluvial Deposits

The alluvial deposits that spread eastward from the Rocky Mountains, and the ancestral Rockies from which they were derived, underlie portions of the increased-longevity area in Colorado, Kansas, Nebraska, and South Dakota. Predominantly these alluvial materials comprise the so-called Pliocene (Tertiary) Ogallala Formation, which was deposited as coalesced and compound alluvial fans about 10 million years ago. In South Dakota, the Arikaree and White River formations (also Tertiary) cover a small area. Where present stream erosion has cut through the Tertiary deposits, it has exposed several Cretaceous sedimentary formations, such as the Dakota Sandstone, Niobrara Limestone-chalk, and Pierre Shale (mudstone).

The geological, mineralogical, and geochemical properties of these alluvial deposits are validly documented by the properties of the Ogallala Formation that were summarized by Frye et al. (1956) and by Prescott (1953, page 69), who wrote

> [T]he sediments of the Ogallala Formation were deposited largely by streams that flowed from the Rocky Mountains. Most of the materials of the Ogallala were derived from the Rocky Mountains. The silts and clays were derived from soils and weathered rocks in the mountain area. Sand and gravel were derived from the weathering of igneous rocks and clastic sedimentary rocks. Much of the calcareous matter that is so abundant in the Ogallala was derived from the weathering of the Paleozoic limestones and calcic minerals in the igneous rocks. Some of the limy material may have been deposited by percolating subsurface water or ground water after the deposition of the rocks....It contains...beds of volcanic ash and bentonitic clay [montmorillonite clay mineral having high ion-exchange capacity and variety elements other than Al, Si, O]....The sand is composed predominantly of quartz but contains subordinate amounts of feldspar and other minerals.

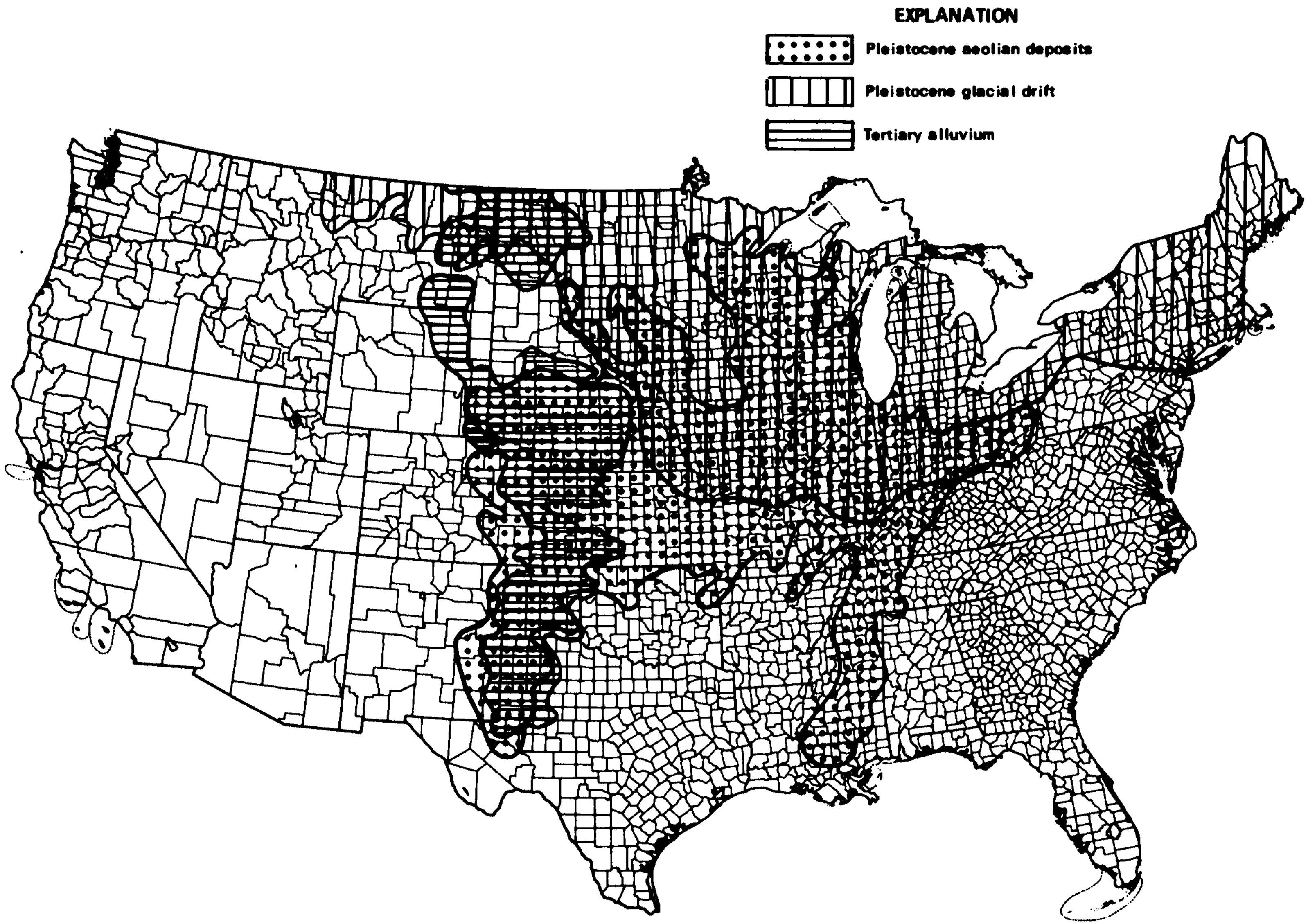

FIGURE 22 Map of the conterminous United States showing areal distribution of Pleistocene Aeolian deposits and glacial drift and Tertiary alluvium. Drafted by the U. S. Geological Survey, Denver, Colorado

The wide diversity in lithological, mineralogical, and chemical composition of the Ogallala is thus related to its diverse source rocks.

Glacial Drift Deposits

Thick, unconsolidated, fragmental deposits, shown by the vertical-lined area in Figure 22, were left by huge, continental glaciers, which moved as ice lobes south from Canada during Pleistocene time (approximately 1 million years ago). Four major glacial advances on the land (apart from evidence provided by marine records of recent deep-sea drill cores) with three interludes of melting and retreat of the glacial front, constituted the glacial episode. The second advance, the so-called Kansan, moved as far south as northeastern Kansas, whereas the last one, the Wisconsin, did not extend far beyond the latitude of southern Wisconsin. During interglacial intervals, windblown dusts, soils, and the cover of vegetation over the soils left materials and records of changing climates and geochemical environments between the sheets of glacial drift deposits.

The properties of continental glacial drift that are significant to the environment of the increased longevity area arise from the glacial processes and the geological work done by the continental ice sheets during their regime. Continental glaciers erode and transport the underlying rocks from the locations of their sources all the way to their melting fronts, often hundreds of miles. For example, igneous and metamorphic rocks and minerals that crop out uniquely in Canada and the Great Lakes region, such as metallic copper ore at Lake Superior, were carried and deposited as glacial erratics as far south as Missouri. These rocks and minerals are thoroughly mixed with one another and commonly with the lithologically incompatible underlying rock. The ice grinds and pulverizes its load, which ranges in size from boulders as large as a house to collodial clay. This grinding and mixing was a mechanical process, without causing chemical decomposition of the rock but preparing it for subsequent decomposition to soil and effective release of nutrient elements. As with the Ogallala alluvial deposits, so are the glacial deposits in the increased-longevity area a series of complex, only partially decomposed mixtures, from diverse sources.

Glacial drift is the surficial rock in the increased-longevity area in Iowa, Minnesota, and Wisconsin, except for the unglaciated Driftless Area, which is covered with wind-deposited loess.

Windblown Loess Deposits

Superimposed upon the alluvial deposits and glacial drift are windblown and wind-mixed materials, whose derivation began in Tertiary time, culminated during the Pleistocene, and actively continues today. Maximum deposition of windblown silts and clay occurred in the intervals following the melting of detritus-laden continental ice sheets. During glacier melting, swollen streams of glacial meltwater, heavily charged with a mineralogical mixture of sand, silt, and clay-sized particles, flooded their valleys and outlying areas and dropped much of their suspended load on their flood plains. Gusty winds, actuated by temperature differences between that which was latitudinally normal for the region and that of the ice, forced down by gravity from the north, whipped up silt and clay from the dusty flood plains and spread the dust upon the uplands. This loess is the major deposit, along with smaller amounts of drifted sand and dunes shown by the stippled pattern in Figure 22.

Over much of western Kansas, overlying the Ogallala Formation, is a long-recognized, geologically mapped loess formation, called the Peoria Loess, of early Wisconsinian age (the last advance of the Pleistocene continental glaciation). Swineford and Frye (1951), who have comprehensively studied the Peoria Loess, described its petrography as follows:

> The surficial material throughout about one-third of [western] Kansas is the Peoria silt (loess). Samples of this loess from an area 400 miles E-W, by more than 200 miles N-S...show the major constituents of the silt-size fraction are quartz (more than half), feldspars, volcanic-ash shards, carbonates, and micas....The clay fraction consists of montmorillonite, illite, calcite, quartz, and feldspar, with a trace of kaolinite minerals.

The source of the loess was described,

> Considering that air currents transported and deposited the extensive blankets of upland loess in Kansas...the valley flats of the major drainageways present the only available source for aeolian silts....These outwash-carrying valley sources...[thus the latest windblown dusts were derived via alluvial processes from glacial outwash sources]. The total volume of silt included in the Peoria is large--57 cubic miles in Kansas if we assume an average thickness of 10 feet over 30,000 square miles.

An average chemical composition (Swineford and Frye, 1951) from 17 analyses of the Peoria Loess follows:

Compound	Percent by Weight
SiO_2	71.36
Al_2O_3 and TiO_2	12.57
Fe_2O_3	3.12
CaO	2.94
MgO	1.62
K_2O	2.68
Na_2O	1.54

Although the Nebraska and Colorado Geological Surveys have not mapped or published reports on the surface deposits in their increased-longevity counties as did Kansas, Lugn (1935, page 16) mapped the Nebraska counties as the "Small Loess Plains," and Scott (in Weimar and Haun, 1960, page 206) wrote of "alluvium and wind-blown loess" east of the Front Range in Colorado. Details of the geology in Kansas are described and discussed in separate county reports of the Kansas Geological Survey Bulletins 89, 99, 105, and 108 (Moore et al., 1951; Frye and Leonard, 1952; Prescott, 1953; Prescott et al. 1954). Pertinent Nebraska geology is treated in the Nebraska Geological Survey Bulletins 10, 14, and 23 (Lugn, 1935; Condra and Reed, 1943; Reed and Dreeszen 1965); and a summary of Colorado geology is in a publication edited by Weimer and Haun (1960).

Although traditional geologic history treats of the earth in ages past, our concern with longevity effects includes also present-day geologic processes. Even though the age of the Peoria Loess has been referred to the Pleistocene, possibly as much dust is being moved today, or more in times of dust storms (Idso, 1976) than in quiet intervals of the Pleistocene. From estimates made from direct measurements at 37 stations distributed between North Dakota and Texas, Hagen and Woodruff (1973, 1975) reported in Figures 23 and 24 that

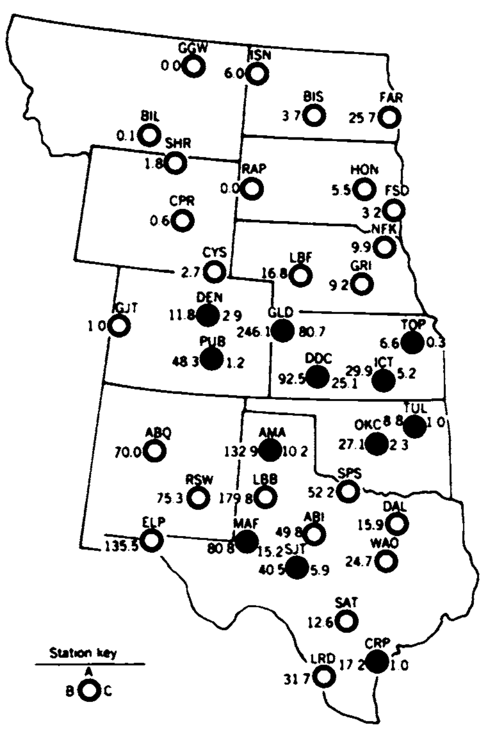

FIGURE 23 Plot of 37 Great Plains locations showing station abbreviation (A), average annual dust passage in thousands of tons per vertical square mile for the 1950's (B), and 1960's at 12 Southern Plains stations (C) (solid circles) (Hagen and Woodruff, 1975).

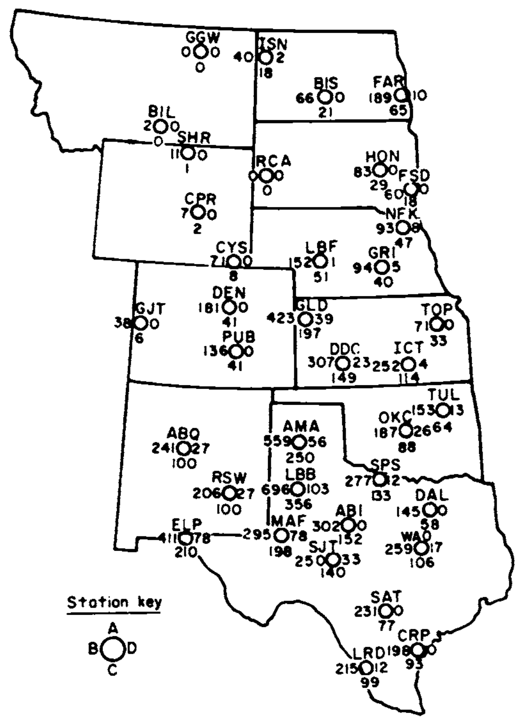

FIGURE 24 Plot of stations showing station abbreviation (A), maximum annual number of dusty hours (B), average annual number of dusty hours (C), and minimum annual number of dusty hours (D) at 37 Great Plains stations during 1950's (Hagen and Woodruff, 1973).

"...we get 244 million tons of dust suspended annually in the 1950's." They quote Smith et al. (1970) from measurements of dust deposition at five rural locations ranging from Nebraska to Texas and "reported 488 lb/acre/yr deposited on the surface." At Goodland, Kansas, it was calculated that 246,000 tons of dust passed through one vertical square mile of the atmosphere. Many of us can recall the severe "dust bowl" conditions of a few decades back. The volume of dust is indeed significant, and dust in the air is as valid a geochemical "rock" agent as are solid rocks on the ground, and certainly more important from a respiratory viewpoint.

Partly decomposed rock dust can furnish to the digestive tract a supply of "delayed action" or "slow release," constituents of the rock, analogous to the television ads showing that "delayed-action aspirin" lasts for x hours. Rock dust, of course, also has furnished nutrients to man via food plants grown on it and in drinking water that has percolated through and dissolved the dust. The potential importance of this phase as a direct source of geochemical material in man is discussed by Hopps in Chapter 12.

Thus, quite clearly, the long-lived residents of the Great Plains increased-longevity belt indeed live intimately with the geological system and geochemical environment of which they are a part. How much this affects their longevity is open to question.

Geochemical and Climatic Factors

A rich, mixed suite of rocks is the initial factor of the geochemical scenario in the increased-longevity area. The rocks serve as (1) the primary materials on which (2) the energy of climate operates (3) to reduce physically the sizes of the rock fragments and to (4) decompose them chemically by action of water, carbon dioxide, oxygen, and organic agents.

The primary rocks (igneous and metamorphic) are composed mainly of minerals in which the metallic cations that serve as major nutrients for plants and animals, e.g., calcium, magnesium, potassium, sodium, and iron are tightly combined as silicates. After chemical weathering, which slowly decomposes the silicates and releases the cations in solution, these elements are available to plants (Keller et al., 1963; Keller and Reesman, 1963). Agents of chemical weathering include water, which acts via hydrolysis of the silicates; oxidation by O_2, especially of Fe^{2+} mineral compounds; carbonation by CO_2 and dissolution in water of calcium, magnesium, sodium, potassium, and iron; and not least, organic reactions that break down silicates at least five ways. These organic reactions include chelation or complexing with organic compounds, the acid of fulvic-humic acid (Huang and Keller, 1970; 1972), the chemical action of bacteria coating the rock and mineral grains, the exchange of H^+ from living root hairs for metal cations (the energy for this reaction is solar-photosynthetic), and reaction with decomposing (dead) organic materials.

Postglacial climate was especially favorable for chemical weathering and the development of rich, organic soil, which is abundant in the highly productive farming areas within the increased-longevity belt. Postglacial plants that grew during the summers and dropped to become ground litter in the fall were decomposed to humus, which was largely preserved in the soil during the cool winter and spring seasons, adding nutrient-rich organic material to the almost black, fertile soil.

Such preservation would not have occurred if the climate had been tropical, where, because of higher year-round temperature, bacteria break down plant residues and accelerate oxidation of the organic compounds to CO_2 and H_2O. Soils then lose organic matter down to a low content and change color from gray to the reds and browns of oxidized iron compounds.

Another feature of chemical weathering in the longevity area today is that it controls the species of clay mineral that are produced. The western part of the increased longevity area now has a semiarid climate where the annual rate of evapotranspiration equals or exceeds the annual precipitation (see Figure 25). The crucial result of this ratio is the dominant drying effect following rain. The rain falling on the loosely consolidated rock particles begins hydrolysis of the silicates or dissolves carbonate mineral if it is present. Where there is semiaridity, the dissolved ions (of calcium, magnesium, potassium, sodium, and strontium) are only partly, or not at all, leached away from the weathering system. Evaporative drying of the rocks, which

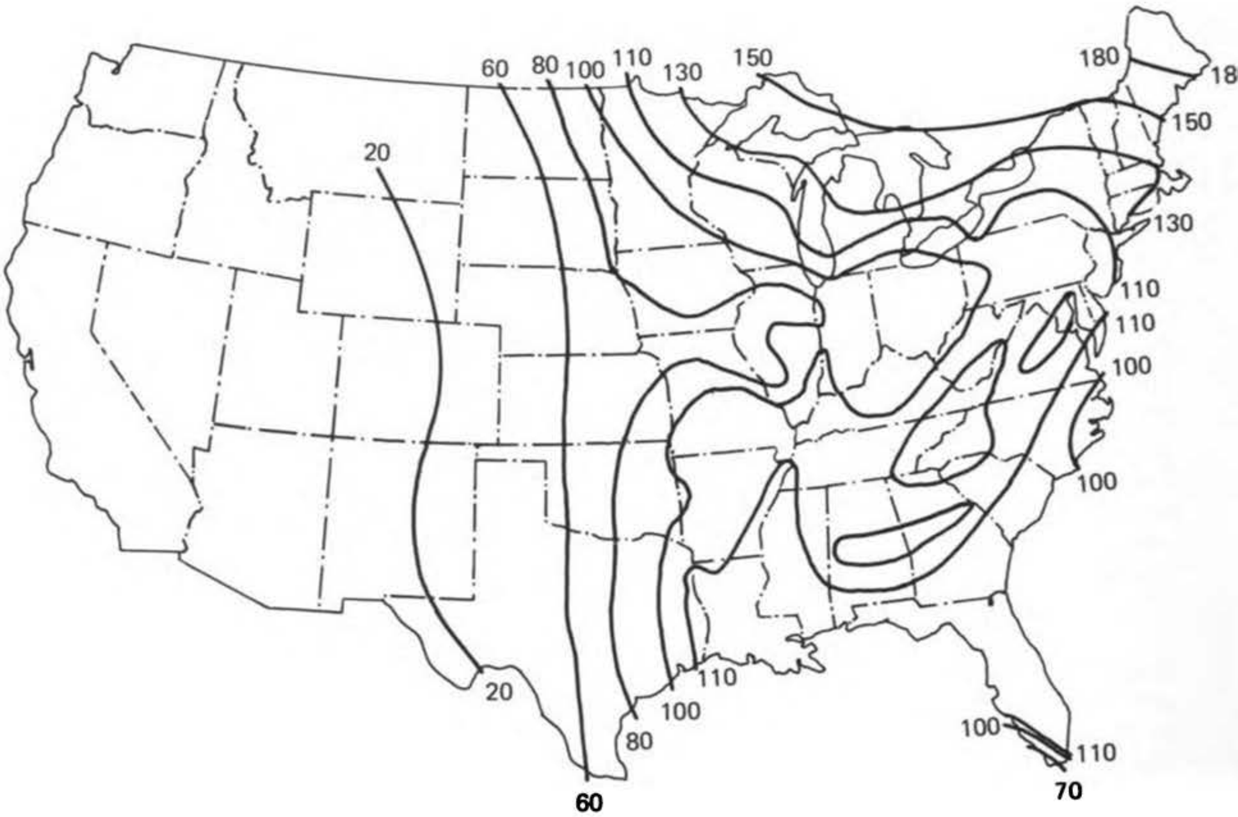

FIGURE 25 Lines showing constant ratios of rainfall to evaporation (times 100) across the United States (Albrecht, 1947; Jenny, 1941).

begins shortly after rain ceases, increases the concentration of dissolved ions in the remaining interstitial water to the extent that those metal cations react with the aluminium-silicate complex to form smectite-type clay minerals.

Smectite clays typically not only contain magnesium and iron in the crystal structure but have a high cation-exchange capacity for calcium, sodium, and potassium, which are loosely held and become easily available for exchange with H^+ ions produced on plant roots during photosynthesis. Thus, the semiarid climate of the increased-longevity area tends to produce a clay mineral that is optimal for rich plant nutrition.

Calcium and magnesium, which are dissolved from carbonate minerals by rain, tend to be carried down or laterally to groundwater. However, in the drying cycle on the surface or in the groundwater aquifer, which alternates in the semiarid increased-longevity area, the groundwater is pulled back up and is evaporated near the land surface, whereupon its dissolved load of calcium and magnesium is deposited as salts (such as carbonate and sulfate) within interstices of the soil or as concretions in the upper parts of loess as formations called loess-kinder and loess-püppchen. Again, calcium and magnesium are retained in the soils in a form easily available for plants, animals, and groundwater and, thence, consumption by the human inhabitants.

Although precise analytical data on trace elements that may be dissolved in the groundwater are scant, the fact that these elements do go into solution when silicate rocks are pulverized under water was clearly demonstrated (Reesman, 1961).

Two items of potential significance to health are implied in the availability of nutrient elements from rocks of the increased-longevity zone. A wide variety of major and (biological) trace elements are available, which presumably satisfied what Williams calls a "balanced team of nutrients" and which "unlike drugs, single nutrients always act constructively like parts of a complicated machine, and are effective as nutrients only when they participate as members of a team" (Heffley and Williams, 1974).

The second item, which is less firmly documented, relates specifically to selenium. As a deoxidant, selenium in favorable concentrations has been suggested as a positive factor in longevity. In the semiarid increased-longevity belt, selenium has been released from the rocks but not entirely leached away. It is the region from which food sources of selenium are obtained from grain-derived foods, such as wheat, bran, and their associated products, some of which enter the human food chain. Thus selenium available from the geochemical environment may be a favorable factor in the increased-longevity region.

Peripheral to the lithosphere, but certainly a part of the geological and geochemical environment in the increased-longevity area, is the atmosphere and its role in climate. Elevation of the land is 300 to 1500 m above sea level in the increased-longevity area. It has been suggested that this may contribute to increased longevity.

ROCKS, DUSTS, AND CLIMATIC FACTORS IN THE DECREASED-LONGEVITY AREA

The rocks underlying the high-death-rate or decreased-longevity area are primarily weakly consolidated sediments of a Coastal-Plain type--i.e., deposits laid down landward and seaward for relatively short distances from an ancient marine shoreline. They range in age from Quaternary (Recent or Holocene) back through the Tertiary into the Upper Cretaceous of the Mesozoic Era.

A brief explanation of nomenclature may aid in clarifying the use of the term "Coastal-Plain sediments" with "Coastal-Plain occurrence" or topography. The high-death-rate area is concentrated in the present "Coastal Plain," southeast of the "Fall Line," where waterfalls occur in the streams as they cross the Appalachian-type, hard rocks on the west to the easily eroded sediments to the southeast. Hence, southeastward, or seaward of the Fall Line, is the low-lying, topographical coastal plain, which extends to the present-day coastline of the Atlantic Ocean on the continent. The sandy and clayey sediments that comprise the surficial rocks of the decreased-longevity area (hence, underlying the topographic coastal plain) were deposited on an ancient coastal plain of Cretaceous age, which has continued to the present at or near the present coastline. Thus both the topography and the rocks are "Coastal-Plain" in type.

Lithologically, the rocks of the high-death-rate area are dominated by relatively clean quartz (SiO_2) sands, kaolinitic ($H_4Al_2Si_2O_9$) clays, and interspersed marls [clayey limestone, $CaCO_3$, and dolostone, $CaMg(CO_3)_2$].

It is these surficial rocks that interface with man's living environment in this high-death-rate area. The weathering regime in this area, however, is geochemically entirely different, indeed opposite, to that in the low-death-rate area modeled by Figure 26. Whereas the geochemical environment of the increased-longevity area is shown at the left-end, or nutrient-rich, part of the graph, the geochemical environment of the decreased-longevity area is represented by the right-end, or nutrient-depleted, part of the graph.

Precipitation in the decreased-longevity region (Figure 20), characteristically exceeds evapotranspiration (see Figure 25). The excess rainwater in the warm climate of the decreased-longevity region consequently has leached and continues to lower the originally scanty nutrient-element contents of the rocks to lower levels, as indicated at the right-hand end of the graph (Figure 26). Only quartz, kaolin clay, and iron oxides remain.

The clay mineral in the soil and in the underlying rocks is kaolinite, $H_4Al_2Si_2O_9$. This mineral contains H^+ in the

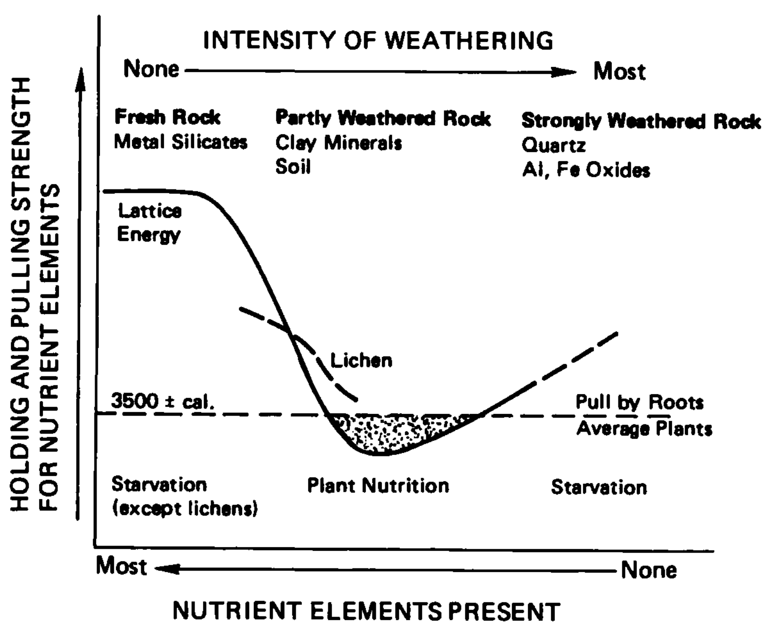

FIGURE 26 Diagrammatic representation of the nutrient, metal cations present on rocks and minerals, their holding (bonding) strengths as affected by the degree of their weathering, and a representative level of exchange bonding energy of plant rootlets. The 3500± cal per chemical equivalent line approximates the mean-free bonding energy of either roots and/or soil for nutrient elements. Roots can pull from soil or the soil can pull nutrient elements from seeds or rootlets (Keller, 1961).

aluminium-silicate complex, rather than calcium, magnesium, and potassium. The latter cations have been leached by excess rain, whereupon H^+ from the water and carbonic acid have taken their place. Even over a marl or clayey limestone, where calcium and magnesium were originally present, they have now been leached, leaving a reddish (iron oxide) kaolinitic residue. Acid soils are produced unless ameliorated by an agstone supplement containing alkaline earth cations.

In support of the foregoing statements that the coastal plain soils are severely leached of calcium and magnesium, analyses of such soils show a CaO content of the order of only 0.1 to 0.4 percent, and MgO usually less in amount than CaO (data from the U.S. Geological Survey Rock Analysis Storage System; Bennett, 1921). These are in accord with Hilgard's average values quoted by Jenny (1941) for alkaline earths in humid soils as CaO, 0.41 percent; MgO, 0.37 percent. They are dramatically lower than the values for the previously cited Peoria Loess, CaO, 2.94 percent; MgO, 1.62 percent, in the increased-longevity area.

With respect to the minor elements in the leached areas of the high-death-rate (decreased-longevity) area, no comprehensive data are available for either mobile or total contents of trace elements, but it seems safe to surmise that they are comparably less, because of leaching, than the amounts of trace elements present in the partially weathered rocks of the increased-longevity area.

The clay mineral most stable, or most nearly stable if lateritic minerals are developed in the leached rocks, is kaolinite. The cation exchange capacity of kaolin clay minerals is about one twentieth that of the smectite minerals. Kaolin is, therefore, less efficient as a conveyor of nutrient cations to plant rootlets.

The organic fraction, although an efficient conveyer of nutrient ions, is significantly lower in amount in the warm decreased longevity area than in the increased-longevity area.

In anticipation of the question commonly asked when such a leached condition of the high-death-rate area is described, "How then is agriculture maintained in this area?", I quote the stock answer of the late W. A. Albrecht, Professor of Soils at the University of Missouri (1947):

> The lushest vegetation grown in the warm, humid region of leached soils is the type characterized by C, H, and O, i.e., genetically characterized by fresh air, water and sunshine (CO_2, H_2O, solar energy). It therefore best produces cellulose (wood), fiber as cotton, and sugar, which are composed mainly of C, H, O.

Lush vegetation does not necessarily mean high-nutrient plant foods.

With appropriate soil management, and the addition of adequate nutrient-supplying supplements, such as either indigenous or introduced organic matter, or rock and mineral fertilizers, the agricultural environment can become highly nutritionally productive. Without nutrient availability, however, the characteristic C-H-O type of vegetation prevails.

Protein production, on the other hand, again quoting Albrecht, inherently comes from regions where "Ca (necessary) and N-fixing elements and processes prevail." Such regions were identified by Albrecht as the regions of buffalo grass and hard wheat, which overlap the increased-longevity area.

Geologic Formations

Brief descriptions of the geological formations typical of the Coastal Plain sediments were given by Sandy et al. (1966) as follows:

> The Tuscaloosa Formation, Cretaceous in age, consists of arkosic sands and gravels, with streaks, lenses, and beds of kaolinitic sands and kaolin. The middle Eocene McBean Formation, which unconformably overlies the Tuscaloosa Formation, consists of calcareous sands and clays mixed with soft, richly fossiliferous limestones and marls. The Barnwell Formation, which unconformably overlies the McBean Formation, consists largely of brick-red sands with beds and lenses of opal claystone (fuller's earth) near the base.

Airborne Rock Dusts, Urban and Rural, as Possible Nontraditional Geochemical Factors Affecting Longevity

Dust, which is pulverized rock (typically in suspension in the air), can adversely affect human health and longevity. If the dust is freshly pulverized quartz, with fresh fracture surfaces, silica can induce silicosis, asbestos can induce asbestosis, and exposure to certain types of coal-mine dust can lead to black-lung disease.

On the other hand, practically no consideration has been given to possible beneficial effect of dust to human health and longevity as, for example, to residents in the increased-longevity area. Certainly in at least the western part of this area, abundant dust is an inescapable daily part of life of the residents in this region.

The dust in the increased-longevity area necessarily will contain, and provide, the major chemical elements cited in the mean analysis of the Peoria Loess, as well as the minor, or trace, elements in those rocks and minerals. Calcium and magnesium carbonate rocks and minerals will supply readily available calcium and magnesium. It seems probable that selenium (deoxidant) would be present in intermediate natural concentrations typical of the rocks. That ambient dust reflects the local geology, ocean vapor, and industrial fumes of an area was well demonstrated by Shacklette and Connor (1973) in their research on the way it occurs and is collected on Spanish moss. Particulate matter inhaled as dust can be ingested by the action described by Hopps in Chapter 12.

Curiously, although quartz is an abundant component of natural dust in the plains region, apparently it does not provoke significant silicosis there. A suggested explanation has been that such "old" quartz dust, whose surface has been exposed to aluminous and other rock-forming compounds, no longer carries active, unsatisfied valence charges on the oxygens at the surface of the quartz particles. On the other hand, freshly fractured quartz, as where freshly pulverized in a mine, carries many active, unsatisfied valence charges of the oxygen ions exposed on the "new" fracture surfaces of the SiO_2 (quartz) compound.

Urban Dust

Corollary to natural dust, anthropogenic dust increasingly created and dispersed in modern industrial and urban centers may well be considered as a factor in environmental health in both the increased- and decreased-longevity areas. Urban dust no doubt reflects the vaporous and particulate contributions of the streets and the residential and industrial activities of the city as effectively as did the examples of rural contributions described by Shacklette and Connor (1973). Reports of mineralogical analyses of urban dusts are not numerous, but as an example, Armstrong and Buseck (1977) found in dust from Phoenix, Arizona, such common, rock-forming minerals as quartz, clay minerals, bauxite, micas, amphiboles, feldspars, calcite, gypsum, pyrite, iron oxides, zircon, ilmenite, and rutile. Accompanying particulates included zinc-bearing tire dust, zinc from a metal plating plant, and zinc from each of two zinc foundries. Zinc from tire dust and the plating plant could be easily distinguished from foundry zinc. Dust from two secondary iron foundries could be differentiated, although the particles from each source had complex compositions that required quantitative analyses of individual particles. Lead concentrations from foundry effluent could be distinguished by individual particle analyses from the lead in auto exhaust. Arsenic and zircon concentrations were higher than normal in air samples taken downwind from a copper smelter. Copper and zinc were concentrated on the surface of the latter particles.

It was found that particles of anthropogenic origin were sorbed on both relatively coarse dust--too coarse to be inhaled under ordinary circumstances--and on very fine dust as could be subject to inhalation. The coarser particles--too coarse to be inhaled--by sorbing would tend, therefore, to be beneficial scavengers of otherwise noxious or toxic substances, whereas the finer particles, which may be inhaled, can act as vehicles to carry toxic substances into the inhaler.

It would be expected that city air and dust will contain aromatic or asphaltic carbon-ring compounds (carcinogenic), pulverized rubber tire dust, asbestos from brake linings and insulation, lead from auto exhaust, sulphur in various compounds, fumes of ferrous and nonferrous metals (including mercury, cadmium, lead, and other toxic concentrations of metals), and fly ash from coal and petroleum combustibles and their unburned compounds. Such dusts and atmospheres are not the ones under which humans evolved or were stabilized. In their effects on health, they are in great contrast to the rural rock dust of the increased-longevity region. Making analyses of the ambient air and the vapors, fumes, and the individual dust particles it carries, using the techniques of microprobe and scanning electron microscope (SEM) as described by Armstrong and Buseck (1977), is a necessary area of research within the geochemical environments related to aging and health.

COMMON DENOMINATORS, SUMMARY, AND PERSPECTIVES

Common Denominators of the Surface Rocks and Climate in the Increased-Longevity Area

The several qualities held in common, i.e., "common denominators," by the surface rocks and climate, contributory to the geochemical environment in the increased-longevity area extending from eastern Colorado to Wisconsin are summarized as follows:

1. The surface rocks are rich mixtures of igneous, sedimentary, and some metamorphic types, encompassing all the major and minor elements on which organic evolution has thrived. The full inorganic fare is there.
2. The surface rocks have been pulverized to a physical condition of near-maximum reactivity to the chemical energies of the aqueous fluids of inorganic, plant, and animal systems. The pulverizing agents were temperature effects, ice, water, and wind.
3. Chemical decomposition of the comminuted rock and mineral particles has progressed only part way, which is the optimum stage for further release of major and minor nutrients (Keller, 1961).
4. Climate has been optimal to produce high ion-exchange clay minerals, and preservation of organic residues, which are also nutrient-rich and high in ion-exchange capacity.
5. The work of the wind has mixed, indeed homogenized, the rock-derived materials, and, because of their fine particle size, the wind has carried them intact into man's living environment, including his respiratory and digestive systems.
6. Climate and rocks have preserved large amounts and high concentrations of calcium and magnesium in the soil, water, and dust in the air--the media of the geochemical environment.
7. The wide range of minor elements that are present in the primary rocks, indeed those on which organic evolution has progressed, are available for human ingestion in the same ratio as they occurred in the rocks. The minor elements may be ingested as rock dust or as products of solution of the rocks in water.
8. The annual rate of precipitation in the increased-longevity area is less than the potential rate of evapotranspiration.
9. The atmospheric climate of the increased-longevity region may be characterized by a barometric pressure typical of moderately high altitude (300 to 1500 m) and as being relatively dry, cool, and typically with air in motion much of the time. The vapor pressure of body fluids via lungs and skin well exceeds the partial pressure, or back pressure, of atmospheric surroundings.

Common Denominators of the Surface Rocks, Dusts, and Climate in the Decreased-Longevity Area

1. The surface rocks are typically Coastal-Plain sediments composed of poorly consolidated sands and clays.
2. Annual precipitation in the area is in excess of evaporation, resulting in removal of water-soluble constituents in the rocks.
3. The warm climate of the region increases the rate of chemical dissolution of the rocks and destruction of organic residues.
4. The relatively porous sands and sandy clays of the region are highly leached and relatively low in essential nutrient elements.
5. The leached residues of the rocks are quartz and other resistant, sand-sized minerals, and lateritic clay compounds, i.e., kaolin, and hydrated aluminum and iron oxides.
6. Chemical analyses of these leached rocks show them to be high in silica, alumina, and iron oxides. Notably low is their content of calcium, magnesium, potassium, and trace elements.
7. The atmospheric climate of the decreased-longevity high-death-rate area may be characterized as low altitude, moderately moist, and warm to subtropical.

Summary and Perspectives

Clearly defineable common denominators in chemical and mineral properties characterize the surficial rocks (those that interface with man's living environment) present in the low- and high-death-rate areas of the United States. The common denominators are strikingly different between the two areas with respect to macro and micro nutrient ions that are available from the rocks to man. The contrasting differences in the properties of the rocks are positively correlative with the differences in death rates in the two areas.

Such correlations, however superficially appealing, do not necessarily prove that the rocks are major contributors to the health and longevity in the low-death-rate decreased-longevity area. Nevertheless, because of the statistical consistency of the connection of the diverse alluvial, glacial, and aeolian surficial rocks to longevity, further extended investigation appears to be merited. In addition to appropriate medical tests, the contribution of rocks to superior nutritious food grown on their soils, to drinking water drawn from their groundwater, and to dust in the atmosphere should be examined in much greater detail.

The properties of the atmosphere as they relate to aging merit more investigation, including the possible effects of relative humidity, mean barometric pressure, ionic charge, and motion of the air on human health. Furthermore, the dust and fumes, both natural and anthropogenic, in the air may not be passive in their action and may actively affect human health.

In a holistic view of general health conditioning, the question should be asked whether the <u>combined</u> effect of the multiple geochemical factors in the two areas studied may be contributing to the differences in life spans? Taking away, or adding, any single one of the rock properties may not affect health and longevity to a quantifiable degree, but all of them in each area may by "team work or synergism" account for the dramatic statistical difference in death rates in the two areas.

REFERENCES

Albrecht, W. A. 1947. Our teeth and our soils. Ann. Dentistry 6:199-213.

Armstrong, J. T., and P. R. Buseck. 1977. The chemical composition, morphology and surface properties of individual airborne particles. Preprint, and Proceedings of the 4th International Clean Air Congress. S. Kasuga, ed., Japan Union Air Pollution Prevention Assns., pp. 617-620.

Bennett, H.H. 1921. The Soils and Agriculture of the Southern States. MacMillan, Inc., New York, N.Y., 300 pp.

Condra, G. E., and E. C. Reed. 1943. Geological Section of Nebraska. Nebraska Geological Survey Bulletin 14. 74 pp.

Frye, J. C., and A. B. Leonard. 1952. Pleistocene geology of Kansas. Bulletin 99. Kansas Geological Survey. Lawrence, Kansas. 225 pp.

Frye, J. C., A. B. Leonard, and A. Swineford. 1956. Stratigraphy of the Ogallala Formation (Neogene) of northern Kansas. Geological Survey of Kansas Bulletin 118. 90 pp.

Geological Society of America. 1952. Pleistocene eolian deposits of the U.S., Alaska, parts of Canada: Map. Geol. Soc. Am., Boulder, Colo. Geological Society of America. 1954. Glacial map of the U.S. east of the Rocky Mountains. Geol. Soc. Am., Boulder, Colo.

Hagen, L. J., and N. P. Woodruff. 1973. Air pollution from dust storms in the Great Plains. Atmos. Environ. 7:323-332.

Hagen, L. J., and N. P. Woodruff. 1975. Particulate loads caused by wind erosion in the Great Plains. Air Poll. Control Assoc. J. 25:860-861.

Heffley, J. D., and R. J. Williams. 1974. The nutritional teamwork approach: prevention and regression of cataracts in rats. Proc. Nat. Acad. Sci. 71:4164-4168.

Huang, W. H., and W. D. Keller. 1970. Dissolution of rock-forming silicate minerals in organic acids. Am. Mineral. 55:2076-2094.

Huang, W. H., and W. D. Keller. 1972. Organic acids as agents of chemical weathering of silicate minerals. Nature, Phys. Sci. 239(96):149-151.

Idso, S. B. 1976. Dust storms. Sci. Am. 235(4):108-114.

Jenny, H. 1941. Factors of Soil Formation. McGraw-Hill, New York, 281 pp.

Keller, W. D. 1957. Principles of Chemical Weathering. Lucas Bros. Publisher, Columbia, Missouri.

Keller, W. D. 1961. Mineral and chemical alluviation in a unique pedologic example. J. Sed. Petrol. 31:80-86.

Keller, W. D., and A. L. Reesman. 1963. Glacial milks and their laboratory-simulated counterparts. Bull. Geol. Soc. Am. 74:61-76.

Keller, W. D., W.D. Balgord, and A. L. Reesman. 1963. Dissolved products of artificially pulverized silicate minerals and rocks: Part I. J. Sed. Pet. 33:191-204; Part II, 420-437.

Lugn, A. L. 1935. Pleistocene geology of Nebraska. Nebraska Geological Survey Bulletin 10. 215 pp.

Moore, R. C., J. C. Frye, J. M. Jewett, W. Lee, and H. G. O'Connor. 1951. Kansas rock column. Geological Survey of Kansas Bulletin 89:132 pp.

Prescott, G. C. 1953. Geology and Groundwater Resources of Sherman County. Geological Survey of Kansas Bulletin 105. 129 pp.

Prescott, G. C., J. R. Branch, and W. W. Wilson. 1954. Geology and groundwater resources of Wichita and Greeley Counties. Kansas Geological Survey Bulletin 108. 133 pp.

Reed, E. C., and V. H. Dreeszen. 1965. Revision of the Classification of the Pleistocene Deposits of Nebraska. Nebraska Geological Survey Bulletin 23. 64 pp.

Reesman, A. L. 1961. Dissolved minor elements in the hydrolysis of 67 silicate rocks and minerals. Unpublished Master's Thesis, Library, University of Missouri-Columbia.

Sandy, J., R. E. Carver, and T. J. Crawford. 1966. Stratigraphy and economic geology of the coastal plain of the central Savannah River area, Georgia. Guidebook, Field Trip No. 3, 1966. Southeastern Section, Geol. Soc. Am., Boulder, Colorado 29 pp.

Shacklette, H. T., and J. J. Connor. 1973. Airborne chemical elements in Spanish moss. U.S. Geol. Survey Prof. Paper 574-E. 46 pp.

Smith, R. M., P. C. Twiss, R. K. Krause, and M. J. Brown. 1970. Dust deposition in relation to site, season, and climatic variables. Soil Sci. Soc. Am. Proc. 34(1):112.

Swineford, A., and J. C. Frye. 1951. Petrography of the Peoria Loess in Kansas. J. Geol. 59:306-322.

U.S. Geological Survey. 1970. The National Atlas of the United States of America. U. S. Department of the Interior, Washington, D.C.

Weimer, R. J., and J. D. Haun, eds. 1960. Guide to the geology of Colorado. Geol. Soc. Am., Boulder, Colorado. 310 pp.

9

CONTRASTS IN DRINKING-WATER QUALITY BETWEEN THE INCREASED-LONGEVITY LOW-DEATH-RATE AREA AND THE DECREASED-LONGEVITY HIGH-DEATH-RATE AREA IN THE UNITED STATES

Gerald L. Feder

Significant differences in the climate and geology of relatively high- and low-death-rate areas (Figure 3, outlining the increased-longevity and decreased-longevity areas compiled by Sauer, Chapter 3) are discussed in Chapters 8 and 10. There are also important differences in the quality of drinking water in these areas. The purpose of this chapter is to compare and contrast available water-quality data from the two areas and to identify significant similarities and differences. Unfortunately, only limited trace-element data are available for drinking waters of these areas; so, of necessity, the emphasis is on major cations and anions. Most of the data used in this report are derived from the Water Quality Data Storage and Retrieval System (WATSTORE) of the U.S. Geological Survey and from reports on county or regional hydrologic studies that contain water-quality data.

WATER QUALITY AND HEALTH

Drinking water may make an important contribution to total dietary intake of required macro and micro elements essential for human health and may affect the desirable balance of these elements. Drinking water in the increased-longevity (low-death-rate) area may supply all, or a large percentage of, the daily Recommended Dietary Allowance (RDA) (NRC Committee on Dietary Allowances, 1980) for many chemical constituents; persons living in the decreased-longevity (high-death-rate) area generally obtain only a small percentage of their RDA from drinking water. In addition to supplying dietary needs, drinking water may contribute certain dissolved substances in toxic concentrations (U.S. Environmental Protection Agency, 1976). Many trace elements found in water may be required for health; however, above certain levels they are toxic. Certain elements even reduce the toxic effects of other elements; for example, selenium is reported to reduce the toxicity of mercury (Parizek *et al*., 1974). Hopps (1978) points out,

> As our environment becomes more and more polluted, it is obvious that the protective actions by essential trace elements...are becoming more and more important. Once again, however, the matter of dose is critical..., because of the

complexity of nutrient-toxicant interactions, heavy metal toxicity can be increased by ingesting too much of certain vitamins or minerals.

None of the waters studied in either area, for which complete chemical analyses were available, had concentrations of toxic elements exceeding EPA guidelines. However, as Craun and McCabe (1975) report, waters may pick up toxic concentrations of trace elements from plumbing, especially in areas using lead pipes. In such areas, the corrosiveness of water to plumbing is considered an important factor. Schroeder and Kraemer (1974) speculated that high cardiovascular death rates related to certain soft-water areas might be caused by cadmium leached from galvanized and copper pipes by corrosive acidic waters; such waters are common in the decreased longevity (high-death-rate) area studied here. Review of the analytical data available indicates that the pH of untreated waters in the decreased-longevity (high-death-rate) area ranges from about 5.5 to 7.0 in contrast to the pH of waters in the increased-longevity (low-death-rate) area, which ranges from about 7.0 to 8.5. If leaching of toxic substances from plumbing is the major water factor in human health, this difference in the pH of waters of the two regions may be more important epidemiologically than the differences in major and essential trace-element composition of the waters. This problem requires further study. Even though acid rainfall has not been determined to be a problem in the decreased-longevity (high-death-rate) area, it should be monitored in the area because of the susceptibility of the low-dissolved-solids low-buffering-capacity waters of this area to effects from acid rainfall. If corrosiveness of the water in this area is shown to be important to health, further lowering of the pH of waters caused by acid rainfall could increase corrosive effects of the already low-pH waters. In addition, systematic studies of concentrations of trace elements and dissolved organic carbon (DOC) compounds in waters of both areas would be helpful in explaining the observed health effects.

WATER HARDNESS

Much of the evidence linking longevity with quality of drinking water relates to the beneficial effects of hard water (Schroeder and Kraemer, 1974; Neri *et al.*, 1972; Masironi *et al.* 1972; NRC Panel on the Geochemistry of Water in Relation to Cardiovascular Disease, 1979); thus, some comments about hard and soft waters are appropriate. Traditionally, hardness has been defined as, "the soap-consuming capacity of a water" (Hem, 1970). Early tests for hardness in water actually used a standard soap solution for titration. It is now generally recognized that alkaline-earth cations (Ca^{2+}, Mg^{2+}, Sr^{2+}, Ba^{2+}) are the main contributors to hardness, and water hardness is now reported as the sum of the equivalents of alkaline-earth cations converted to an equivalent amount of $CaCO_3$. Because calcium and magnesium are usually the predominant alkaline-earth cations in most natural waters, most hardness calculations are at present based on these cations. The following calculations are most common:

$$\text{milliequivalents per liter (meq/l Ca + meq/l Mg) } 50.05 = \text{total hardness as milligrams per liter (mg/l) } CaCO_3 \quad (1)$$

$$[\text{mg/l Ca } (0.04990) + \text{mg/l Mg} (0.08226)]\ 50.05 = \text{total hardness as mg/l } CaCO_3 \quad (2)$$

In Equations (1) and (2), the idea is to make a hypothetical solid ($CaCO_3$) by converting all the ions of the alkaline-earth metals in the analyzed water to calcium ions, and reacting the calcium ions with enough $CO_3^=$ ions (not necessarily present in the water sample) to produce solid $CaCO_3$. For example, using Equation (2), a water containing 100 mg/liter Ca^{2+} and no Mg^{2+} would have a total hardness of 249 mg/liter as $CaCO_3$.

As described above, total hardness is only related to the alkaline earth content of a water; actual anions present have no effect on the above calculations. A water containing 100 mg/liter Ca^{2+} and 50 mg/liter Mg^{2+} would have a total hardness of 455 mg/liter as $CaCO_3$ whether the predominant anion was Cl^-, SO_4^{2-}, or HCO_3^-. By these same criteria, if a water had very high HCO_3^- or $CO_3^=$ (used to calculate alkalinity) and no Ca^{2+} or Mg^{2+}, it would be very soft. The generally accepted classification for water hardness is as follows (Hem, 1970):

mg/liter Total Hardness as $CaCO_3$	Description
0-60	Soft
61-120	Moderately hard
121-180	Hard
More than 180	Very hard

Another commonly used method to describe hardness is as carbonate hardness and noncarbonate hardness. When using these descriptors, carbonate hardness is calculated by taking that fraction of hardness that is equivalent to alkalinity and reporting it as equivalent $CaCO_3$. If there are more equivalents of hardness than alkalinity, then excess hardness is reported as noncarbonate hardness.

The following calculations are used:

$$\text{meq/liter } (HCO_3^- + CO_3^=)^* \times 50.05 = \text{carbonate hardness, as } CaCO_3\text{, in mg/liter;} \quad (3)$$

$$[\text{meq/liter hardness} - \text{meq/liter } (HCO_3^- + CO_3^=)] \times 50.05 = \text{noncarbonate hardness, as } CaCO_3\text{, in mg/liter.} \quad (4)$$

*(HCO_3^- + $CO_3^=$) up to sum of meq/liter hardness

Whichever method is used, hardness is always based on the alkaline-earth content of the water. A water supply can have very high dissolved solids, but if it has little or no calcium or magnesium, it will be soft. For example, see Table 2, Samples B and C: both water

TABLE 2 Selected Chemical Analyses of Groundwater from the Increased-Longevity (Low-Death-Rate) Area

Sample	A	B	C
State	Minnesota	Nebraska	Nebraska
County	Fillmore	Dawson	Banner
Depth of Well	30 m	18 m	260 m
Calcium mg/liter	110	180	4.3
Magnesium mg/liter	28	58	1.1
Hardness (as $CaCO_3$) mg/liter	390	690	16
Hardness (noncarbonate) mg/liter	54	280	0
Sodium mg/liter	13	260	490
Potassium mg/liter	1.3	42	5.3
Bicarbonate mg/liter	410	492	886
Chloride mg/liter	27	48	250
Fluoride mg/liter	0.4	0.6	1.5
Sulfate mg/liter	34	740	44
Silica mg/liter	17	50	13
Total dissolved solids mg/liter	433	1650	1210
pH	7.6	7.6	8.0
Aluminum μg/liter	–	<10	<10
Arsenic μg/liter	2	10	2
Barium μg/liter	600	<10	<10
Boron μg/liter	60	350	3900
Cadmium μg/liter	<10	<2	<2
Chromium μg/liter	10	<10	<10
Cobalt μg/liter	–	<10	<10
Copper μg/liter	<10	3	6
Iron μg/liter	2700	40	190
Lead μg/liter	<100	<5	<2
Lithium μg/liter	–	50	50
Manganese μg/liter	80	<10	<10
Mercury μg/liter	<0.1	<0.1	<0.1
Molybdenum μg/liter	–	22	10
Nickel μg/liter	–	1	5
Selenium μg/liter	<1	–	<10
Strontium μg/liter	–	1300	220
Vanadium μg/liter	–	14	3.5
Zinc μg/liter	300	10	50

samples have more than 1000 mg/liter dissolved solids; however, Sample B represents a very hard water, while Sample C is a soft water.

DESCRIPTION OF AREAS

Water Quality in the Increased-Longevity (Low-Death-rate) Area

The increased-longevity (low-death-rate) area under consideration extends from Wisconsin and Minnesota, with a continental climate, to Colorado, with a semiarid climate. The precipitation in this area ranges from less than 40 to over 80 cm per year. In the northeastern part of the area, the ground surface is underlain by glacial drift up to several hundred feet thick. This unconsolidated material is only slightly leached and generally yields groundwater that is hard and contains relatively high concentrations of dissolved solids. A typical analysis is shown in Table 2 (Sample A).

The southwestern part of the increased-longevity (low-death-rate) area was not glaciated and is underlain by slightly weathered sediments consisting mostly of sandstones, shales, and some coals. These sedimentary rocks also yield groundwaters that are predominantly very hard with relatively high dissolved-solids concentrations. Owing to cation-exchange reactions with abundant clays in most aquifers in this region, groundwaters are softened as they move deeper in aquifers (Feder et al., 1977). These exchange reactions replace calcium, magnesium, and strontium in solution with sodium; total dissolved solids in the softened waters remain high. Typical analyses of groundwater from this region are shown in Table 2 (Samples B and C). Almost all rural households and most small towns (less than 10,000 population) in this area use groundwater for drinking-water supplies.

In areas where groundwater undergoes natural softening (Table 2, Samples B and C), very large differences in water quality may occur between adjacent households that use groundwater. Figure 27 shows this process diagrammatically and includes the effects of sulfate reduction by bacteria, which may also change the water quality. This change includes reduction of sulfate concentration to sulfide and precipitation of insoluble metal sulfides. Sulfides of most metals are very insoluble (Table 3), so that groundwaters that have undergone sulfate reduction to sulfide generally not only contain few trace metals in solution but the water containing sulfide ions would not be expected to dissolve metals from plumbing. Groundwaters that contain dissolved organic compounds (DOC) may transport trace elements as organic complexes or as adsorbed species; this may occur despite the presence of sulfide in the water. Most groundwater in the increased-longevity (low-death-rate) area probably contains less than

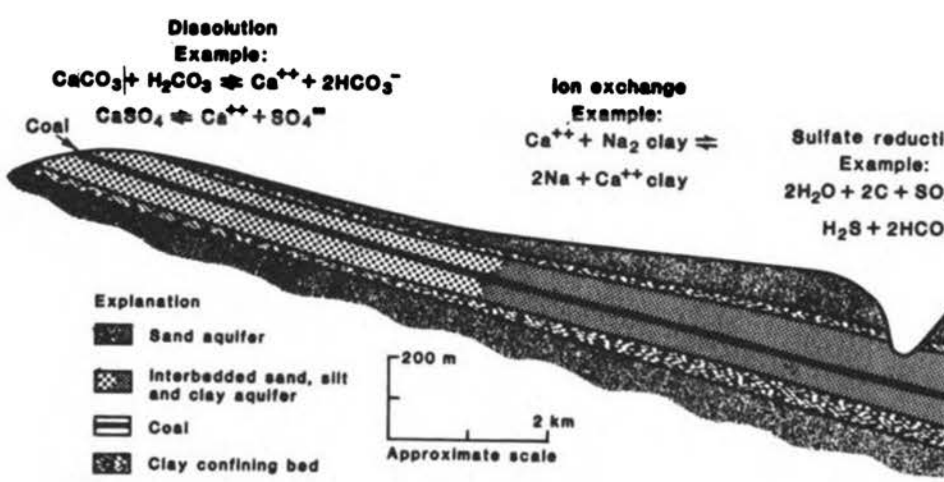

FIGURE 27 Diagram showing geochemical changes in groundwater resulting from ion-exchange and sulfate-reduction processes.

TABLE 3 Solubility-Product Constants of Common Metal Sulfides at 25°C, as Determined under Laboratory Conditions

Compound	Solubility Product Constant, K_{sp}
Manganese (II)[a] sulfide	8×10^{-14}
Iron (II) sulfide	4×10^{-17}
Zinc sulfide	1×10^{-20}
Cobalt (II) sulfide	5×10^{-22}
Nickel (II) sulfide	1×10^{-22}
Lead sulfide	4×10^{-27}
Cadmium sulfide	6×10^{-27}
Copper (II) sulfide	4×10^{-36}
Silver sulfide	1×10^{-50}
Mercury (I) sulfide	1×10^{-45}
Mercury (II) sulfide	1×10^{-50}

[a] I or II is the valence state of ion involved in metals with more than one valence state. For example, mercury (I) (Hg^{+} or mercurous sulfide) *at conditions given in heading*, is more soluble (10^{-45}) than mercury (II) (Hg^{++} or mercuric sulfide) (10^{-50}). Source: Gregg, 1963.

1.0 mg/liter of DOC. Leenheer et al. (1974) report a value of 1.0 mg/liter of DOC in groundwater from the Ogallala Formation.

Water Quality in the Decreased-Longevity (High-Death-Rate) Area

The decreased-longevity (high-death-rate) area under consideration is concentrated in the Coastal Plain physiographic province (Fenneman, 1938) in North Carolina, South Carolina, Georgia, and Alabama. The area is humid, with average annual precipitation of about 130 cm. Most of the near-surface sediments in this region are highly leached, except for a few formations containing carbonate minerals. Groundwater obtained from formations containing carbonate minerals is generally hard, with calcium the predominant cation. In contrast to the hard groundwaters of the increased-longevity (low-death-rate) area, these waters contain little magnesium. A typical analysis of groundwater from a carbonate formation is shown in Table 4 (Sample A). Groundwater obtained from formations without carbonate minerals is generally very soft and low in total dissolved solids. Groundwater from shallow wells in the Tuscaloosa Formation is generally among the softest and lowest in dissolved solids in this area. Table 4 (Sample B) shows a chemical analysis of groundwater typical of the Tuscaloosa. Almost all rural households and many small towns (less than 10,000 population) in this area use groundwater for domestic supplies. Where surface-water supplies are used, they are generally quite similar to shallow groundwater supplies. Table 4, Sample C, shows an analysis of a municipal water supply obtained from a stream draining a terrane predominantly underlain by rocks equivalent to the Tuscaloosa Formation; note the similarity of the analysis to the groundwater obtained from the Tuscaloosa Formation.

TABLE 4 Selected Chemical Analyses for Drinking Water Supplies from the Decreased-Longevity (High-Death-Rate) Area

Sample	A	B	C
State	Georgia	Georgia	North Carolina
County	Telfair	Houston	Richmond
Well Depth or Stream	195 m	119 m	Falling Creek
Calcium mg/liter	46	0.6	0.4
Magnesium mg/liter	9.2	0.4	0.6
Hardness (as $CaCO_3$) mg/liter	150	3	4
Hardness (noncarbonate) mg/liter	0	0	0
Sodium mg/liter	4.6	1.0	1.4
Potassium mg/liter	2.0	0.2	0.5
Bicarbonate mg/liter	200	4	4
Chloride mg/liter	6.0	2.0	3.2
Fluoride mg/liter	0.1	0.1	0.1
Sulfate mg/liter	2.4	<1	1.2
Silica mg/liter	26	7.9	4.7
Total dissolved solids mg/liter	196	15	28
pH	7.7	5.4	5.5
Aluminum μg/liter	<10	–	–
Arsenic μg/liter	<1	–	–
Barium μg/liter	–	–	–
Boron μg/liter	<10	–	–
Cadmium μg/liter	–	–	–
Chromium μg/liter	–	–	–
Cobalt μg/liter	–	–	–
Copper μg/liter	<1	–	–
Iron μg/liter	50	–	530
Lead μg/liter	<1	–	–
Lithium μg/liter	<10	–	–
Manganese μg/liter	50	–	<10
Mercury μg/liter	–	–	–
Molybdenum μg/liter	–	–	–
Nickel μg/liter	–	–	–
Selenium μg/liter	–	–	–
Strontium μg/liter	730	–	–
Vanadium μg/liter	–	–	–
Zinc μg/liter	50	–	–

Even though there are few data on the DOC content of the waters from this area, many old chemical analyses show a large difference between the dissolved-solids content of the water calculated from concentrations of inorganic ions and the dissolved-solid content measure by evaporating the water and weighing the residue. The 50 to 100 percent higher value often obtained for the calculation based on evaporative residue most likely reflects the dissolved organic constituents in the surface water and groundwater. The majority of the dissolved organic constituents are probably humic and fulvic acids (R. L. Wershaw, 1978, U.S. Geological Survey, oral communication). Fulvic and humic acids are strong complexing agents (Jenne and Luoma, 1977) and can bind many trace elements, reducing their availability to humans, even though these elements are present in drinking water.

Moreover, in the digestive tract, ingested fulvic and humic acids may bind trace elements normally available from other sources. This would be most likely to occur if the water contained very low concentrations of trace elements to begin with, as in parts of the southeast Coastal Plain area.

Comparison of Water Quality in the Increased- and Decreased-Longevity (Low- and High-Death-Rate) Areas

There have been no systematic areal studies of trace elements in water of either the increased-longevity (low-death-rate) area or the decreased-longevity (high-death-rate) area. However, many data are available on the dissolved major chemical constituents in waters of these areas. Figures 28-30 summarize available water quality data for some major chemical constituents in both these areas. The data points represent either a single value from water of a county within the study

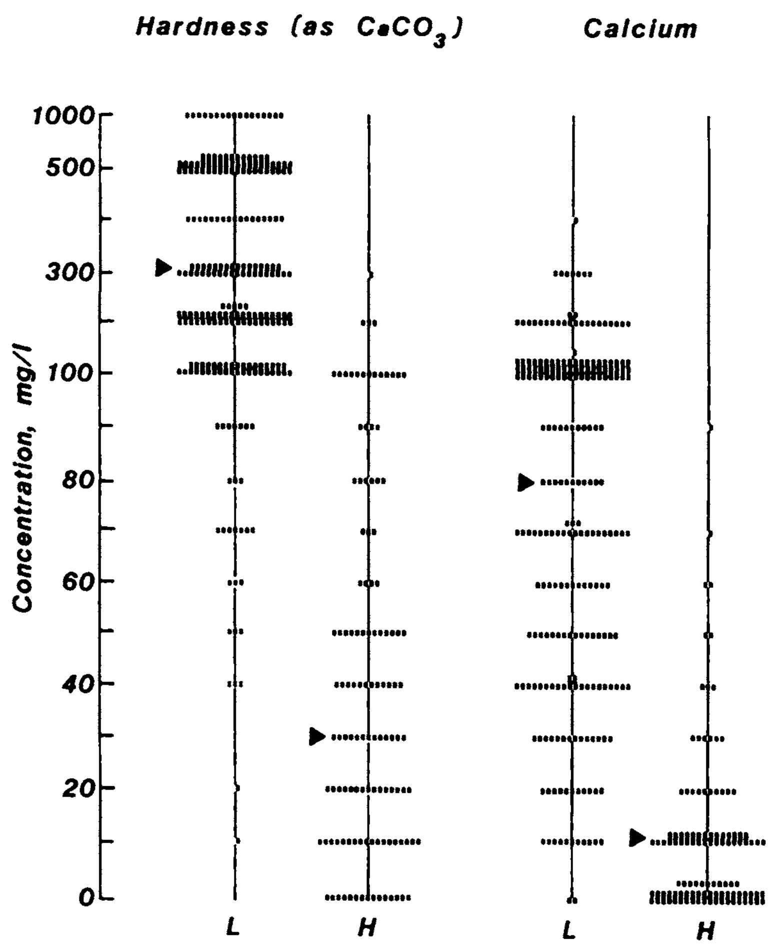

FIGURE 28 Differences in concentration of calcium and hardness in drinking water supplies for the low- and high-death-rate areas. Arrows point to median values.

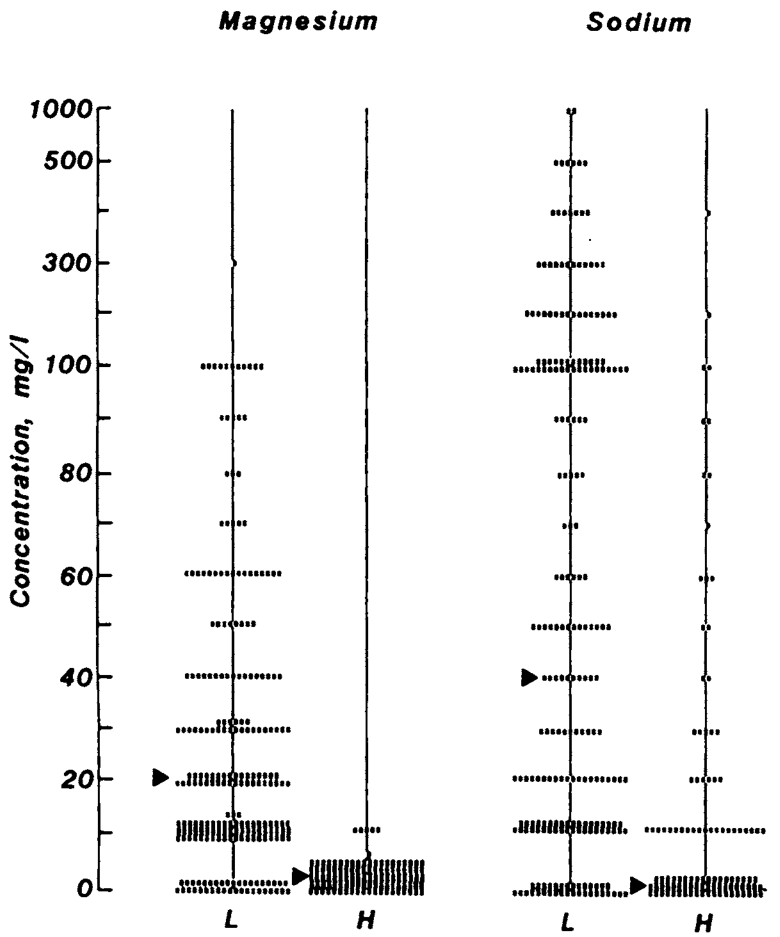

FIGURE 29 Differences in concentration of sodium and magnesium in drinking water supplies for the low- and high-death-rate areas. Arrows point to median values.

areas, or, where two or more chemical analyses were available (from different locations in a county), the data point represents one sample randomly chosen from the available analyses. Where no water analyses were available from a county, the data point was omitted. Figures 28-30 show that, for all chemical constituents plotted, concentrations are generally higher in the increased-longevity (low-death-rate) area. In contrast, water supplies in most of the counties in the decreased-longevity (high-death-rate) area have significantly lower concentrations of dissolved chemical constituents.

CONCLUSIONS

The data are limited, but reasonably consistent differences were found in chemical characteristics of drinking-water supplies in the two geographic regions studied: one identified as having a relatively high-death-rate (decreased-longevity) area; the other, a relatively low-death-rate (increased-longevity) area.

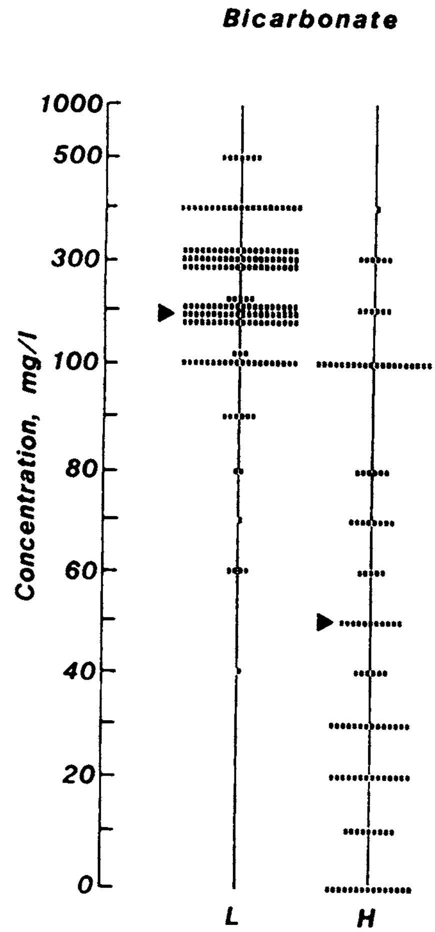

FIGURE 30 Differences in concentration of bicarbonate in drinking water supplies for the low- and high-death-rate areas. Arrows point to median values.

In general, drinking-water supplies in the decreased-longevity (high-death-rate) Area had the following:

1. Low dissolved solids (<50 mg/liter), except for those obtained from carbonate aquifers (dissolved solids >100 mg/liter);
2. Soft waters (<25 mg/liter) total hardness, except for those obtained from carbonate aquifers (total hardness >100 mg/liter as $CaCO_3$);
3. Low calcium (<10 mg/liter), except for those obtained from carbonate aquifers (calcium >20 mg/liter);
4. Very low magnesium (<5 mg/liter) except for those obtained from carbonate aquifers--Table 3, analysis A;
5. Low sodium (<10 mg/liter);
6. Low bicarbonate (<100 mg/liter), except for those obtained from carbonate aquifers (bicarbonate >100 mg/liter);
7. Relatively high in dissolved organic compounds, especially in surface waters.

In contrast, drinking-water supplies in the increased-longevity (low-death-rate) area had the following:

1. High dissolved solids (>300 mg/liter), including many with over 1000 mg/liter of dissolved solids;
2. Very hard waters (>200 mg/liter), including many with over 500 mg/liter hardness, as $CaCO_3$;
3. High calcium, (>50 mg/liter), including many with over 100 mg/liter of calcium;
4. High magnesium, (>30 mg/liter), from limestone aquifers generally having <10 mg/liter of magnesium--some contained over 100 mg/liter of magnesium;
5. High sodium (>50 mg/liter), with sodium quite variable, ranging from less than 10 mg/liter to over 1000 mg/liter;
6. High bicarbonate (>200 mg/liter);
7. Relatively low dissolved organic compounds.

The possibility that these spatial associations reflect cause-effect relationships is considered, and potential causal mechanisms are discussed in succeeding chapters.

REFERENCES

Craun, G. F., and L. J. McCabe. 1975. Problems associated with metals in drinking water. J. Am. Water Works Assoc. 67:593-599.

Feder, G. L., R. W. Lee, J. F. Busby, and L. G. Saindon. 1977. Geochemistry of ground waters in the Powder River Coal Region, in (U.S. Geological Survey) Geochemical Survery of Western Coal Regions, Fourth Annual Progress Report, July, 1977: U.S. Geol. Survey Open-file report No. 77-872, pp. 173-179.

Fenneman, N. M. 1938. Physiography of Eastern United States. McGraw-Hill, New York, 714 pp.

Gregg, D. C. 1963. Principles of Chemistry. 2nd ed. Allyn and Bacon, Boston, 716 pp. (adapted from appendix A-5).

Hem, J. D. 1970. Study and interpretation of chemical characteristics of natural water, 2nd edition. U.S. Geol. Survey Water Supply Paper 1473. U.S. Government Printing Office, Washington, D.C. 363 pp.

Hopps, H. C. 1978. The geochemical environment in relationship to health and disease. In Nutrition in Transition, P. L. White and N. Selvey, eds. American Medical Association, Monroe, Wisconsin, pp. 306-325.

Jenne, E. A., and S. N. Luoma. 1977. Forms of trace elements in soils, sediments, and associated waters. An overview of their determination and biological availability. In Biological Implications of Metals in the Environment, R. E. Wildung and H. Drucker, eds. CONF-750929, NTIS, Springfield, Virginia, pp. 110-143.

Leenheer, J. A., R. L. Malcolm, P.W. McKinley, and L. A. Eccles. 1974. Occurrence of dissolved organic carbon in selected ground-water samples in the United States. J. Sci. Res. 2(3):361-369.

Masironi, R., A. T. Miesch, M. D. Crawford, and E. I. Hamilton. 1972. Geochemical environments, trace elements, and cardiovascular diseases. World Health Organization Bull. 47:139-150.

NRC Committee on Dietary Allowances. 1980. Recommended Dietary Allowances, ninth revised ed. National Academy of Sciences, Washington, D.C. 185 pp.

NRC Panel on the Geochemistry of Water in Relation to Cardiovascular Disease. 1979. Geochemistry of Water in Relation to Cardiovascular Disease. Subcommittee on the Geochemical Environment in Relation to Health and Disease, National Academy of Sciences, Washington, D.C. 98 pp.

Neri, L. C., J. S. Mandel, and D. Hewitt. 1972. Relation between mortality and water hardness in Canada. Lancet 7758:931-934.

Parizek, J., J. Kalovskova, A. A. Babicky, J. Benes, and L. Pavlik. 1974. Interaction of selenium with mercury, cadmium, and other toxic metals. In Trace Element Metabolism in Animals, 2nd ed. W. G. Hoekstra, J. W. Suttie, H. E. Ganther, and W. Mertz, eds. University Park Press, Baltimore, Maryland. 750 pp.

Schroeder, H. A., and L. A. Kraemer. 1974. Cardiovascular mortality, municipal water, and corrosion. Arch. Environ. Health 28:303-311.

U.S. Environmental Protection Agency. 1976. National interim primary drinking water regulations. U.S. Government Printing Office, Washington, D.C. 159 pp.

10

SOIL AS AN ENVIRONMENTAL FACTOR IN AGING

Kenneth C. Beeson

Because our food supply, either directly or indirectly, comes mainly from plants grown in soils, it is natural to suspect that any regional differences in the health of man might be associated with some aberrations in the soil. The soils of the southeastern Coastal Plain are clearly different from those of the north-central United States, and this difference correlates with differences in longevity in man. The purpose of this discussion is to examine the facts available concerning soils in the two regions and to reveal, if possible, any facts that suggest a causal relationship of one or more soil properties to longevity. A glossary of soil terms is Table 5.

SOILS OF THE SOUTHEASTERN COASTAL PLAIN

Eleven selected high-risk counties in the southeastern Coastal Plain (Figure 3) have been grouped into six categories depending on soil characteristics and geological provinces (Table 6). Although within each county there are soil types that differ from each other in important agricultural aspects, the practical problem of evaluating a large area such as the Coastal Plain requires the use of a much higher soil category than the soil type. Hence, the Great Groups of the soil-classification system have been used for that purpose (Soil Science Society of America, 1973). Thus, for each county or group of counties the dominant Great Group is listed along with the Great Group associated with it in that region. Other factors of the environment--climate, elevation, and native vegetation--are noted although they are reasonably uniform throughout the region.

The dominant soils in this region fall into two orders, Entisols and Ultisols, and four suborders, Aquents, Psamments, Udults, and Aquults. Characteristics of the Entisols--Aquents and Psamments--have been described by Craddock and Wells (1973) and of the Ultisols--Udults and Aquults--by Perkins et al. (1973). The following discussion is based on their reports and on material from the Soil Survey Division (1938).

Members of the Entisols order are dominant in the counties of Chesterfield and Barnswell in South Carolina, and they also are found in association with other orders throughout many of the selected

TABLE 5 Glossary of Soil Terms

Order	Suborder	Great Soil	Brief Description of Order
Alfisols	Boralfs	Glossoboralfs	Medium to high in bases; subsurface accumulation of clay
	Udalfs	Hapludalfs	
		Paleudalfs	
Aridisols	Argids	Haplargids	Low in organic matter; never moist as long as 3 months
Entisols	Aquents	Psammaquents	No distinct development in the horizon, Aquents are wet soils; Psamments have texture of loamy fine sand or coarser
	Orthents	Ustorthents	
	Psamments	Quartzipsamments	
		Udipsamments	
		Ustipsamments	
Mollisols	Aquolls	Calciaquolls	Nearly black, friable, organic-rich surface horizons; Borolls occur in cool climates, the Udolls in moderate climates, and Ustolls in semiarid regions
		Haplaquolls	
	Borolls	Haploborolls	
	Udolls	Argiudolls	
		Hapludolls	
	Ustolls	Arguistolls	
		Haplustolls	
		Paleustolls	
Spodosols	Orthods	Haplorthods	Low in bases
		Fragiorthods	
Ultisols	Aquults	Ochraquults	Low in bases; the Aquults are wet soils; the Udults usually moist
		Paleaquults	
	Udults	Fragiudults	
		Paleudults	
		Hapludults	
		Rhodudults	

counties as well as in counties adjacent to them from North Carolina through Georgia.

The upland sandy Entisols--particularly in the Sand Hills region of the two counties--have a native vegetation that includes members of the Quercus species, some longleaf pine (Pinus palustre), and native grasses. The soils do not retain moisture and have weathered and leached to such an extent that only coarse-textured, hard minerals such as quartz are found in depths greater than 2 m. The quartzipsamments, for example, are composed of 95 percent, or more, quartz or other insoluble minerals. These soils are loose and incoherent and are developed from loose beds of sand and gravel.

These dry sandy soils are used mostly for woodland. Some cleared areas are used for peaches, watermelons, small grains, and truck crops. The wet Entisols, Psammenquents, have higher water tables and are used for woodland, pasture, and truck crops.

Soils of this type are inherently low in plant nutrients and organic matter and are stongly acid in reaction. Yields are very low unless adequate amounts of plant essential elements are supplied. The soils are poorly buffered, and applications of limestone to correct acidity may reduce the availability of micronutrients such as manganese and boron for most crops. The area is classified by Kubota et al. (1967) as a variable selenium area--50 percent of forage samples contain less than 0.10 ppm selenium in the moisture-free material. Other nutrient problems include deficiencies of copper and zinc for certain fruit crops (Beeson, 1955).

TABLE 6 Some Characteristics of Soils in Selected Counties of the Southeastern United States

Great Group Soils Associated Soils	Parent Material	Relief	Native Vegetation
Union Co., South Carolina *Province:* Piedmont; elevation 400-600 feet *Climate:* Humid, subtropical; precipitation, 47-60 inches; mean temperatures, Jan. 40° F, July 75° F *Agriculture:* Pasture and general row crops, corn, cotton, and soybeans			
Hapludults 90% Rhodudults Paleudults	Granites and diorites	Rolling to steep	Oak, hickory
Hapludalfs 10% Paleudults Rhodudults	Dark-colored crystalline hornblends and gneiss	Undulating to very steep	
Williamsburg Co., South Carolina *Province:* Coastal Plain; elevation 25-70 feet *Climate:* Humid, subtropical; precipitation, 45-50 inches; mean temperatures, Jan. 45° F, July 80° F *Agriculture:* A generally good potential, forestry			
Hapludults 70% Ochraquults Psammaquents	Clay and sandy material	Nearly level	Loblolly, short-leaf pine
Paleudults 30% Paleaquults	Marine sands, sandy clays, clay sediments	Nearly level to gently sloping	
Chesterfield Co., and Barnwell Co., South Carolina *Province:* Coastal Plain; elevation 280 feet *Climate:* Humid, subtropical; precipitation, 43-49 inches; mean temperatures, Jan. 48° F, July 80° F *Agriculture:* Fair to good general agricultural land, pasture and forests; with irrigation, watermelon, peaches, truck crops			
Quartzipsamments 60% Paleudults Fragiudults	Sandy and loamy Coastal Plain sediments	Gently sloping to hilly	Loblolly, short-leaf pine
Hapludults 30% Hapludalfs			
Paleudults 10% Paleaquults			
Marlboro Co., South Carolina *Province:* Coastal Plain; elevation 280 feet *Climate:* Humid, subtropical; precipitation, 64 inches; mean temperatures, Jan. 61° F, July 80° F *Agriculture:* Good general agricultural land, excellent forests			
Paleudults 80% Paleaquults	Sandy clay, clay sediments	Nearly level	Loblolly, short-leaf pine
Quartzipsamments 20% Paleudults Fragiudults	Sandy and loamy Coastal Plain deposits	Gently sloping to hilly	
Russell Co., Alabama *Province:* Coastal Plain; elevation 200-500 feet *Climate:* Humid, subtropical; precipitation, 48-50 inches; mean temperatures, Jan. 50° F, July 80° F *Agriculture:* Primarily in forest, but valleys adapted to row crops and pasture			
Paleudults Hapludults Paleudults	Marine sand	Gently rolling	Loblolly, short-leaf pine
Emanual Co., Dodge Co., Jeff Davis Co., Atkinson Co., and Clay Co., Georgia *Province:* Coastal Plain *Climate:* Humid, subtropical; precipitation, 45-48 inches; mean temperatures, Jan. 51° F, July 81° F *Agriculture:* Variety of regional crops–soybeans, tobacco, corn, and cotton–on well-drained soils; pasture and forest			
Paleudults 47% Paleaquults	Marine sands, sandy clays, clay sediments	Nearly level to gentle slopes	Longleaf pine
Paleudults 30% Paleaquults Quartzipsamments	Marine and sandy loam sediments	Nearly level to gentle slopes	Longleaf pine
Paleudults 23% Quartzipsamments Paleaquults	Sandy and loamy marine sediments	Nearly level to gentle slopes	Longleaf pine

The dominant soils in the southeastern Coastal Plain including the remainder of the selected counties are members of the Ultisols order (Table 6). Geological formations from which these soils developed range in age from Precambrian rock of the Piedmont Province to Quaternary sediments of the Coastal Plain. The native vegetation varies greatly but is generally forest. Along the Coastal Plain, it is subclimax forest of pine with mixed hardwoods.

Ultisols are soils with B horizons that contain an appreciable amount of translocated silica clay but few bases. They generally have sandy or loamy surface horizons if erosion has not been too severe. Most subsurface horizons are loamy or clayey in texture. These soils are acid in reaction and relatively infertile. They have a low base saturation--less than 35 percent. The dominant Ultisols in the selected counties are the Paleudults and the Hapludults (Table 6), but several other members of the Udult suborder occur in association with them.

The Paleudults have thick argillic (silty) horizons. Primary minerals that release cations upon weathering are either low or are absent in the sand and silt fractions. Clay activity tends to be low. Basic cations are primarily in the organic matter of the surface soil and the upper horizon. Such bases are biologically recycled. Kaolinite is normally the dominant clay mineral, although others do occur.

The Hapludults are not so thick or so highly weathered as the Paleudults. They have an argillic horizon ranging from a few centimeters to about 1.6 m (5 ft) in thickness and are free-draining soils. Many Hapludults have primary minerals in the sand and silt fractions of the argillic horizon that weather releasing cations. These soils have a relatively low base saturation and are moderately to strongly acid throughout their depth. Natural fertility is not so low as in the Paleudults. Activity of the clay is usually low. Clay minerals are of the kaolinic type in the majority of these soils, although other types are frequently present.

It is instructive to note that the soils in Union County and adjacent areas differ from those in the other selected counties mainly in the nature of their parent materials. They are developed from granites, diorites, hornblendes, and gneiss of the Piedmont Province. The other counties are located in the Coastal Plain, where the soils are developed on outwash sediments derived from similar igneous rock and from marine deposits. The Rhodudults of the suborder Udults developed from dark-colored crystalline rocks are examples. Areas of this soil are undulating to steep, acid in reaction, well drained, and relatively infertile. The acreage, however, is small compared with that of other members of the Udults subgroup (Perkins _et al_. 1973).

A wide range of row crops is grown on the Ultisols, including corn, soybeans, small grains, and grain sorghums. High-income crops, such as vegetables, are usually grown on soils suitable for irrigation. Most of the Ultisols have been in cultivation for some time, but during the past 25 to 50 years, considerable acreages of the less-productive, as well as same productive, Ultisols have reverted to brush and forest.

Micronutrient element availability is limiting in most of these soils with respect to specific crops. Manganese, zinc, copper, iron, and boron are frequently required for tung, peaches, pecans, cotton, or other crops. Selenium in forages is variable but, apparently, not limiting with respect to cattle (Kubota et al., 1967). Cobalt is limiting only in the lower levels of the Coastal Plain (Beeson, 1955). In the selected counties, however, only a small area of Williamsburg County, South Carolina, is involved.

SOILS OF THE NORTH CENTRAL STATES AND COLORADO

The 17 selected counties in this area (Figure 3) may be grouped in 11 categories, depending on the physiographic province and the dominant soil group in each county (Table 7). As in the grouping of counties in the southeastern United States, the soil-classification system of the National Cooperative Soil Survey (Soil Science Society of America, 1973; U. S. Geological Survey, 1969) is the basis for the following discussion.

The soils in the north-central region comprise a wider range of conditions with greater differences in climate, vegetation, and soil parent materials than do those of the Southeast (Soil Survey Division, 1938; Austin, 1972; Odell, 1960; Starr, 1964). Thus, in the selected north-central counties five of the highest soil orders and eleven of the suborders occur. The striking differences in soils of the north-central region are caused by climate and, conjunctively, the native vegetation. For example, minor areas of Spodosols--a typical cool, wet-climate soil--occur in Wisconsin, while Aridisols--a typical arid-climate soil--occur in Colorado.

The soils in the cool, humid climate of the northeastern section of this region are level to gently rolling and occupy a substantial portion of the land surface in the three selected counties (Polk, Buffalo, and Clark) in Wisconsin. The remaining topography is steep and used mostly for forest and pasture. The agricultural soils of the area are moderately productive.

The dominant soils of the three counties and adjacent Wisconsin counties are Hapludalfs, a Great Group in the suborder Udalfs and the order Alfisols. These soils have developed under a forest cover of either deciduous or coniferous trees, or a mixture of both. The climate is subhumid with a mean annual temperature of 35°F. The parent materials are usually unconsolidated, glacial deposits laid down during the Wisconsin stage of glaciation. These soils may have a very thin layer of organic matter above the A horizon. In a virgin soil, this A horizon may be either slightly alkaline or slightly acid, but the lower horizons are strongly acid with a base saturation of 40 to 75 percent. Crops including grain and hay are produced for feeding dairy cattle.

Selenium is variable in this section of Wisconsin (Craddock and Wells, 1973), and scattered copper and zinc deficiencies in the soil have been reported for some crops (Beeson, 1955).

From Wisconsin west to Washington County, Colorado, soils of the Mollisol order predominate. Exceptions include portions of McLeod County, Minnesota, where both Alfisols and Mollisols occur, and in counties of the Sand Hill area in Nebraska. The latter area will be discussed separately.

TABLE 7 Some Characteristics of Soils in Selected Counties of the North-Central States and Colorado

Great Group Soils Associated Soils		Parent Material	Relief	Native Vegetation
Polk Co., Wisconsin *Province:* Laurentian Upland; elevation 1000+ feet *Climate:* Cool, humid; precipitation, 31 inches; mean temperatures, Jan. 13°F, July 68°F *Agriculture:* Dairy farming, potatoes on level land, forest				
Hapludalfs Haplaquolls	67%	Two to four feet of loess over a brown, sandy clay loam till	Gently rolling to hilly	Deciduous forest
Haplorthods Fragiorthods	33%	Acid outwash sand and gravel	Nearly level	
Buffalo Co. and Clark Co., Wisconsin *Province:* Central Lowlands; elevation 1000+ feet *Climate:* Cool, humid; precipitation, 30 inches; mean temperatures, Jan. 13°F, July 68°F *Agriculture:* Dairying and livestock				
Hapludalfs	90%	Loess over limestone bedrock and on thin loam over sandstone	Gently rolling to steep	Deciduous forest, some conifers
Udipsamments Hapludalfs Haplaquolls	10%	Deep sands	Nearly level	
Dodge Co., Minnesota *Province:* Central Lowlands; elevation 1000 feet *Climate:* Cool, humid; precipitation, 25-30 inches; mean temperatures, Jan. 13°F, July 71°F *Agriculture:* Corn, oats, hay, livestock, and dairying				
Argiudolls Hapludalfs Haplaquolls	90%	Loess of Wisconsin age on bedrock limestone	Gently rolling	Tall grass
Haploborolls	10%	Clay loam till of Iowan age	Gently sloping to level	
Rock Co., Murry Co., and Lac Qui Parle Co., Minnesota *Province:* Central Lowlands; elevation 1000 to 1500 feet *Climate:* Humid, continental; precipitation, 25-30 inches; mean temperatures, Jan. 13°F, July 71°F *Agriculture:* Corn, soybeans, oats, hay, and livestock				
Haploborolls Haplaquolls Calciaquolls	96%	Calcareous loam till of Wisconsin age	Level to rolling	Tall grass
Hapludolls Haplaquolls	4%		Gently sloping	
McLeod Co., Minnesota *Province:* Central Lowlands; elevation 1000 feet *Climate:* Humid, continental; precipitation, 25-30 inches; mean temperatures, Jan. 13°F, July 71°F *Agriculture:* Corn, oats, soybeans, hay, and livestock				
Hapludalfs Argiudolls	80%	Calcareous loam till of Wisconsin age	Level to rolling	Tall grass
Hapludolls Haplaquolls	20%	Calcareous loam till of Mankato age	Undulating to rolling	
Jackson Co., Minnesota *Province:* Central lowlands; elevation 1000-1500 feet *Climate:* Humid, continental; precipitation, 25-30 inches; mean temperatures, Jan. 13°F, July 71°F *Agriculture:* Corn, oats, hay, and livestock				
Hapludolls Haplaquolls		Calcareous loam till of Wisconsin age	Level to rolling	Tall grass

TABLE 7 (continued)

Great Group Soils Associated Soils		Parent Material	Relief	Native Vegetation
Lyon Co., Iowa, and Cedar Co., Nebraska *Province:* Central lowlands; elevation 1000-1500 feet *Climate:* Subhumid; precipitation, 25 inches; mean temperatures, Jan. 20°F, July 75°F *Agriculture:* Corn, oats, hay, and livestock				
Hapludolls Ustorthents		Loess-mantled till plain or moderately thick loess	Gentle to moderate slopes	Tall grass
Mellette Co., South Dakota *Province:* Great Plains; elevation 2000 feet *Climate:* Subhumid; precipitation, 20 inches; mean temperatures, Jan. 20°F, July 75°F *Agriculture:* Livestock and some grain farming				
Haplustolls Ustorthents		Cretaceous shale bedrock or calcareous marine clays	Undulating to steep	Short grasses
Todd Co. and Mellette Co., South Dakota *Province:* Great Plains; elevation 2000 feet *Climate:* Subhumid; precipitation, 20 inches; mean temperatures, Jan. 20°F, July 75°F *Agriculture:* Livestock and some grain farming				
Argiustolls Ustipsamments	75%	Calcareous, loamy and sandy beds of Tertiary age	Undulating	Short grasses
Hapludolls Ustorthents	25%	Calcareous sandstone	Undulating to steep	
Rock Co., Blain Co., and Arthur Co., Nebraska *Province:* Great Plains; elevation 2000-4000 feet *Climate:* Semiarid; precipitation, 15-20 inches; mean temperatures, Jan. 20°F, July 75°F *Agriculture:* Beef cattle production on native pasture				
Ustipsamments	90%	Loess, Aeolian sands	Undulating to steep	Short grasses
Argiustolls Ustipsamments	10%	Calcareous loam and sands	Undulating	
Washington Co., Colorado *Province:* Great Plains; elevation 4000-4500 feet *Climate:* Subhumid; precipitation, 14-17 inches; mean temperatures, Jan. 20°F, July 75°F *Agriculture:* Grain, summer fallowing farming, and livestock				
Argiustolls Haplargids Ustorthents Paleustolls	90%	Loess, Aeolian sands	Plains	Shrubs and grass
Haplustolls Argiustolls Ustorthents	10%	Wind-worked alluvium, Aeolian, and lacustrine sands		

Soils of the Mollisols order have thick, dark-colored horizons high in bases and are developed in climates ranging from semiarid to humid moisture regimes and warm to hot temperatures. In Minnesota, Iowa, and eastern Nebraska, two suborders of the Mollisols are important--the Udolls and the Borolls. The Udolls are without carbonate accumulation and are slightly acid. They may have up to 5 percent organic matter in the surface soil. The Borolls are similar to the Udolls but are developed in the colder regions of the area. This section of the north-central states is in the corn belt, and the soils are among the most productive in the world. Selenium is adequate and micronutrient deficiencies for crops are rare.

A third suborder of the Mollisols, the Ustolls, occurs in Todd and Mellette counties of South Dakota as well as in large areas of South Dakota, Nebraska, and Washington County, Colorado. These soils developed in a temperate and subhumid climate under a grass vegetation. Mean annual rainfall is about 14 inches. The content of organic matter in the plow layer is about 3 to 5 percent and decreases from the surface downward. Base saturation is high and only the A horizon is free from carbonates. The upper B horizon is without carbonate accumulation, and the reaction may vary from mildly acid to alkaline. Carbonate accumulation begins with the lower B horizon. These soils are very fertile and are used for wheat and other grains, corn, and grain sorghums. Some toxic areas of selenium occur (Craddock and Wells, 1973), and iron and zinc deficiencies occur in these soils of western Nebraska and eastern Colorado (Beeson, 1955).

In central and western Nebraska, including Arthur, Blaine, and Rock counties, a series of soils has been developed on the Sand Hills of Nebraska. They are moderately well stabilized, and if the native vegetation is not disturbed, their topography will not vary materially. The soils in this area, Ustipsamments, are members of the Alfisols order. They are gently rolling to moderately steep. They have a good sod cover with a slightly dark surface horizon and are slightly acid. When properly stocked, these soils produce high yields of native grasses.

SUMMARY AND CONCLUSIONS

Soils in the two general areas selected for this study, the southeastern Coastal Plain and certain north-central states, have one thing in common: they are productive under proper management. However, the soils were developed under different climates and different vegetation. Hence, such soil factors as the inherent fertility, based saturation of the colloids, the soil reaction, organic matter content, and the degree of leaching are generally more favorable in the north-central region.

The overall range of soil properties is greater in the north-central region than in the southeastern Coastal Plain. Soil reaction, for example, varies from the acid soils of Wisconsin to the moderately acid to neutral soils of Minnesota and Iowa to the basic soils of Colorado. In many of the soils of South Dakota, Nebraska, and

Colorado, zones of carbonate accumulation occur. In the Coastal Plain, all soils are acid and base saturation is low. Except in the Wisconsin soils, the organic matter content of the north-central soils ranges from 1 to 5 percent, or more. In the Coastal Plain, little or no accumulation of organic matter occurs. Important areas of soils developed on sands occur in both regions, but those in Nebraska are subject to much less leaching, and the inherent fertility is greater than in those of the Coastal Plain.

The highly leached acid soils of the southeastern Coastal Plain are deficient in a number of the micronutrient elements, and applications of all the macronutrient elements are required for optimum crop production. In the north-central region, phosphorus is frequently a limiting factor, and a few soils require potassium. Nitrogen is widely used, and a few soils require limestone to correct acidity. Micronutrient element deficiencies are infrequent; boron, copper, manganese, and zinc are occasionally applied for special crops. Except for a few areas of toxic selenium problems in Nebraska and South Dakota, the selenium supply as measured by its content in alfalfa and by animal requirements, appears to be similar in both regions--variable to adequate.

There is an abundance of generalized knowledge concerning the effects of different soil factors, climate, management practices, and genetic factors on the nutrient content of the many different species of food plants. However, specific information permitting meaningful comparative evaluation of the concentrations of the required mineral nutrients or of the presence of toxic elements in the locally grown foods in the two regions under consideration is inadequate.

Between the initial source of the mineral elements, the rock, and man, there are at least two important systems that exert high buffering actions--the soil and the plant. Each exercises a selective action on the uptake of the mineral elements available to it, thus restricting the kinds and quantities of the elements that eventually reach man. The implication of these blocks in the food chain must be realized in assessing the role of the geochemical environment in problems of health and disease in man.

The matter of the total food supply of a specific community only compounds the problem relating a local environment to man. Obviously, the assessment of such a relationship must include studies not only of locally produced foods but also of the actual food intake by the human population. A study of this nature would be a productive one in identifying the impact of the local environment on man's health, including the phenomena of aging.

REFERENCES

Austin, M. E. 1972. Land resource regions and major land resource areas of the United States. Agricultural Handbook 296, 82 pp. and maps. Soil Conservation Service, U.S. Department of Agriculture, Washington, D.C.

Beeson, K. C. 1955. The quality of crops in the relation to the nutrition of animals an man in the United States. Landwirtsch. Forsch. Suppl. 8, 127-138.

Craddock, G. R., and R. D. Wells. 1973. Entisols--soils that show no profile development. In Soils of the Southern States and Puerto Rico. S. W. Buel, ed., Southern Cooperative Series, Bull. 174, pp. 24-28 and maps.

Kubota, J., W. H. Allaway, D. L. Carter, E. E. Cary, and V. A. Lazar. 1967. Selenium in crops in the United States and relation to responsive diseases of animals. Agric. Food Chem. 15(3):448-453.

Odell, R. T. 1960. Soils of the North Central Region of the United States. North Central Regional Publication No. 76, Bull. 544, Agricultural Experiment Station, Madison, Wisc. 192 pp. and maps.

Perkins, H. F., H. J. Byrd, and F. T. Richie, Jr. 1973. Ultisols--light colored soils of the warm, temperate forest lands. In Soils of the Southern States and Puerto Rico. S. W. Buol, ed., Southern Cooperative Series Bull. 174, pp. 73-86.

Soil Science Society of America. 1973. Glossary of Soil Science Terms. Soil Science Society of America. Madison, Wisc., 33 pp.

Soil Survey Division. 1938. Soils of the United States. Part V in Soils and Men. The Yearbook of Agriculture, U.S. Department of Agriculture. U.S. Government Printing Office, Washington, D.C. pp. 1019-1161.

Starr, W. A., Chairman, 1964. Soils of the Western United States. Washington State University. 69 pp. With maps.

U.S. Geological Survey. 1969. Distribution of principal kinds of soils: Orders Suborders and Great Groups. National Cooperative Soil Survey Classification of 1967. Map, Sheet 86, U.S. Geological Survey, Washington, D.C.

11

ABNORMAL ABSORPTION OF TRACE ELEMENTS BY PLANTS: INDICATOR AND ACCUMULATOR PLANTS

Kenneth C. Beeson

Plant species indicative of specific soil or bedrock conditions have long been known to both geologists and agriculturists, who have identified and used plants for such purposes (Beath *et al.*, 1934; Beeson *et al.*, 1955; Brooks, 1972; Cannon, 1957, 1971). Plant species utilized in making surveys can be classified into three groups: (a) those species that have a high requirement for a nutrient element; (b) those species that are more tolerant to some soil condition than are the normal flora in a particular environment and are, therefore, better able to compete with other plants; and (c) those plant species that naturally absorb significantly larger quantities of a particular element than will the majority of the species common to a region.

Those species in the first two groups are generally called indicator plants because they offer a visual indication of a particular situation. An indicator plant may also be an accumulator plant, but this is a secondary property. Thus a good growth of legumes indicates a favorable content of calcium and a desirable pH in a soil. Certain members of the *Astragalus* species may indicate the presence of excessive levels of selenium in the soil and its parent material (Byers *et al.*, 1938).

The third group includes avid absorbers of mineral elements--often not required by the plant--including cobalt and selenium (Beeson *et al.*, 1955; Byers *et al.*, 1938). The concentrations of such elements are, generally, severalfold that found in associated vegetation, hence these plants are called accumulator plants. Accumulators have been used as relative measures of the uptake of cobalt by other plants and, hence, the available cobalt in a soil (Kubota and Lazar, 1958). The presence of species that require little copper has been used to identify copper deficiency in soils and in forages for animals (Gomez *et al.*, 1966).

The concentrations of the micronutrients vary markedly among the different food crops, and very few instances of unusual accumulations of these nutrients or of other trace metals in the edible portion of the crops have been reported. Robinson and Edgington (1945) reported high concentrations of barium in the brazil nut and the pecan. Cannon (1955) reported extremely high levels of zinc in vegetable crops grown on certain peat soils in New York. In a recent publication, Shacklette (1980) reported the concentrations of 27 elements in the ash of several fruits and vegetables collected from important production areas in the United States. The edible portion of each plant was dried and ashed prior to analysis. The ranges of nutrients such as copper, zinc, and calcium appear to be normal. While the concentration ranges for many nonnutrient elements are often wide, there is no indication that levels toxic to either plants or man were found. The reason for so little information probably lies in the fact that food crops do not tolerate high levels of many of the mineral elements, particularly the heavy metals. Examples of failure to grow or of retarded yields on soils contaminated with heavy metals are numerous in the agronomic literature.

Solution culture techniques were used by Page et al. (1972) to study the response of several crops to cadmium levels in the range of 0.1 to 10 ppm of cadmium. At a level of 0.2 ppm of cadmium in the nutrient solution, the growths of beets, beans, and turnips were less than half of those obtained in a cadmium-free solution. The relative uptake of cadmium by the crops was in the following order: turnip > lettuce > beet > corn > cabbage > tomato > pepper > barley > beans. The concentrations of cadmium were determined only in the leaves of these plants. Similar toxicities had been found with tomatoes and turnips grown in nutrient solutions containing abnormal levels of zinc, copper, manganese, molybdenum, iron, and boron (Lyon and Beeson, 1948).

Among the micronutrients, the effect of high levels of zinc on growth and uptake has received attention. Boawn and Rasmussen (1971) in field plot tests determined the uptake of zinc where different levels of zinc had been applied to the soils. The order of zinc uptake by the marketable portion of the crops was: swiss chard > spinach > parsley > chinese cabbage > leaf lettuce > head lettuce > mustard > romaine lettuce > collards > brussels sprouts > cabbage. They define swiss chard and spinach as accumulator plants. When grown in soils with normal levels of zinc, spinach contained 139 ppm of zinc and swiss chard 80 ppm compared with 22 ppm of zinc in cabbage. Among the above vegetables, lettuce and spinach appeared to be most tolerant to high levels of zinc in the nutrient medium.

A similar study of selenium uptake by food crops has been reported from Wyoming (Hamilton and Beath, 1964). When grown on a soil containing 3 ppm of selenate-selenium applied to it, the following order of uptake by the plants was found: cabbage > broccoli > spinach > swiss chard > string beans > onions > peas, immature > radish > rutabaga > tomato > parsnip > beet, root > eggplant > leaf lettuce > carrot > potato > cucumber. Cabbage and broccoli with 160 ppm of selenium and 150 ppm of selenium, respectively, could be classified as accumulator plants in comparison with the remainder of the concentrations, which ranged from 89 ppm in spinach down to 18 ppm in the cucumber. It should be noted that these crops were grown in the greenhouse in soil cultures containing an added soluble selenate and do not represent normal cultural conditions. Yield data are not presented, but it is assumed that no toxic effects were encountered.

There is a growing awareness of heavy metal uptake by plants following the use of municipal effluents and sewage composts. In the nearly 100 papers on this subject over the last 15 years, only a few reports of heavy-metal concentrations in the edible portion of the plant are available. Such data are also rare in the general agronomic literature. Much greater emphasis has been placed on the effect on yields.

CONCLUSION

Very little is known about the maximum range of concentrations of nonnutrient elements in the edible portion of plants where yields are normal, or at least acceptable. It seems, therefore, that any speculation concerning the available content of such trace mineral elements in rocks and soils in relation to health and disease in man is without merit unless something is known about the probable concentration of these elements in the edible portion of the plant.

In any evaluation of the soil-plant relationship to health and disease or longevity, we need to consider, therefore,

- The minimum level in the edible portion of plants of any plant nutrient also required by man that will sustain a normal acceptable yield of a crop.
- The maximum level in the edible portion of plants of any nutrient element also required by man that can occur in a plant without affecting the yield of the plant. Tables of food composition provide a mean that includes the minimum levels but not the possible maximum levels.
- The range of nonnutrient elements, particularly the heavy trace elements, that can occur in plants without adversely affecting yields.
- The effect on the health, including longevity, of man of these ranges of elements in the edible portion of plants.

REFERENCES

Beath, O. A., J. H. Draize, and C. S. Gilbert. 1934. Plants poisonous to livestock. Wyo. Agric. Exp. Sta. Bull. 200, 84 pp.

Beeson, K. C., V. A. Lazar, and S. G. Boyce. 1955. Some accumulators of the micro-nutrient elements. Ecology 36(1):155-156.

Boawn, L. C., and P. E. Rasmussen 1971. Zinc accumulation characteristics of some leafy vegetables. Soil Sci. Plant Anal. 2(1):31-36.

Brooks, R. R. 1972. Geobotany and Biogeochemistry in Mineral Exploration. Harper and Row, New York. 240 pp.

Byers, H. G., J. T. Miller, K. T. Williams, and H. W. Lakin. 1938. Selenium occurrence in soils with a discussion of related topics. Third Report. U.S. Dept. Agric. Tech. Bull. 601. 74 pp.

Cannon, H. L. 1955. Geochemical relations of zinc-bearing peat to the Lockport Dolomite, Orleans County, New York. Geol. Surv. Prof. Bull. 1000-D. U.S. Geological Survey, pp. 119-185.

Cannon, H. L. 1957. Description of indicator plants and methods of botanical prospecting for uranium deposits on the Colorado Plateau. U.S. Geol. Surv. Bull. 1030-M. 516 pp.
Cannon, H. L. 1971. Use of plant indicators in ground water surveys, geologic mapping and mineral prospecting. Taxon 20(2/3):227-266.
Gomez, G., T. Aguilar, and K. C. Beeson. 1966. Calidad Nutricion de los Forrajees del Valle del Huallaga Central. An. Cien. Unive. Agraria 4:147-161.
Hamilton, J. W., and O. A. Beath. 1964. Amount and chemical form of selenium in vegetable plants. J. Agric. Food Chem. 12:371-374.
Kubota, J., and V. A. Lazar. 1958. Cobalt status of soils of Southeastern United States, II. Ground water podzols and six geographically associated soil groups. Soil Sci. 56(5):262-268.
Lyon, C. B., and K. C. Beeson. 1948. Influence of toxic concentrations of micronutrient elements in the nutrient medium on vitamin content of turnips and tomatoes. Botanical Gaz. 109:506-520.
Page, A. L., F. T. Brigham, and C. Nelson. 1972. Cadmium absorption and growth of various plant species as influenced by solution cadmium concentration. J. Environ. Qual. 1:288-291.
Robinson, W. O., and G. Edgington. 1945. Minor elements in plants and some accumulator plants. Soil Sci. 60:15-28.
Shacklette, H. T. 1980. Elements in fruits and vegetables from areas of commercial production in the conterminous United States. Geol. Surv. Prof. Paper 1178. U.S. Government Printing Office, Washington, D.C.

12

HOW MIGHT GEOCHEMICAL FACTORS AFFECT SENESCENCE AND AGE-ASSOCIATED PATHOLOGY?

Howard C. Hopps

The enormous geographic variation in geochemical environment related to its content of elements important for human health is not generally recognized. Table 8 shows the range of several important trace elements in rocks, waters, soils, and plants.

Our major problem is to determine whether the geochemical characteristics of high-mortality regions, as compared with those of low-mortality regions, are merely associative or are causally related. This chapter considers the ways in which the geochemical environment could contribute to longevity.

In the context of this discussion, we are concerned primarily with the elements and simple inorganic compounds of the rocks, soil, and water that are ingested or inhaled by humans. General relationships and mechanisms are shown in Figure 31.

The geographic sources of many foods are widespread, but in nonurban areas significant amounts of food are often produced and consumed locally, reflecting close relationships between man and soil. The geographic connections between source of water and place of its

TABLE 8 Ranges of Values of Selected Trace Elements in Geochemical Materials and in Certain Categories of Edible Plants[a]

Sampled Materials	Chromium	Copper	Zinc	Selenium	Cadmium
Rocks, ppm					
Basaltic igneous	40-600	30-160	48-240	0.05[b]	0.006-0.6
Granitic igneous	2-90	4-30	5-140	0.05[b]	0.003-0.18
Shales and clays	30-590	18-120	18-180	0.6[b]	0-11
Limestones	10[b]	4[b]	20[b]	0.08[b]	0.05[b]
Phosphorites	30-3000	10-100	20-300	1-100	0-170
Water–finished municipal water μg/liter	ND[c]-35	<0.61-250	<1.0-400	0.1-400	<0.7-1.0
Soils, ppm	7-300	7-150	25-190	0.04-100	0.01-0.7
Plants, ppm (dry weight)					
Forage grasses	0.42-0.95	0.29-60	2.0-80	<0.01-9	0.03-2.4
Forage legumes	0.13-2.2	1.5-40	11.4-210	0.075-0.7	0.04-0.05
Vegetables and fruits	<0.06-10	<1-30	2.5-200	0.01-0.2	0.01-0.96

[a]From data presented by Michael Fleischer and by Helen Cannon. Source: Hopps, 1978. (Reprinted with permission of the American Medical Association.)
[b]Average.
[c]Not detected.

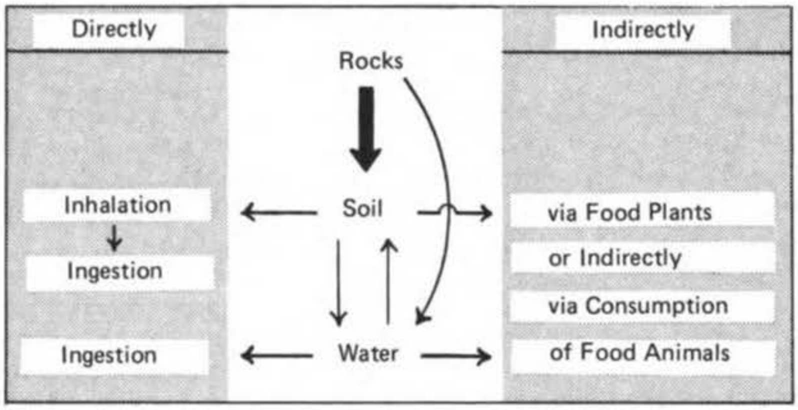

FIGURE 31 Schema showing relationships between the geochemical environment and man.

consumption is, of course, much more direct--and this includes the water in a large proportion of most beverages, e.g., coffee, tea, soft drinks, beer, and milk. Connections between soil and man are mainly indirect, through ingestion of plant foods, or even more indirectly, through consumption of meat, milk, and eggs derived from animals that subsist on plants. But there is a direct connection between soil and man, particularly among the farming communities, which has been ignored until recently (Hopps, 1978)--the ingestion of windborne particles of soil. A large portion of inhaled particles in the range of 2-20 μm impinge upon the mucous surfaces of the nasopharynx and larger pulmonary air passages to be swept by ciliary action of the mucosal cells to the hypopharynx, then swallowed, digested, and absorbed, at least in part.

Having established that there is marked geographic variation in the geochemical environment, and that there are direct and indirect nutritional relationships between man and his geochemical environment, we are ready for the following question:

HOW MIGHT GEOCHEMICAL ENVIRONMENT CONTRIBUTE TO LONGEVITY?

There is an analogy between the aging of people and things. To assure a long, productive life for both requires sound structural design, excellent materials, and high-quality workmanship. These critical factors are influenced profoundly in humans by genes and by nutrition--prenatal as well as during the early growth years. The rate and extent of wear and deterioration in both people and things are also greatly influenced by the care that they receive after they are made, which implies minimal physical and chemical injury.

One of the feasible, positive approaches to delaying the ravages of time is nutritional. And among the nutritional factors, important ones related to geochemical environment include an adequate supply and balance of essential macroelements and microelements. The geochemical environment can also contribute favorably to health by providing minimal amounts of primarily toxic elements such as mercury, lead, and cadmium.

Most of the controlled research studies on the effects of too many and too few macroelements and microelements have been done on experimental animals, and the hazards of extrapolating from such studies directly to man are well known. The following comments relate to humans under essentially uncontrolled conditions.

Abnormal levels of macroelements are often caused by associated disease that disturbs homeostatic mechanisms--renal dysfunction, causing hypokalemia or hyperkalemia, for example. Nutritionally induced abnormalities occur too, of course, as illustrated by the altered bone structure resulting from inadequate intake of calcium (or abnormal balance of calcium/phosphorus) and cardiac arrhythmia because of magnesium deficiency.

Much of our interest is in the essential micro (trace) elements, many of which are metals, and considerably less is known about human disorders associated with nutritional deficiency or excess of these substances.

The biochemical roles of metals, in general, are much too numerous and complex to review here. The functions of and mechanisms by which metals serve as regulators of heme metabolism provide a suitable model, however, illustrating the complexities that characterize interactions of trace metals in physiological systems related to aging.

Heme, a porphyrin with a central chelated metal atom, is bound to certain proteins in physiological systems. In turn, these heme proteins bind oxygen or function as components of membrane-bound electron transport chains. Among its essential functions--aside from the obvious one performed by hemoglobin--heme is necessary for cellular respiration, energy generation, and oxidative biotransformations, the latter playing a major role in the degradation of a wide variety of toxic substances, both endogenous (e.g., bilirubin) and exogenous (e.g., many drugs and some carcinogens).

Maines and Kappas (1977) present evidence that

> ...the rate of both heme biosynthesis and degradation may primarily be a function of metal ion concentrations at appropriate regulatory sites in the cell....

and conclude that

> The consequences of the metal actions on heme synthesis and degradation are to deplete cellular contents of heme and heme proteins and to impair oxidative activities dependent on these compounds. Many of the metal ions that have the biological properties described above gain entrance to the body in numerous and diverse ways. Moreover, a number of these metals tend to accumulate in various tissues throughout life.

Among the metals that can cause marked degradation of heme, are some of the transition elements, also cadmium, chromium, copper, gold, iron, lead, manganese, mercury, nickel, platinum, selenium, tin, and zinc. There is considerable tissue specificity in their effects; cobalt is particularly active in liver tissue, tin and nickel in renal tissue, and mercury in cardiac tissue.

An important aspect of this account is that the effects of at least some of these elements are beneficial in that they act as physiological regulators of heme metabolism. It is interesting that many of the trace elements that can degrade heme systems are essential nutrients, and their degradative effects depend on the concentration at specific regulatory sites in the cell. From this illustration it is obvious that broad generalizations about beneficial or harmful effects of essential trace elements, such as copper, iron, selenium, and zinc, are inappropriate at the biomolecular level.

At the systems level we are quite aware of the acute and subacute disorders resulting from deficiency of iodine and iron. Effects from deficiency of zinc are less obvious but also well recognized--delayed wound healing, for example, and, in extreme cases, dwarfism with failure to develop secondary sexual characteristics. But the relationship of chromium deficiency to diabetes mellitus and the possible role of copper deficiency in degenerative arterial diseases of the aged, for example, are not so clearly evident. And we know practically nothing about the effects on man of deficiency in manganese, molybdenum, nickel, selenium, silicon, and vanadium, all of which are trace elements that have been proved to be essential or at least beneficial for experimental animals.

There is much that we do not know about the effects of geochemical environment on humans, but from what is known, we can say that the geochemical environment could favorably affect the quantity and quality of human life by one or more of the following means:

1. Contributing to favorable nutrition by supplying proper amounts of macroelements and microelements, <u>in appropriate balance</u>, particularly the essential trace elements. (The most pronounced effects would be expected during the early stages of development and growth of the individual.)
2. <u>Not</u> contributing predominately toxic elements such as cadmium, lead, and mercury, or toxic levels of essential elements
3. Providing appropriate kinds and amounts of nutrient elements that inhibit the effects of ingested toxic elements
4. Providing elements that act to moderate injurious agents and mechanisms, such as free radicals and lipid peroxidation, which appear to contribute directly to senescence
5. Providing elements with specific protective effects against diseases, such as atherosclerosis and cancer, which cause premature mortality.

Items 1 and 2 seem fairly obvious, but we know relatively little about the effects of nutrient macroelements and microelements on human longevity. (See Chapter 14.) Nor do we know much about the effects of very-long-term, low-toxicity levels of essential trace elements or of primarily toxic trace elements, for example, thallium. Effects from such chronic toxicity would probably be quite different from those observed in acute and subacute poisoning. And in both items 1 and 2 the problem of interaction is difficult indeed. Underwood and Danbara (1976) summarized it as follows:

> Metabolic interactions among the trace elements at both the absorptive and at the tissue cell are now known to be so common and to be so powerful that a particular dietary intake of a given element, for example copper, can be deficient, marginal or toxic to the animal depending upon the extent to which the elements with which it interacts are present or absent from the diet.

With respect to item 3, inhibitions of toxic elements, evidence continues to accumulate indicating that essential micronutrients derived from the geochemical environment can be quite effective. In fact, a major factor in the essentiality of some trace elements may relate to their ability to protect against toxic injury. Levander (1977) has recently reviewed this subject, and the following comments are based, in large measure, on his report. Selenium has been shown to have protective action against inorganic forms of mercury as well as methylmercury. Selenium is also an antagonist of cadmium and arsenic. Iron offers some protection against cadmium, whereas deficiency of iron or copper or calcium can aggravate cadmium toxicity. Zinc, in appropriate amounts, antagonizes cadmium, and it appears that the zinc/cadmium ratio may be more important than the level of cadmium alone. There is also evidence that high levels of zinc offer some protection against lead intoxication. As Levander emphasizes, however, the inhibitory effects of these essential elements depend not only on absolute concentrations but, oftentimes, on relative concentrations in achieving an effective balance with other interactive elements.

There is considerably less known about item 4, elements that act to moderate the agents and mechanisms that contribute directly to senescence. From the available evidence, such elements could affect the formation and persistance of free radicals (discussed in Chapter 7). They could also act by limiting lipid peroxidation. The reports are at some variance as to the effectiveness of agents in prolonging life by protecting against free radical and lipid peroxidation reactions, however. Tappel (1978) presents the positive view, citing beneficial effects from butylated hydroxytoluene (BHT) and ascorbic acid, both potent antioxidants. Discussing his own experiments, he states,

> ...selenium, sulfur amino acids, and vitamin E act synergistically at the nutritional level to protect tissues from oxidative damage.

Sacher (1977) presents a rather negative view in his discussion of life prolongation, which includes a review of many experiments in which free-radical inhibitors and chemical antioxidants were used. He makes the point that under experimental conditions, where the quality and quantity of stress is carefully controlled, longevity in itself is not a sufficient measure of the rate of senescence because increased longevity can result from a decrease in vulnerability to injury. He concludes that

> The failure to affect a decreased aging rate with antioxidants should also be viewed with the perspective that no other chemical agent has yet been shown to reduce the rate of actuarial aging, even when life expectancy is increased.

He also points out that, although caloric restriction and reduction of body temperature (in poikilotherms) prolong the period of life, this effect can be explained as a consequence of decreased rates of energy metabolism, an entirely different mechanism of action than is proposed for specific chemical agents such as antioxidants and free radical scavengers.

Somewhat related to the efforts to inhibit peroxidation of membrane lipids by means of free radical scavengers and antioxidants are the studies directed to increasing the stability of cellular membranes, particularly those of lysosomes (see p. 54). As yet, only a few organic compounds (corticosteroids, antihistamines, and aspirin) have been shown to have significant effects (Sacher, 1977).

Trace metals could also indirectly prevent cellular injury, which contributes to senescence, by regulating the actions of heme protein complexes (and other metal-proteins), as has been described.

Item 5, concerning protection against diseases that cause premature mortality, has received a great deal of attention, reflecting western medicine's primary concern with disease rather than with health. Several of these relationships have already been discussed and many of them are considered in detail in an earlier publication (NRC, GERHD, 1978).

- Some forms of diabetes mellitus are clearly linked with abnormal levels of glucose tolerance factor, which complex includes chromium--and chromium deficiency has been observed to cause diabetes mellitus in humans.
- There is increasing evidence that chronic, low-level cadmium intoxication contributes to hypertensive disease.
- Imbalance of macroelements and microelements is an important cause of urinary lithiasis.
- Zinc deficiency can seriously retard wound healing and may be a major factor in the faulty regeneration of complex parenchymal tissues, as in cirrhosis of the liver. Zinc deficiency can also seriously inhibit immunity, thus predisposing to infectious diseases.

The most important of these age-associated diseases are cardiovascular disease (CVD) and cancer, which together account for more than two thirds of deaths among the aged, as shown in Figure 32. Mortality from each of these diseases can be modified either positively or negatively by trace elements derived from the geochemical environment. Since there is an extensive literature about this and recent reviews that deal specifically with the geochemical environment and cancer (Hopps et al., 1978) and cardiovascular disease (McMillan et al., 1978; NRC Panel on the Geochemistry of Water in Relation to Cardiovascular Disease, 1979), the evidence for this relationship will be summarized briefly.

Epidemiologic evidence indicates that in most parts of the world there is a significant inverse relationship between mortality from CVD and hardness of drinking water. Comstock (NRC Panel on the Geochemistry of Water in Relation to Cardiovascular Disease, 1979) summarizes the situation well in his statement: "...there can be little doubt that the negative associations of water hardness with cardiovascular mortality are not spurious" and evaluates several reports on the level of increased risk of cardiovascular deaths in soft water as compared with hard water areas in the United States, Canada, and England and Wales. Because this grouping according to precise cause of death varies, the data are not entirely compatible, but the risk factor appears to be in the neighborhood of 1.20. This seems a weak association, but when one considers that nearly a million persons in the United States die each year from cardiovascular disease--approximately 3 times as many as from cancer--an increased risk of 20 percent becomes significant indeed. Two major explanations have been

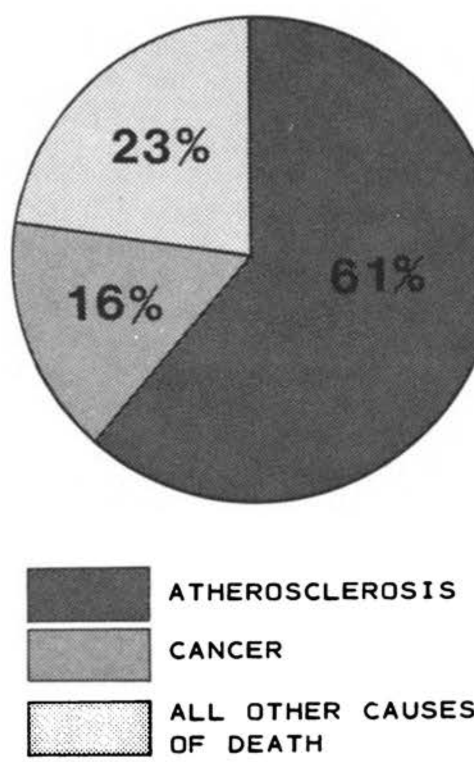

FIGURE 32 The proportion of deaths caused by atherosclerosis (cardiovascular diseases) and cancer in the population group 65+ years of age.

offered: (1) that one or more macroelements (e.g., magnesium) or microelements protect the heart from fatal ventricular fibrillation in response to an acute ischemic episode (usually causally associated with atherosclerosis); and (2) that soft water, which is usually more corrosive than hard water, dissolves cardiotoxic elements such as cadmium, antimony, and lead, from water pipes. [Less direct effects on CVD result from effects of trace elements on the occurrence and severity of diabetes mellitus or hypertension, both of which contribute to the development of atherosclerosis.]

With respect to cancer, several essential trace elements have been incriminated in its cause: iron deficiency, magnesium deficiency, and iodine deficiency as well as excess. In a review article relating diet to cancer, Berg (1975) lists the following trace elements for which there are statistically significant, positive correlations between metal concentrations and cancer death rates: arsenic, beryllium, cadmium, lead, and nickel.

Macroelements and microelements can also provide protection against cancer, however. One important mechanism is by antagonizing some of the potentially carcinogenic elements (arsenic, cadmium, and lead), listed above. Another mechanism is by what appears to be interference with the process of carcinogenesis itself; this has been reviewed by Shamberger (1978). One of the possible mechanisms, for which there is some experimental evidence, is that selenium facilitates repair of chromosomal breaks. If this is true, selenium might favorably affect the aging process.

REFERENCES

Berg, J. W. 1975. Diet. In Persons at High Risk of Cancer: An Approach to Cancer Etiology and Control, J. E. Fraumeni, Jr., ed. Academic Press, New York, 544 pp.

Hopps, H. C. 1978. The geochemical environment in relationship to health and disease. In Nutrition in Transition, P. White and N. Selvey, eds. American Medical Association, Chicago, pp. 306-325.

Hopps, H. C., J. F. Annegers, P. Correa, C. Cuello, J. E. Enstrom, W. Haenszel, L. T. Kurland, M. C. Pike, and R. Shamberger. 1978. Cancer. In Geochemistry and the Environment, Volume III: Distribution of Trace Elements in Relation to the Occurrence of Certain Cancers, Cardiovascular Diseases, and Urolithiasis. Subcommittee on the Geochemical Environment Related to Health and Disease. National Academy of Sciences, Washington, D.C., pp. 81-113.

Levander, O. A. 1977. Nutritional factors in relation to heavy metal toxicants. Fed. Proc. 36:1683-1687.

Maines, M. D., and A. Kappas. 1977. Metals as regulators of heme metabolism. Science 198:1215-1221.

McMillan, G. C., chairman. 1978. Cardiovascular disease. In Geochemistry and the Environment, Volume III: Distribution of Trace Elements Related to the Occurrence of Certain Cancers, Cardiovascular Diseases, and Urolithiasis. Subcommittee on the Geochemical Environment in Relation to Health and Disease. National Academy of Sciences, Washington, D.C., pp. 114-132

NRC Panel on the Geochemistry of Water in Relation to Cardiovascular Disease. 1979. Geochemistry of Water in Relation to Cardiovascular Disease. Subcommittee on the Geochemical Environment in Relation to Health and Disease, National Academy of Sciences, Washington, D.C., 98 pp.

Sacher, G. A. 1977. Life table modification and life prolongation. In Handbook of the Biology of Aging. C. E. Finch and L. Hayflick, eds. Van Nostrand and Reinhold Co., New York, pp. 582-638.

Shamberger, R. 1978. Some effects of selenium and zinc on cancer in experimental animals and humans. In Geochemistry and the Environment, Volume III: Distribution of Trace Elements Related to the Occurrence of Certain Cancers, Cardiovascular Diseases, and Urolithiasis. Subcommittee on the Geochemical Environment in Relation to Health and Disease. National Academy of Sciences, Washington, D.C., pp 105-108.

Tappel, A. P. L. 1978. Protection against free radical lipid peroxidation reactions. In Pharmacological Intervention in the Aging Process. J. Roberts, R. C. Adelman, and V. J. Cristofalo, eds., Plenum Press, New York, pp. 111-131.

Underwood, E. J., and H. Danbara. 1976. Role of trace elements in nutrition. In Proceeding of the Tenth International Congress of Nutrition, H. Koishi, K. Yasumoto, K. Iwai, M. Kanamori, Y. Muto, and T. Tanaka, eds., Proceedings Subcommittee of XICN, Kyoto, Japan, pp. 72-73.

13

SUMMARY AND CONCLUSIONS

Howard C. Hopps

SUMMARY

One portion of this report deals with specific geographic areas of increased and decreased longevity and the geochemical characteristics of these regions. Another portion concerns the problem of senescence in more general terms, considering causes, mechanisms of development, and effects, both direct and indirect.

To consider specific aspects first, a major problem was the definition of "aged," how to measure it, and how to identify appropriate geographic regions of increased longevity and decreased longevity. These problems are discussed in Chapters 2, 3, and 4. The areas selected for specific study are best described by the maps presented as Figures 2 and 3. Brief consideration has also been given to regions in Soviet Georgia, Kashmir, and southern Ecuador because of their reputation as increased-longevity areas--Chapter 4 and Appendix.

Geochemical characterizations of the two increased- and decreased-longevity regions in the United States were considered in terms of surface rocks and their common denominators (Chapter 8), contrasts in drinking-water quality (Chapter 9), soil as an environmental factor in aging (Chapter 10), and abnormal absorption of trace elements by plants (Chapter 11). Summaries and conclusions from these evaluations follow some general aspects of senescence. The Appendix comprises a tabular characterization of some environmental factors that may be related to reputed increased human longevity in the Georgian SSR; Kashmir, Pakistan; and regions of the Andes Mountains--southern Ecuador to the Altiplano.

"Aged," a state of postmaturity, is as difficult to define as "immaturity." Certainly the extent of deterioration associated with age cannot be measured by elapsed time; some persons 90 years old are less aged, functionally and pathologically, than others who are 60. This is a major reason why more and more research is being directed to the aging process--to separate the normal from the pathologic and to see whether the normal physiological process can be slowed. This general aspect of the problem, and methods of approach, is discussed in Chapter 2, which contains general considerations on aging and senescence.

Effects of senescence, in general, are the result of adverse changes, both quantitative and qualitative, affecting the structure, chemical composition, and function of all cells and tissues. This not only causes a decrease in the amount of function by cells and tissues but a distortion of their function, which involves time as well as substance; response to stimuli is delayed. Some of the most important functional changes act by interfering with homeostatic mechanisms that normally (in the mature) play such an important role in preventing serious disease or, if disease does occur, in effecting an efficient response. In an infectious disease such as lobar pneumonia response among the aged is characteristically too little and too late with respect to fever, leukocyte response, and antibody formation. And if the aged patient does recover, convalescence is prolonged and apt to be complicated. Chapter 5, on physiologic characteristics, and Chapter 6, on pathologic versus nonpathologic aspects of senescence, consider these problems.

Death is inevitable, but its how and when vary and are subject to some control. In this context it is probably counterproductive to consider a disease, such as atherosclerosis, an inevitable consequence of aging. On the other hand, although disorders such as cataracts and aortic ectasia are probably inevitable with time, even they are subject to control.

Old age is the time when defective parts formed during early life--or even in utero--may reveal their inadequacy for the first time. As a result, some of the so-called degenerative diseases (manifestations of generative defects) occur earlier than usual or are more severe than would otherwise have been the case. Moreover, the composite effects of injuries accumulated during the early and mid years produce defects in cells and tissues that may not become evident except under stress. Unfortunately, the gradually diminishing effectiveness of homeostatic mechanisms, an inherent characteristic of senescence, contributes to progressively increasing stress during old age.

Long life requires avoiding premature death from accident or disease. This means that consideration must be given to diseases notorious for their high mortality within the older age groups, e.g., atherosclerosis and cancer--which are discussed in Chapter 6.

In "quality of life," conditions that cause morbidity (illness) are every bit as important as those that cause mortality (death). Major so-called age-associated diseases causing death and/or disability include the following.

Wear and tear syndromes are numerous. One major category reflects decreased elasticity of elastica and stretching of collagen and reticular fibers, which leads to wrinkling of the skin, ptosis of abdominal organs, and dilation of the aorta and major arteries (ectasia), which causes altered blood pressure--characteristically an increased systolic with decreased diastolic pressure, e.g., 160/70. Some of the harder tissues are particularly vulnerable to wear from trauma, e.g., the teeth and the articular surfaces of bones. Osteoarthritis ("degenerative arthritis") is an important age-associated disease that often causes very serious problems.

Traumatic injury is important among the aged because instability, poor vision, and hearing loss all predispose to accidents. Moreover, the resulting injury is likely to be more severe because protective action is delayed during a fall. Also the bones are more fragile and the muscles bruise more easily. Finally, recovery is delayed and often complicated by infection or circulatory problems, e.g., pulmonary edema in the bedridden, also bed sores. The depressed homeostatic mechanisms make serious fluid electrolyte imbalance much more likely.

Increased susceptibility to infection has many contributing causes: less attention to body cleanliness, proneness to accidents and the increased prevalence of skin and mouth lesions (opening portals for infection), and inefficient mechanical "cleansing" mechanisms in the respiratory tract (e.g., emphysema, mucous plugs in bronchi) and urogenital tract (e.g., hyperplasia of the prostate). Inefficient homeostatic mechanisms have been mentioned. Decreased ability to produce antibodies is also a major factor.

Among the cardiovascular diseases, atherosclerosis is dominant, in part because it is so common and is a slowly progressive process. Almost surely this is a pathologic process, not a normal consequence of aging, because there are many parts of the world where this disease is rarely a serious problem, even in the aged population. Major specific conditions include arteriosclerotic heart disease--life is often terminated abruptly by sudden coronary occulsion; and arteriosclerotic brain disease--life is often terminated suddenly by "stroke."

Central nervous system (CNS) disorders include two major conditions: (1) gradual loss of individual nerve cells from toxic injury, viral infection, and local hypoxia related to microcirculatory phenomena, all of which are associated with gliosis--a contributing factor to so-called senile dementia; and (2) destruction of large groups of nerve cells, most often by ischemia or hemorrhage. Condition (2) includes infarction and "cerebral hemorrhage," both common causes of stroke.

Most kinds of cancer increase with age, but there are notable exceptions. In general, sarcomas are more common among the young, suggesting early exposure to short-acting carcinogens. Other exceptions include Hodgkins disease, tumors of the brain, carcinoma of the lung (peak incidence around 65 years), and carcinoma of the cervix (which levels off at about age 50-55).

In contrast to prevention of premature death, a more positive approach is to attack the aging process directly--seeking to understand the mechanisms of its action, then looking for ways by which the mechanisms can be blocked or slowed.

Many theories of senescence have been advanced to explain the aging process--as discussed in Chapter 7. It is doubtful that any one of them offers "the" answer. Almost surely, several of them, acting in concert, account for the major changes. Theories of aging fall into three major categories:

1. It results from intrinsic limitations in the cells molecular information system--a programmed event or a consequence of spontaneous errors in replication of DNA or in transcription of information.

2. It is a consequence of extrinsic injury--the culmination of damage from many incidents received throughout the years.

3. Major effects result from damage of key integrative tissues, particularly: (a) the interstitial connective tissues, (b) the neuroendocrine system, (c) the immune system, and (d) the liver.

These theories are summarized in Figure 33.

The question--How might geochemical factors affect senescence and age-associated pathology?--has been considered in Chapter 12. It was concluded that the geochemical environment could favorably affect the quantity and quality of human life by one or more of the following means:

1. By contributing to favorable nutrition by supplying proper amounts of macroelements and microelements, in appropriate balance, particularly the essential trace elements (the most pronounced effects would be expected during the early stages of development and growth of the individual.)

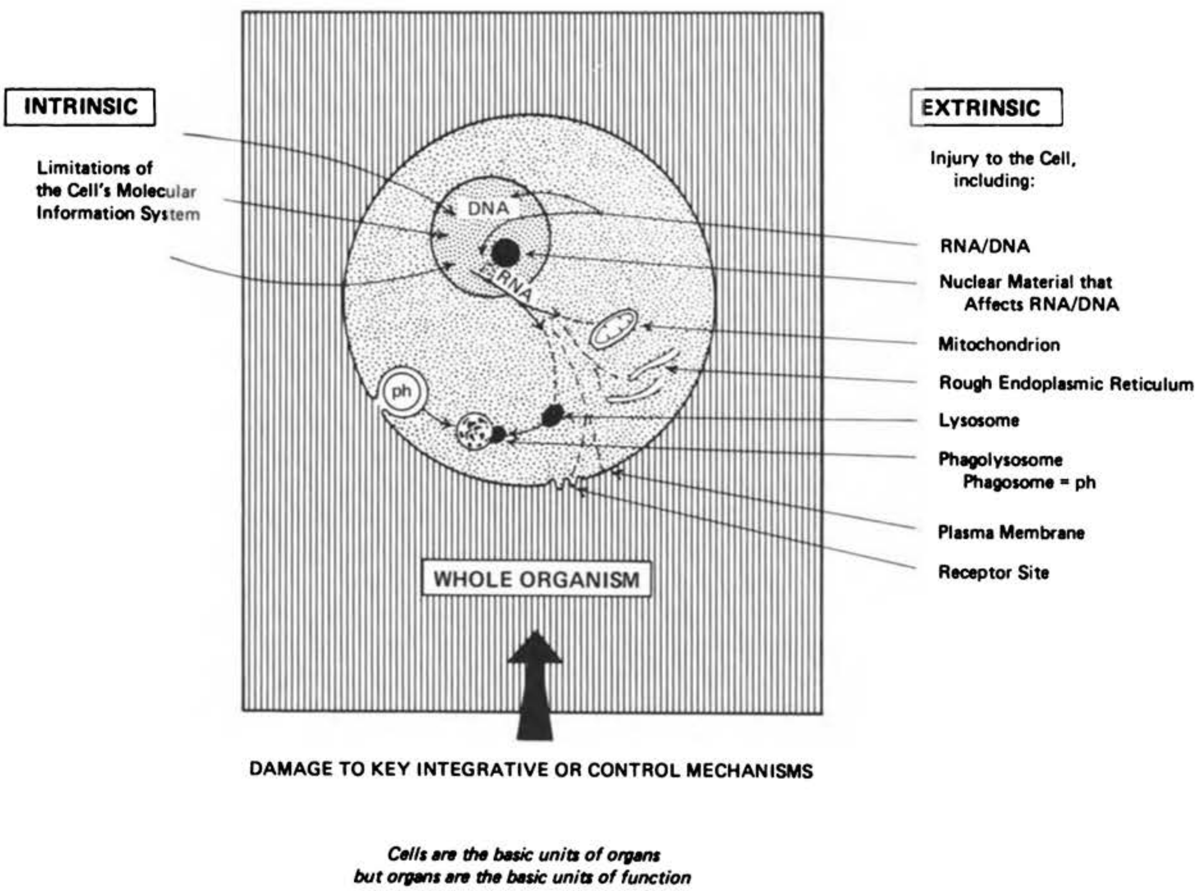

FIGURE 33 A schematic presentation of major theories and mechanisms concerning the causes of senescence.

2. By not contributing predominately toxic elements such as cadmium, lead, and mercury or toxic levels of essential elements.

3. By providing appropriate kinds and amounts of nutrient elements that inhibit the effects of ingested toxic elements.

4. By providing elements that act to moderate injurious agents and mechanisms, such as free radicals and lipid peroxidation, that appear to contribute directly to senescence.

5. By providing elements with specific protective effects against diseases, such as atherosclerosis and cancer, that cause premature mortality.

SUMMARY OF "GEOCHEMISTRY OF SURFICIAL ROCKS AND CLIMATIC FACTORS IN THE INCREASED-LONGEVITY LOW-DEATH RATE AND DECREASED-LONGEVITY HIGH-DEATH-RATE AREAS"

Clearly defineable common denominators in chemical and mineral properties characterize the surficial rocks, which interact with man's living environment, present in the low- (increased-longevity) and high- (decreased-longevity) death-rate areas of the United States that we have studied. The common denominators are strikingly different between the two areas with respect to nutrient ions, both major and trace, that are available from the rocks to man. The contrasting differences in the properties of the rocks are correlated with the differences in death rates in the two areas.

Such correlations, however superficially appealing, do not necessarily prove that the rocks are the major contributors to the health and longevity in the low-death-rate (increased-longevity) area. Nevertheless, because of the statistical consistency of the diverse alluvial, glacial, and aeolian surficial rocks to longevity, further extended investigation appears to be merited. In addition to appropriate medical tests, the contribution of rocks to nutritious food grown on their soils, to drinking water drawn from their groundwater, and to dust in the atmosphere should be looked at in greater detail.

The properties of the atmospheres in the two areas merit more investigation, e.g., the possible effects of relative humidity, mean barometric pressure, motion of the air, and net ionic charge on human health. Furthermore, the dust and fumes (both natural and anthropogenic) in the air may exert an active effect, either negatively or positively, on human health in the areas.

From a holistic viewpoint of general health conditioning, it seems reasonable that the combined effect of the several factors, favorable and unfavorable, in the two geographic regions studied may contribute to the differences in lifespans. Taking away, or adding, any single one of the rock properties may not affect health and longevity to a quantifiable degree, but all of them in each area may, by synergism, contribute significantly to the dramatic statistical difference in death rates of the two areas.

SUMMARY OF "CONTRASTS IN DRINKING-WATER QUALITY BETWEEN THE INCREASED-LONGEVITY LOW-DEATH RATE AREA AND THE DECREASED-LONGEVITY HIGH-DEATH-RATE AREA IN THE UNITED STATES"

Significant differences were found in chemical characteristics of drinking-water supplies in the two geographic regions studied.

In general, drinking-water supplies in the decreased-longevity area had the following:

1. Low dissolved solids (<50 mg/liter), except for those obtained from carbonate aquifers (dissolved solids >100 mg/liter);
2. Soft waters (<25 mg/liter) total hardness, except for those obtained from carbonate aquifers (total hardness >100 mg/liter as $CaCO_3$);
3. Low calcium (<10 mg/liter), except for those obtained from carbonate aquifers (calcium >20 mg/liter);
4. Very low magnesium (<5 mg/liter), except for those obtained from carbonate aquifers--analyses A;
5. Low sodium (<10 mg/liter);
6. Low bicarbonate (<100 mg/liter), except for those obtained from carbonate aquifers (bicarbonate >100 mg/liter);
7. Relatively high in dissolved organic compounds, especially in surface waters.

In contrast, drinking-water supplies in the increased-longevity area had the following:

1. High dissolved solids (>300 mg/liter), including many with over 1000 mg/liter dissolved solids;
2. Very hard waters (>200 mg/liter), including many with over 500 mg/liter hardness, as $CaCO_3$;
3. High calcium, (>50 mg/liter), including many with over 100 mg/liter calcium;
4. High magnesium, (>30 mg/liter), from limestone aquifers generally having <10 mg/liter of magnesium--some contained over 100 mg/liter of magnesium;
5. High sodium (>50 mg/liter), with sodium quite variable, ranging from less than 10 mg/liter to over 1,000 mg/liter;
6. High bicarbonate (>200 mg/liter);
7. Relatively low dissolved organic compounds.

The possible causal relationships of some of these striking associations has been considered in Chapter 12.

SUMMARY OF "SOIL AS AN ENVIRONMENTAL FACTOR IN AGING"

Soils in the two general (increased-longevity and decreased-longevity) areas selected for this study, the southeastern Coastal Plain and certain north-central states, have one thing in common: they are productive under proper management. However, the soils were developed under different climates and different vegetation; hence, such soil factors as the inherent fertility, base saturation of the colloids, the soil reaction, organic matter content, and the degree of leaching are generally favorable to the north-central region.

The overall range of soil properties is greater within the north-central region than in the southeastern Coastal Plain. Soil reaction, for example, varies from the acid soils of Wisconsin to the moderately acid to neutral soils of Minnesota and Iowa to the basic soils of Colorado. In many of the soils of South Dakota, Nebraska, and Colorado, zones of carbonate accumulation occur. In the Coastal Plain, all soils are acid in reaction and base saturation is low. Except in the Wisconsin soils, the organic matter content of the north-central soils ranges from 1 to 5 percent or more. In the Coastal Plain, little or no accumulation of organic matter occurs. Important areas of soils developed on sands occur in both regions, but those in Nebraska are subject to much less leaching, and the inherent fertility is greater than in those of the Coastal Plain.

The highly leached acid soils of the southeastern Coastal Plain are deficient in a number of the micronutrient elements, and applications of all the macronutrient elements are required for optimum crop production. In the north-central region, phosphorus is frequently a limiting factor, and a few soils require limestone to correct acidity. Micronutrient element deficiencies are infrequent; boron, copper, manganese, and zinc are occasionally applied for special crops. Except for a few areas of toxic selenium problems in Nebraska and South Dakota, the selenium supply as measured by its content in alfalfa and by animal requirements, appears to be similar in both regions--variable to adequate.

There is an abundance of generalized knowledge concerning the effects of different soil factors, climate, management practices, and genetic factors on the nutrient content of the many different species of food plants. However, specific information permitting meaningful comparative evaluation of the concentrations of the required mineral nutrients or of the presence of toxic elements in the locally grown foods in the two regions under consideration is inadequate.

Between the initial source of the mineral elements, the rock, and man there are at least two important systems that exert very high buffering actions--the soil and the plant. Each exercises a selective action on the uptake of the mineral elements available to it, thus restricting the kinds and quantities of the elements that eventually reach man. The implications of these potential blocks in the food chain must be realized in assessing the role of the geochemical environment in problems of health and disease in man.

Consideration of the total food supply of a specific community compounds the problem of relating a local environment to man. Obviously, the assessment of such a relationship must include studies not only of locally produced foods but also of the actual food intake by the human population. A study of this nature would be a productive one in identifying the impact of the local environment on man's health, including the phenomenon of aging.

Likewise, a study of inhaled dust as a contributor to the mineral status of humans merits greater attention. This pathway from the geochemical environment to man is far less confused than the food chain, particularly in Western society.

SUMMARY OF "ABNORMAL ABSORPTION OF TRACE ELEMENTS BY PLANTS: INDICATOR AND ACCUMULATOR PLANTS"

There is a growing awareness of heavy metal uptake by plants following the use of municipal effluents and sewage composts. In the nearly 100 papers on this subject over the last 15 years, only a few reports of heavy metal concentrations in the edible portion of the plant are available. Such data are also rare in the general agronomic literature. Much greater emphasis has been placed on the effect on yields; hence, little is known about the maximum range of concentrations of nonnutrient elements in the edible portion of plants where yields are normal, or at least acceptable. It seems, therefore, that any speculation concerning the available content of such trace mineral elements in rocks and soils in relation to health and disease in man is without merit unless something is known about the probable concentration of these elements in the edible portion of the plant.

In any evaluation of the soil-plant relationship to health and disease, or longevity, we need to consider, therefore:

1. The minimum level in the edible portion of plants of any plant nutrient also required by man that will sustain a normal acceptable yield of a crop.
2. The maximum level in the edible portion of plants of any nutrient element also required by man that can occur in a plant without affecting the yield of the plant. Tables of food composition provide a mean that includes the minimum levels but not the possible maximum levels.
3. The range of nonnutrient elements, particularly the heavy trace elements, that can occur in plants without adversely affecting yields.
4. The effects on the health, including longevity, of man of these ranges of elements in the edible portion of plants.

CONCLUSIONS

Senescence, defined as the progressive deterioration of the whole person after maturity, carries with it an ever-increasing, age-associated risk of death. From our evaluations it seems reasonable to conclude the following:

1. There is an absolute limit to age--a narrow range of years, not a fixed number--tied to the integrity of molecular information within the cell, that governs cellular reproduction and maintenance.
2. All cells are susceptible to injury by external environmental forces, and, in general, the more highly specialized the cell, the more vulnerable its structures are to injury.

3. Severe malfunctions of any one of several critical systems can profoundly affect the whole person by interfering with essential, integrated functions of multiple organs.

Senscence, then, is almost certainly the result of multiple processes, many of which operate at a cellular level. Some of these processes are internally regulated, perhaps genetically programmed; others are brought about by external factors.

In addition to the chemical, functional, and morphologic changes that characterize late stages of the aging process, i.e., senescence, a variety of age-related pathologic disorders occur with increasing frequency. Many of these are causally related to decreased homeostasis.

Most pathologic processes are preventable, at least in theory. Senescence, on the other hand, is considered to be a physiological process, and we have no reason to believe that it is preventable--but there is good evidence that it can be either delayed or accelerated. Thus there are two general ways of increasing the quantity and quality of life: (1) by preventing, delaying, or moderating the pathologic processes that cause (nonfatal) illness or premature death and (2) by favorably modifying the physiological mechanisms responsible for senescence.

Based on these conclusions, which are strongly supported by observations on patterns of human longevity, it appears that the "absolute" limits to life are rarely reached, because, before this time occurs, vital cellular mechanisms are critically damaged by environmental factors. In other words, the light bulb usually burns out before it is turned off.

The material presented in this report supports the view that a favorable geochemical environment may be an important factor in preventing or delaying important pathologic process and that it may, perhaps, influence favorably the aging process. Although positive evidence of cause/effect relationships is meager, the evidence certainly justifies an accelerated and intensified research effort in this area.

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RECOMMENDATIONS FOR FURTHER RESEARCH

Howard C. Hopps

Recommendations for additional research to determine the effects of the geochemical environment of aging are grouped in three general categories:

1. Further define geographic regions of increased longevity and decreased longevity, with special consideration for the very old, also for the quality of health among the aged. It is also important to investigate mortality in relation to the amount of time the individual has lived in the region.
2. Further define common geochemical denominators in areas of increased longevity and decreased longevity, also the biological relationships of these geochemical factors to the persons who live there.
3. Further define mechanisms by which geochemical environment can (a) prevent premature death, (b) improve the quality of health among the aged, and (c) favorably modify the aging process.

CATEGORY 1

In the study reported in this volume, a single increased-longevity area has been compared with a single decreased-longevity area. Increased and decreased longevity in other geographic regions should be defined and compared in terms of their geochemical environment. Also, different criteria for identifying increased- and decreased-longevity regions should be examined, including geographic distribution of "certified" centenarians.

More precise information about causes of death in high- and low-longevity populations is urgently needed, also information about mortality with respect to percentage of life spent in the region. The matter of quality of health among the aged also should be addressed in much greater detail. Although quality of health is difficult to determine precisely, a reasonable evaluation could be based on considerations of data pertaining to nursing home occupancy, frequency and duration of hospitalizations, requirements for home nursing services, and the like.

CATEGORY 2

In general, there is a need to expand geographically and sharpen, both quantitatively and qualitatively, the search for common denominators in regions or areas of contrasting longevity.

Information about rocks is deficient in areas of major concern to studies, such as those described in this report. This is because, historically, interest about structure of rocks has focused mainly on the time and conditions of their formation rather than on their mineral and chemical compositions. This is not so great a problem as it might seem, however, because the biological effects of rocks are mainly indirect--from their effects on the soils that they produce and on the waters that flow through or over them. It would be quite useful to have detailed geochemical and mineralogical information about rocks, particularly the surficial layer, but this would require an extensive and expensive program.

Water data of past decades are generally quite deficient with respect to many of the trace elements now known to be important to man. Analyses performed during the last few years have been much more comprehensive--and accurate--but emphasis has been on specific cations. Although there has been considerable study of fluorine and selenium, anions such as sulfides and borates are undoubtedly important and require much more attention. Metal sulfides, in particular, are variable and complex. A major need with respect to present-day water data is more precise characterization--a breakdown of the specific types of hard water, for example. Data processing problems with respect to water, as well as rocks and soils, are becoming much more complex as we explore the important biological interactions among the elements, for example, molybdenum and sulfur, zinc and copper, and iron and cadmium.

As to the biological relationships between people and their geochemical environment, we need much more data about consumption of water and information about how the water may have been modified by the local distribution systems, including water softeners and other treatment devices. Such information is essential to determine water's contribution of various macroelements and microelements, including primarily toxic ones.

There is a paucity of information about the effects of different soils on the trace element concentration ranges in the edible portions of plants grown on those soils. Much more information is needed about the concentration ranges of macroelements and microelements essential to man (but not plants) in various food plants--and this must take into account not only the species and variety of the plant but the soil, water, and climatic conditions under which the plant was grown. Much more information is also required as to the concentrations in food of plant origin of elements toxic to man in relatively small amounts. This will require determinations of the ranges of all such elements, particularly the heavy trace metals, that can occur in various kinds of plants without limiting their yields.

Much more information is needed about the chemical composition of windblown soil and rock dust--the amounts inhaled or ingested and the subsequent metabolic processing of this finely divided particulate material in the gastrointestinal tract.

Indirect biological relationships with soil and water are also important. Most of the extensive reports on human aging, including those long-term observations resulting from the Framingham and Tecumseh studies (recently reviewed by Dawber, 1980), have not included data that permit evaluation of effects from macroelements and microelements, much less effects of the geochemical environment as such. The following portions of two letters (from representatives of the Department of Health, Education, and Welfare, now the Department of Health and Human Services and the U.S. Department of Agriculture-Agricultural Research Service, now Science and Education Administration-Agricultural Research) clearly support the above statement:

Related to elderly persons participating in a Nationwide Household Food Consumption Survey,

> "National data on food intakes of elderly persons were obtained as a part of the 1965-66 Nationwide Household Food Consumption Survey. All elderly persons in households participating in the April-June 1965 quarter were asked to provide 24-hour recalls of their food intakes. Quantities of calories and 8 nutrients in each diet were developed by computer. The tape data contain no values for trace elements, unless you include iron."

Related to a 10-State Survey,

> "I regret that we are unable to fill your request of June 3, 1977 for dietary intake of trace elements by the elderly, by geographic region. The only mineral values which were calculated from the 24-hour recall data were for calcium and iron, and because of insufficient number, the data was not analyzed by individual states or by regions, but rather only by two 5-State groupings of high and low income ratio states.
>
> "The limitations of the 10-State Survey were clearly expressed in the final paragraph of the Highlights summary volume (enclosed). Two sentences from this paragraph follow. 'It must be realized that this and other current surveys are limited to the study of only a few of the essential nutrients--some dozen nutrients of the more than forty known to be essential for good health.... Current research suggests that a variety of essential but poorly studied nutrients--zinc, magnesium and vitamin E, for example--may in fact be significant for some fraction of the population.'"

CATEGORY 3

A basic mechanism by which the geochemical environment contributes to longevity as well as to quality of health is nutritional. All the macroelements and microelements essential for health are derived directly or indirectly from the geochemical environment--also the primarily toxic elements. This is the reason that it is necessary to get much more information about the amounts of important macroelements and microelements actually incorporated into the body, as discussed above. When such information is available, we will be in a much better position to evaluate effects of the geochemical environment, including synergistic and antagonistic reactions among the elements.

With respect to prevention of premature death, the disease of major importance is atherosclerosis, as this is the underlying cause of most cardiovascular deaths during middle and old age, and also of most strokes. We need to know much more about the following:

- The "hard-water factor" that in some instances appears to decrease risk of cardiovascular death;
- The role of zinc and copper in atherosclerosis by its effects on serum cholesterol levels;
- The role of cadmium in hypertension and the mechanisms by which other elements antagonize or reinforce toxic effects of cadmium;
- The role of chromium in diabetes mellitus (both hypertension and diabetes mellitus hasten the onset and greatly increase the severity of atherosclerosis).

Though less important than atherosclerosis, cancer is also a major cause of death among the aged, and we need much better information about the following:

- Trace elements that can act as carcinogens or cocarcinogens, and under what conditions;
- Trace elements that, when deficient, may predispose to cancer (e.g., zinc);
- Trace elements that may inhibit carcinogenesis (e.g., selenium).

With respect to improving the quality of health among the aged, all items mentioned above are important because they are related to morbidity as well as mortality. Specifically, we need much better information about the extent to which prolonged marginal or low level deficiency or excess of various macroelements and microelements contributes to a wide variety of disease/disorders, particularly osteoporosis, osteoarthritis, muscular weakness, ineffective wound healing and tissue regeneration, "senile dementia," infectious diseases in general, and autoimmune disorders.

With respect to favorably modifying the aging process, much more information is needed about macroelements and microelements that individually or because of imbalance can:

- Interfere with the cellular information system by inducing mutations, or by direct damage, or by damaging other cellular components (for example, lysosomes), especially by contributing to free radical formation and/or mechanisms of lipid peroxidation;

- Affect the structural and functional integrity of the interstitial connective tissues;
- Affect the structural and functional integrity of the neuroendocrine system;
- Affect the structural and functional integrity of the immune system;
- Affect the structural and functional integrity of the liver.

There is a large amount of circumstantial evidence pointing to the significant role of the geochemical environment in longevity and quality of life among the aged. Much additional research is required to identify the plus and the minus factors and to exploit the information thus gained by providing the necessary "environmental" ingredients to increase longevity and quality of life regardless of geographic location. This area is of great importance though enormously complicated, and it is not reasonable to anticipate quick, easy answers to the many questions that require them.

REFERENCE

Dawber, T. R. 1980. The Framingham Study: The Epidemiology of Atherosclerotic Disease. Harvard University Press, Cambridge, Mass., 257 pp.

APPENDIX

Environmental Factors in Relation to Longevity in Man[a]

Region	Environmental Factors
TOPOGRAPHY	
Georgian SSR, USSR	Three main structural regions: the Greater Caucasus Range on the north; the tectonic depression in the center; the mountains of Transcaucasia on the south. Undifferential vertical relief in the mountains. Elevations: sea level to 8000 ft to the mountain meadows; maximum, 12,000 to 18,000 ft
Kashmir, Pakistan	Greater Himalayas on the north; Lesser Himalayas on the south; valleys of the Vale of Kashmir between. Elevations: Vale, 5200 ft to 20,000 and 28,000 ft on mountain peaks
Andes Mountains Southern Ecuador to the Altiplano	Intermountain basins, elevations 7000 to 8000 ft dissected by rivers in steep channels down to 5000-ft elevation. Pasture and cultivated crops up to 14,000 ft. Maximum elevations, 27,000 ft
CLIMATE	
Georgian SSR, USSR	Western section bordering on the Black Sea, 40 in. on the coast to 100 in. of rain in the mountains. Drier in the eastern part. Hot summers with cool winters, subtropical
Kashmir, Pakistan	Rainfall in the Vale about 10 in. The temperature ranges from 11 to 99°F with wide variations depending on altitude. Subtropical, hot summers, cool winters
Andes Mountains	Moderate to cool days, cold nights with little change throughout the year. Average temperatures: 8000 ft, 56.8°F; 11,000 ft, 51.2°F; and 14,000 ft, 35.4°F
SOILS AND NATIVE VEGETATION	
Georgian SSR, USSR	Bog and alluvial soils in the central depression; typical Brown Forest soils on the lower south slopes; mountain meadow soils under the xerophytic forest cover. Vegetation: lowland, subtropical with palms, bamboo, and eucalyptus; lower slopes, oak, beech, ivy, and climatus; higher slopes, conifers, firs, and spruces, rhododendron and azaleas; drier areas in the eastern part, a characteristic steppe vegetation on the plains
Kashmir, Pakistan	Vegetation: below 5000 ft, shrubs, bamboo, and poplar trees; higher elevations, spruce and blue pine up to the alpine or mountain meadows. Mainly alluvial fans in the valleys
Andes Mountains	Mainly a grass or steppe vegetation with some trees along the streams
CROPS	
Georgian SSR, USSR	Central depression, medium late crops, corn (maize), sunflower, soybean, rice, and sugar beets; mountain meadows, grazing and vegetables
Kashmir, Pakistan	Vale, saffron (*Crocus sativa*), rice, corn (maize), barley, rape, mustard, and linseed; Upland, pastures
Andes Mountains	Native pasture grasses (low in protein, phosphorus, and copper), alfalfa (fertilized soils), several leguminoseae, sweet potatoes, cucumbers, papaya; corn, up to 11,000 ft, quinoa (a chenopodiaceae, high protein), wheat, up to 12,000 ft, potatoes, up to 14,000 ft

[a]Prepared by Kenneth Beeson.