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# *Geochemistry and the Environment*

*VOLUME III*

## DISTRIBUTION OF TRACE ELEMENTS RELATED TO THE OCCURRENCE OF CERTAIN CANCERS, CARDIOVASCULAR DISEASES, AND UROLITHIASIS

A Report of the Workshop at South Seas Plantation
Captiva Island, Florida
October 6–11, 1974
under the Auspices of the
Subcommittee on the Geochemical Environment
in Relation to Health and Disease
U.S. National Committee for Geochemistry
Assembly of Mathematical and Physical Sciences
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# *Dedicated to*

HENRY LAURENCE LUCAS, JR. (1916–1977)

"CURLY" LUCAS, *William Neal Reynolds Professor of Statistics and Director of the Biomathematics Program at North Carolina State University, was a Fellow of the American Statistical Association and a Fellow of the American Association for the Advancement of Science. He was the first Chairman of the Committee of Presidents of Statistical Societies in 1962 and wrote the guidelines under which it still operates. As an investigator and as a teacher, he was a major contributor to the development of quantitative methods for research in animal and plant physiology, in agriculture, and in environmental science.*

*He died of cancer June 8, 1977.*

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# *Preface*

This volume concludes the trilogy of reports of workshops held by the Subcommittee on the Geochemical Environment in Relation to Health and Disease (GERHD) at Asilomar, Capon Springs, and Captiva Island. These reports and the workshops are all outgrowths of discussions and actions begun at the 1968 meetings of the American Association for the Advancement of Science (AAAS) in Dallas, where interested individuals from widely divergent fields resolved to further interdisciplinary studies of ways to prove or disprove causal relations between naturally occurring chemical elements in the environment and animal (including human) health. Since then, interest in the natural and man-made occurrence of trace substances in the environment and their possible health effects has grown immensely. The Society for Environmental Geochemistry and Health has been established, and its official publication, *Interface*, provides a much-needed link between the specialists with diverse interests that comprise the Society's membership.

The NAS-NRC Subcommittee on GERHD has more recently adopted a panel format in which *ad hoc* panels prepare reports and make recommendations on timely subjects and go out of existence when their job is complete. Four such panels are currently operating: the Panel on the Geochemical Environment and Urolithiasis (POGU), the Panel on Aging and the Geochemical Environment (PAGE), the Panel on the Geochemistry of Water in Relation to Cardiovascular Disease (POWC), and the Panel on the Trace Element Geochemistry of Coal Resource Development Related to Health (PECH); their reports are expected to begin emerging soon. Several federal agencies also support similar health-related committee and panel activities in other parts of the National Research Council, as well as similar research in national laboratories, universities, and other institutions, both public and private. Earlier volumes in this series carried references to other symposia and conferences on the general topic of trace elements and health, but the formulation of such a list has become a project in itself, carried out at the Oak Ridge National Laboratory, P.O. Box X, Oak Ridge, Tennessee 37830.

## TRACE ELEMENTS

The term "trace elements," as used herein, conforms most closely to its biomedical definition. That is, trace elements are those that ordinarily comprise less than 0.01 percent of an organism. Although ambiguity is apt to occur in only a relatively few instances, geochemists and geologists ordinarily regard trace elements as those other than the eight abundant rock-forming elements (oxygen, silicon, aluminum, iron, calcium, sodium, potassium, and magnesium) found in the earth's crust. Mineralogists consider trace elements as those that are nonessential components found in small quantities, ordinarily comprising less than 1 percent of a mineral.

## GEOCHEMISTRY AND THE ENVIRONMENT

In the *Geochemistry and the Environment* series, Volumes I and II emphasize the health aspects of certain selected trace elements in man's environment contributed from *natural* sources. In both, individual chapters are devoted to individual or closely related elements. Most of the elements considered were studied because of their essentiality to man. Volume III, which is based on a 1974 workshop and some updated material, begins to apply some of the concepts and facts learned in preparing the earlier reports; it considers the sources and pathways by which these trace elements get to man through the food chain from rocks, water, and soils to plants and food. From there, it considers three disease groups that may be both causally implicated and significantly distributed geographically. The three disease areas are esophageal, stomach, and colorectal cancer; cardiovascular disease including hypertension and stroke; and urolithiasis, or more particularly kidney stones, rather than bladder stones. The text of the volume closes with brief assessments of how innovations in geography, cartography, remote sensing, and data-information systems may be brought to bear on such broad and difficult problems. The appendixes contain information or examples of major data sources and concepts.

# Acknowledgments

The Captiva Island Workshop of the Subcommittee on the Geochemical Environment in Relation to Health and Disease was made possible by support from the U.S. Environmental Protection Agency, the U.S. Atomic Energy Commission (later the Energy Research and Development Administration and now the Department of Energy), and the Division of Advanced Environmental Research and Technology, Research Applications, National Science Foundation, under Contract NSF-C310, Task Order 206; the U.S. Bureau of Mines and the U.S. Geological Survey under Contract S0144074; and the National Cancer Institute under Contract N01-CP-45616. The participatory support from these agencies and their representatives, as well as the financial support, is gratefully acknowledged.

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H. R. van der Vaart, a colleague of Dr. Lucas' in the Department of Biomathematics at North Carolina State University, kindly worked with the editor to complete the work on Dr. Lucas' section following the latter's untimely death.

The Subcommittee also thanks the chairmen of the various Work Groups and the other participants for their contributions of time, effort, and scientific expertise both at the Workshop and since—their help added much to the value of the report.

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# Contents

# I

# *Introduction, Summary, Recommendations, and Keynote Address*

## INTRODUCTION

The third Workshop of the Subcommittee on the Geochemical Environment in Relation to Health and Disease (GERHD) was held at Captiva Island, Florida, on October 6–12, 1974. This volume is an extended and updated proceedings of that Workshop. As with the other two Workshops, the participants sought to learn more about the positive aspects of the role that the geochemical environment plays in maintaining health and in causing specific diseases of man and other animals. To this end, scientists and specialists from many different disciplines were invited to come together in an effort to interact and consider ways of attacking this broad and complex problem.

Each of the various disciplines represented at the Captiva Island Workshop was selected for two principal reasons. The first reason was to keep those in other disciplines from going out on a long, thin limb by forcing them to the reality expressed by the statement: "That may sound like a good idea, but it won't work, because premise *X* is false." The other reason is a bit more positive. Each discipline brought its own perspective and provided a basis for suggesting correlations that those in other disciplines might have missed. This became clearly evident in the development of important information that occurred during the Workshop and subsequently, when participants were putting their new ideas on paper. Each of the participants made considerable advance preparation for the Workshop; thus a good part of the data base was available at the time. But a much greater pool of pertinent data—at the beginning of the session, at any rate—remained stored in the participants' minds, because it did not seem pertinent *at that time*. Many of these data emerged during the conference—and later, because of the effective communication and true interaction that occurred among scientists of widely varied disciplines. Once again, group effort, represented in this instance by the Workshop, has developed a whole that is considerably greater than the sum of its individual parts.

The Captiva Island Workshop was a natural outgrowth of the two that preceded it. They concentrated on specific trace elements and looked for possible effects that deficiency or excess of the individual trace elements might have on health and disease. Unlike its predecessors, however, the Captiva Island Workshop approached the problem by considering environmental factors related to the disease. Three broad disease categories were examined to see which trace elements might contribute to, cause, or act to modify the course of the disease in question, under what circumstances, and how. At the outset, the Workshop participants were presented with, and accepted, eight basic tenets as a guide to their deliberations. These fall in a logical sequence, as follows:

- Disease is the consequence of multiple factors acting together, but not always simultaneously.
- Some of these causes are intrinsic; others are extrinsic.
- Extrinsic factors are more important from a pragmatic viewpoint.
- If extrinsic factors are not randomly distributed, then

their location is important, as spatial coincidence with disease occurrence represents an association that *may* be causal.

- Merely knowing where things are is not enough; we need to know how much, in what form, and when.
- The more we learn about the ecology of health and disease, the more evident becomes the importance of causal factors that are related to the geochemical environment.
- Spatial distribution of the quantitative levels of environmental factors and disease distribution can be very effectively portrayed in map form.
- The data are so numerous and so complicated that selection of the primary components often requires sophisticated mathematical approaches and computer science technology.

The immediate, tangible objective of the Captiva Island Workshop was to discover associations between the geochemical environment and particular diseases that would lead to the *shrewd guess*—to provide the sort of insight that is so often the basis for the crucial experiment. Obviously, it is premature to estimate the value of these new leads at this time. It will be years before we know what important discoveries may have been stimulated by one or more of the new ideas presented in this volume. If past experience continues to be a reliable guide to the future, the most important of these ideas will most likely turn out *not* to be something esoteric but something relatively simple and imminently useful.

HOWARD C. HOPPS
*Workshop Chairman*

## SUMMARY

This volume, the result of a multidisciplinary effort to identify cause–effect relationships between the geochemical environment and specific diseases of man and other animals, focuses on causal effects of trace elements and certain simple inorganic substances such as nitrates. It has been a productive effort, as the contents of this volume clearly demonstrate.

One of its most important yields is the enormous number of concise data that have been gathered together *and correlated*, some in the form of maps that show distribution patterns of various substances and conditions, others in tabular form that consider qualitative and quantitative aspects of the geochemical environment that may affect health and disease in human beings and other animals. Another important yield is the precise identification of serious defects in the data base at three levels:

- It is evident that there are *insufficient* data within each of the disciplines represented—for example, more data are needed not only as to the kinds and amounts of metals in water of different regions but also as to their chemical speciation.
- There are problems in *integrating* data drawn from the different disciplines that lack unifying characteristics. Not only is there the problem of jargon, i.e., the language peculiar to each discipline, but there is a broader semantic problem in that the same word may have different implications when used by the geologist, the agronomist, the epidemiologist, or the pathologist. For example, health áspects of soils are most commonly related to yield and quality of plants (which require only 5 of the 14–16 trace elements considered essential for humans), or, if the data do address disease in animals, they deal mainly with nutritional problems of grazing animals.
- Many of the data are so closely tied to discipline-oriented problems that their *pertinence* to other situations is sharply limited. For example, most of the available data on the three categories of disease that comprise the focal point of this study concern the characteristics, course, and treatment of the established disease rather than the multicausal factors responsible for its inception. To be sure, there is considerable information on distribution patterns, but the most reliable information of this sort is based on mortality figures that reflect the end point of a process that took many years to develop; thus the geographic place of occurrence may not be sufficiently well defined to allow meaningful connection with environmental factors.

Perhaps the most important yield of all is the group of specific recommendations as to what additional work must be done to further identify and characterize important causal relationships between geochemical environment and health and disease so that the quality of health may be improved and certain diseases may be prevented altogether or their course favorably modified.

This report is logically divided into three major parts, which consider the following:

- The source of the trace elements—how they get into man and other animals and in what form.
- What they do once they get there in terms of contributing to cause and/or behavior of certain diseases.
- How to deal most effectively with selection and processing of the data so that they will yield maximal information about cause–effect relationships.

Each of these three parts is divided into chapters that are listed below, along with descriptive accounts (rather than summaries) of their contents. Thus what follows is intended to serve as a guide for the reader—to provide an overview of the concepts and aspects considered in each of the chapters and how various problems are approached. (The roman numerals in the following paragraphs correspond with the chapter numbers.)

II. Rocks: The Geologic Source of Most Trace Elements. The distribution and geochemical character of surficial rocks are discussed, as is the manner in which they

contribute trace elements and simple inorganic compounds (such as nitrate) to water and soil. Geochemical reconnaissance surveys are considered in some detail, including the ongoing extensive program in the United Kingdom based on stream sediment analysis. Special considerations are given to radioactive elements, selenium, molybdenum, and lead. Some observations on cancer occurrence as related to particular types of garden soils are briefly discussed, including their geochemical significance. An important section deals with pollution sources of metals.

III. Water: Trace Elements in Solution. This chapter begins with a rather detailed consideration of the chemical characteristics of surface water and groundwater, including the biologic importance of metal speciation. Problems of accurate sampling and analyses are treated at some length. This is followed by a pertinent description of the effects of treatment on natural water and some of the important things that can happen to finished water in the course of its travels through regional distribution systems and the various pipes and plumbing fixtures within the home before it finally emerges from the tap. The section dealing with hard water includes consideration of the buffering effect that decreases toxicity of a variety of trace substances. This has a particularly important bearing on some of the cardiovascular diseases discussed in Chapter VII. The chapter concludes with a general discussion of the relation between water quality and health and disease.

IV. Soils: Their Distribution, Uses, and Trace-Element Concentration. The various classifications of soil types are discussed and related to the basic soil map that is presented. This is followed by a review of the considerable information about trace elements in the soil related to fertility. Nutritional problems in grazing animals are discussed, using cobalt and selenium to provide illustrative examples of trace-element effects. The nature and usefulness of interpretive maps are considered, also some of the recently developed trace-element maps of the United States. Finally, there is a highly pertinent consideration of bioavailability of mineral elements in soils and the use of plants as a tool for bioassay. Much of the important content of this chapter is in the form of tables and map information, which show the abundance and distribution of trace elements in soils of different types and regions.

V. Plants and Foods of Plant Origin. Soil–plant relationships are discussed in some detail, especially the mechanisms by which plants incorporate minerals from the environment and factors that affect these mechanisms. Considerable data are provided as to normal values of trace elements in plants, including the localization of minerals within different portions of specific plants. Iron, zinc, and arsenic are given special attention. The importance of accumulator plants is discussed, with emphasis on selenium, fluorine, and zinc accumulators. Turning to a different aspect, there is an important consideration of bioavailability of mineral elements within plants, including effects—both synergistic and antagonistic—of interacting substances within plants, e.g., phytates. A separate section deals with the effects of food processing on its mineral content, discussing in some detail the enhancement of foods with iron and with iodine. Another section deals with what foods are eaten, how often, and by whom. The chapter concludes with a section on a particularly timely but fast-moving field: the effects of sewage-recycling activities and land application of coal fly ash on the trace-elements concentration in foods of plant origin, which emphasizes the potentially harmful additions of lead, copper, zinc, chromium, cadmium, and nickel. Except for the foregoing, the contribution of fertilizers to the distribution and availability of trace elements has received little attention here.

VI. Cancer. The chapter begins with a general discussion of geographic patterns of cancer and some relevant environmental associations. Problems in determining cause–effect association are emphasized in a review of the complex, multistage process of carcinogenesis. Specific trace elements that have been implicated in carcinogenesis are identified, and the role of nitrates and nitrites as precarcinogens is discussed. Difficulties in diagnosis of cancer, especially specific categories arising in the stomach and sigmoid-rectum are considered in some detail. A separate section on the epidemiology of colorectal cancer considers the beef and fat hypothesis and the fiber hypothesis and focuses on the accumulation and evaluation of evidence linking consumption of beer with colorectal cancer, using this as a model study to illustrate the epidemiologic approach to determining cause. The etiology of gastric cancer is considered in a separate section, which, among other things, emphasizes the importance of subdividing such categories as carcinoma of the stomach into histologically defined subtypes in a search for cause–effect relationships. The final section deals with some protective effects of selenium and of zinc on cancer in experimental animals and humans. In the relation between environmental selenium and cancer in humans, several caveats are appropriate:

- The data must be pertinent with respect to their use; the selenium content of forage in a region is not necessarily an index of human intake of selenium.
- The size of the geographic area from which one derives representative data is critically important. If the area is too large with respect to the item measured, the values may vary so widely that an average figure has little significance. The selenium content of soil is notoriously variable in this regard.
- Mere association of a factor with a condition does not in itself imply a cause–effect relationship.

VII. Cardiovascular Disease. The importance of precise characterization of the particular cardiovascular disease under consideration is stressed and related to the fact that cause–effect relationships vary enormously among the different types. General characteristics of causal factors are discussed, with emphasis on the way that they act, e.g., as continuous variables that are dose-related versus variables that have an all-or-none effect, depending on whether they fall above or below a specific threshold level. Interrelation among coronary arterial disease, stroke, and hypertension are considered. This is followed by a discussion of mechanisms by which trace elements could act to affect the occurrence and behavior of specific cardiovascular diseases. The association between consumption of soft water and risk of death from coronary heart disease is dealt with in some detail. A separate section examines the role of cadmium in hypertension. Another important section considers the complex interactions among elements, and with binding ligands, as these affect health and disease, particularly diseases of the cardiovascular system. A pertinent section deals with descriptive associative methodology, which, although directly related to cardiovascular disease, is also appropriate to the other diseases considered in this volume. The identification of 200 extreme-rate counties in the United States for death from cardiovascular disease and their localization in map form represent an important new aggregation and display of mortality data. The chapter concludes with a section on water hardness and geochemistry, which supplements and complements the material in Chapter III.

VIII. Urolithiasis. This chapter begins with a discussion of effects from the formation of kidney stones, pointing out that, because morbidity far outweighs mortality, the conventional, statistical (mortality) data do not adequately reflect the importance of the problem. Geographic distribution of urolithiasis is discussed and supplemented by presentation of a map of distribution in the United States. The chemical characteristics of renal stones are discussed, along with the mechanisms of their formation. Association of renal lithiasis with certain soil types and water quality is discussed, and some possible causal relationships are suggested.

IX. Geography–Cartography. The importance of maps as a mode of displaying disease data and associated environmental factors is developed. Pertinent technical aspects of map production are discussed, emphasizing the importance of appropriate classification and choice of class interval. New information, in terms of its arrangement and display, includes ten maps, which accomplish two things:

- Generally, they demonstrate clearly that a significant proportion of many plants consumed directly by humans are derived from quite small, well-defined geographic areas; and
- Specifically, they show the locations of these areas for important plant foods.

An interesting section deals with the potential of remote sensing for inventorying surface features on earth and their possible use as a means of evaluating geochemical environment. An important section concerns methods by which medical data presented in map form (at a high level of resolution) may be directly correlated with other variables, including environmental factors, using a relatively new technique of automated cartography developed by the Bureau of the Census. A valuable list of useful base maps and reference maps is included in this chapter.

X. Data and Information Systems. This chapter begins with a general consideration of the application of computers to manipulation of data and their display in various forms, including maps. One section deals with the problems involved with large data bases such as those that may be appropriate in determining effects of geochemical environment on health or specific diseases.

There are not very many new data in this volume, but there is much new *information*. The important accomplishment has been to bring existing data together in new ways so that relations previously overlooked have become evident. William Warntz's description of this sort of accomplishment is appropriate: "The gains come from a shift in point of reference, different ways of restricting variables, cleverness in manipulating data." Goethe said it more succinctly: "Everything has been thought of before, but the difficulty is to think of it again."

HOWARD C. HOPPS
*Workshop Chairman*

## RECOMMENDATIONS

The major recommendations that emanated from the Captiva Island Workshop are discussed toward the ends of the various chapters or sections throughout this volume. They are also compiled here so that they may be more easily considered as a group, although this removes them from their proper context. Readers are, therefore, urged to refer to the accompanying material within the volume.

The more significant recommendations contained in the text follow (the roman numerals refer to the chapter numbers in the text).

### II ROCKS: THE GEOLOGIC SOURCE OF MOST TRACE ELEMENTS

#### *Long-Range Plan for Comparing Geochemical and Disease Data*

A long-range plan for action by rock geochemists should include the following:

- Preliminary compilation of computerized maps of geochemical provinces in the United States showing existing data on elemental distribution, carefully assessed as to its source and anomalous character in view of the reason for collection.
- Additional surveys at appropriate densities to gather meaningful information about bedrock/overburden geochemistry to provide systematic data in areas of present insufficiency and to disclose regional facies variations within the geologic units.
- Production of general maps by automated proce-

dures, which lend themselves to the superimposing of multielement patterns of elemental distribution, to permit comparison of disease incidence with more than one element at a time. Elemental data based on rock, stream sediment, and soil analysis should be supplemented by interpretive notes on the source and mode of dispersion of those elements of prime interest.

• Comparison of these maps with maps of disease incidence by medical epidemiologists.

• Performance of closed-spaced sampling and epidemiological studies in target areas that emerge from the overall study as being particularly anomalous, i.e., high or low.

*Short-Term Plan for Immediate Implementation*

• Because geochemical and disease data for the three diseases in question are not available for all parts of the country and the acquisition of total coverage will be time-consuming and expensive, a compromise for immediate implementation is suggested. Epidemiologists who have access to such data for stomach cancer and heart disease should furnish rock and water geochemists with lists of 100 highest-incidence counties and 100 lowest-incidence counties in the United States for the specific diseases on which they work. From these, ten or more counties from each group for which pertinent elemental information exists should be chosen for comparative study. Rock, water, and disease data should then be sent to soil and plant specialists for further study, and then to the epidemiologists for final evaluation. It is also recommended that a group be formed from Workshop participants, from interested government agencies, such as the Bureau of Mines and the Environmental Protection Agency, and from private industry, such as sanitary engineering firms, to assess the effect of industrial pollution in these particular counties.

• Information is also available to permit a study of trace element distribution and availability of metals in peats of the United States from existing U.S. Geological Survey files.

## III WATER: TRACE ELEMENTS IN SOLUTION

• Increase the usefulness of existing data on both surface-water and groundwater geochemistry (mostly major-element data—calcium, magnesium, sodium, potassium, $HCO_3^-$, and chlorine) by developing maps of water-quality data on a distribution-system basis using low-, medium-, and high-order streams, terms that stream morphologists use to classify streams according to their number of tributaries.

• More information on concentrations in water of all the trace elements mentioned in this study is needed. Except for iron, manganese, nitrate, and phosphate, insufficient effort is routinely directed toward determination of trace elements in water.

• Water-quality maps that separate concentrations of calcium and magnesium, rather than combining them on a hardness map, might be of considerable value. Maps of trace-element speciation in natural water systems would be even more valuable. Further refinement is needed in the manner of reporting data. Large amounts of data reported as "less than" are of little value to those attempting to make comparisons between incidence or absence of a particular health problem.

• Until the water-quality data situation improves, physicians and epidemiologists should select small study areas with high- and low-incidence rates for a given disease to permit evaluation of available water-quality data for the area. This procedure would provide better balanced data for statistical evaluation. Alternatively, areas of high or low concentration may be identified for correlation with available morbidity or mortality data.

• Additional support should be made available for training people for the water-treatment industry to permit establishment of reliable information on water quality and the effects of water treatment on trace elements. The development of uniform standards for sampling and analysis is also in need of support. State agencies charged with the collection of data concerning the quality of water consumed at the tap should be given more assistance, so that the information needed by epidemiologists may be made available.

• A system must be developed for collecting an accurate data base on specific aquifers and for determining the quality of the tap water derived from these aquifers. Such data on groundwater would generally be more reliable for epidemiological work, because its quality normally varies within a smaller range than does the quality of surface water.

• More data are needed on the concentration of those waterborne trace metals that may be associated with specific diseases. These data should be based on the chemistry of the water at the tap.

• There should be a concomitant development of uniform standards for collecting, storing, and analyzing water collected at the tap. It is absolutely necessary that the many disciplines involved in research on water quality use compatible techniques to permit valid comparisons.

• Initially, a data-source information system should be developed so that epidemiologists may select prime study areas. Ultimately, however, a completely compatible information storage and retrieval system should be established to allow researchers of various disciplines to retrieve data and maps quickly. For information to be truly effective, it must be current, multidisciplinary, and available on a demand basis.

• There is a need to develop a data base and analytical procedures on the chemical form of the metals associated with disease. In particular, it is necessary to know what anions are associated with the metals in high- and low-risk areas and whether organometallics are a major problem. Singer (1973), has reported clear evidence that organic compounds materially increase the mobility of metals in an aqueous environment. Perhaps the same phenomenon also makes these metals more available to biological systems.

- More chemical data are needed to characterize the surface-water and groundwater supplies that are used in the United States, particularly for areas with very high and very low incidences of disease.
- Long-term multidisciplinary studies should be made of the relation between the geochemical environment and disease, particularly in areas where the existing data base is reliable. The studies should receive stable funding of sufficient duration so that complete data collection and analysis can be made without the constant stress of fund seeking.

## IV SOILS: THEIR DISTRIBUTION, USES, AND TRACE-ELEMENT CONCENTRATION

Various kinds of soil maps may be useful in evaluating the role of soils in the incidence of the human diseases.

- An assessment of the role of soil in human health and disease may be greatly enhanced when evaluations are focused on specific elements or suites of elements. Deficiencies in existing information should serve as a stimulus for additional research.
- Greater use of the soil maps available in most countries should be made to evaluate disease incidence among people living in similar climates in different parts of the world, which will permit assessment of their different dietary habits.
- Soil surveys should be developed to help assess within-area differences in mortality rates. Their application may lead to the identification of important environmental factors, including soils that contribute to mortality rates. Current summaries by counties undoubtedly mask out important within-county differences in mortality rates that contribute to ill-defined patterns of disease incidence. Detailed soil surveys for high-incidence counties are available from local and state offices of the Soil Conservation Service, the State Agricultural Experiment Stations, and libraries of the land-grant colleges and universities.

## V PLANTS AND FOODS OF PLANT ORIGIN

### *Research Needed on Relation of Mineral Elements in Foods to Disease*

There are valid leads to suggest a role of mineral elements, particularly those occurring in trace amounts in water and food, in the etiology of human disease. Hence, it is necessary to understand how much of the variability in human illness is attributed to the variability in intake of these elements.

The geochemical environment, embracing rocks, water, soils, and plants, plays a leading part in contributing to this variability in intake and, consequently, in the occurrence of disease. It is important in considering mineral elements as they relate to specific disease to keep in mind that a large proportion of the total mineral element intake is derived from deliberate food enrichment practices, e.g., iron, and inadvertent entry of mineral elements into the food supply because of technical practices, e.g., iodine.

The commercial production and distribution of fruits and vegetables is so concentrated in a relatively few regions, and the difficulties of relating rock, soil, and plant composition to diseases of man are so profound, that it is recommended that research be directed toward the development of methods for the study of trace-element concentration and degrees of variability in prepared individual foods, meals, and total diets, including foods of animal origin, that are ***actually eaten*** by various segments of the population.

Such investigations would necessarily stress the possibility that certain accumulator plants (those that tend to concentrate in their tissue unusual quantities of a chemical element from the soil) will enter the human diet. Special attention should be given to those elements that are considered to be toxic when present in appreciable quantity in the edible portions of such plants.

The methods of study developed and the knowledge acquired concerning the composition of individual foods, meals, and total diets can be directed, in collaboration with workers in other disciplines, to trace-element intake by man in specific target areas. Unusually high-disease-incidence areas can be compared with areas of low incidence to develop possible relationships of one or more mineral elements to a specific disease.

### *Research Needed on Bioavailability of Trace Elements in Foods to Man*

The role and importance of the metal complexes in plants and the factors in plants that influence the utilization of those metals by man should be the subjects of an accelerated investigation emphasizing new approaches to bioavailability such as the single- and double-isotope techniques of labeling foods and added nutrients. Both the antagonisms and synergisms that may exist among the mineral elements as they affect biological availability should be investigated, along with greater emphasis on the effects of fertilizers.

The possibility of developing a breeding program with plants with the objective of eliminating or reducing the concentration of phytic acids, oxalic acids, or other inhibitors to utilization, should also be considered.

### *Research Needed on Recycling of Sewage Sludge and Effluents and Land Application of Coal Fly Ash*

There is a growing tendency to reduce the dumping of waste materials into rivers and other bodies of water and to use soils for this purpose. While there are advantages—the conservation of nitrogen and phosphorus and the need for irrigation waters in some regions—disadvantages such as the accumulation in soils of high concentrations of the heavy metals, often as organic complexes, and their subsequent uptake by food crops and the acreage of land ultimately required must be carefully considered. Accordingly, we make the following recommendations:

- For long-range action, remove heavy metals from industrial wastes prior to entry into municipal treatment plants.
- For short-term action, require periodic analyses as the basis for restraints to application to soils of sewage effluents containing zinc, copper, nickel, mercury, and cadmium and fly ashes containing molybdenum and boron.
- Sludges should not be incinerated, as considerable proportions of cadmium, lead, and mercury, for example, are thereby volatilized. Binding of such materials to clay and organic particles of soils may be preferable to inhaling them.
- More data should be obtained on the movement by recycling into the food chain of nickel, mercury, cadmium, and other elements.
- Measure the flow of elements in ecosystems by alternative disposal procedures.

## VI CANCER

### *Recommendations for Research*

- Much more information is needed on the time, place, and circumstances in which specific (human) cancers begin their development.
- Much more information is needed on the origins, chemical forms, and distribution patterns of those trace elements in the geochemical environment that are suspected to affect the occurrence and behavior of cancer.
- Considerable additional research and development remains in the broad area of data evaluation, manipulation, and output, including computer production of maps.
- Additional research is required to develop mathematical models that will further elaborate factors and parameters that connect geochemical environment with occurrence and behavior of specific cancers.
- In terms of cause of or protection from cancer, much more information is required about differences in the biological action of individual trace elements, depending on whether they are derived from water or vegetable or animal foods.
- There have been many suggestions that certain types of soil "favor" occurrence of human cancer. Such relationships need to be explored in much greater depth.
- Additional information is needed concerning those trace elements that have significant effects on intestinal microflora, including whether they act to affect the *in vitro* production or destruction of carcinogens or cofactors.
- More information is required about the factors that effect conversion of nitrites to nitrosamines, in the context of significant human exposure, and the mechanism of their action.
- A great deal more work needs to be done to determine effects of geochemical environment, particularly deficiency of certain trace elements, on production of carcinogenic intermediary metabolites by microorganisms under natural conditions, e.g., *Aspergillus flavus*/aflatoxin.
- Additional information is necessary to determine whether the apparent protective action of selenium (and zinc) against cancer is real, and if so, the optimal intake of these elements, the optimal tissue levels, the most effective chemical forms, and, finally, determination of the significance of the relationship between (available) selenium content of the soil and prevalence of different types of human cancer occurring in the region.
- More information is needed about the role of certain trace elements that present rather consistent, marked variations in concentration in the blood and tissues of patients with cancer, e.g., copper. Some of these elements may have significant effects on metabolism of the tumor, which can be exploited in prophylaxis or therapy.

## VII CARDIOVASCULAR DISEASE

### *Policy*

- Interagency and interscientist communication should be improved to optimize research opportunities.

### *Environment*

- Practical support mechanisms for research on the *chronic* effects of trace elements should be sought. Attempts should be made to ascertain the contribution of foods and geochemical environment as well as water to the trace-element environment of the individual.
- The mapping of food origins and consumption at local sites of interest should be undertaken.

### *Fundamental Studies of Metabolic Nature*

- Better understanding of the fundamental metabolism and functions of trace elements is needed. Studies of the bioavailability of elements of interest should be undertaken.
- Improved understanding and techniques for measuring these elements are needed with particular reference to stores, balance, and turnover. Interactions such as that between zinc and cadmium in relation to hypertension need to be elucidated.

### *Associative Studies of Cardiovascular Disease*

- Survey studies of relations of water composition to cardiovascular disease should be strengthened and refined.
- Opportunities should be sought to observe communities in which water hardness or other circumstances

of trace-element exposure are anticipated to change or have recently changed.

- The data base of observations relating cadmium accumulation in the body (kidney) with hypertension should be improved. The prevalence of the association should be ascertained and an effort made to define incidence of cadmium hypertension.

### *Descriptive Methodology*

- Health statistics should be collected in terms of total mortality as well as for the specific disease at issue.
- High- and low-extreme incidence rates should be collected on either a county or state-economic-area basis with due attention to corrections for such factors as resident institution populations and migration patterns. These should then be related to appropriate geochemical environmental maps.
- The obverse of this, i.e., high- and low-extreme maps, by county or economic area for elements of interest, should be developed and related back to disease of interest.
- Specific maps showing locations of high- and low-trace-element compositions in water, stratified according to multiple combinations of elements of interest, would be of special interest.
- An array of data that will minimize confounding by other environmental, socioeconomic, genetic, and measurement techniques should be sought.
- The numbers of samples, measurements, and individuals examined should be adequate to yield a significant conclusion according to prestated assumptions when specific comparisons are proposed. Measurements will require adequate specificity, sensitivity, and quality control.

## VIII UROLITHIASIS

- Epidemiological data on the incidence of urolithiasis and calculus composition should be routinely reported on a more discrete, local basis.
- The possibility of using grouped zip codes or telephone area codes in compiling Professional Standards Review Organizations (PSRO) information concerning urolithiasis should be evaluated.
- The urgent need for water-composition data to match the more discrete urolithiasis occurrence data should be established as a goal and fulfilled.
- The hard- and soft-water interrelations with urolithiasis, especially with calcium, magnesium, and sodium intakes, should be carefully evaluated.
- The potential influence of certain trace elements as potentiators or as inhibitors of urolithiasis should be examined in detail.
- A better oxalate-detection method is acutely needed, and support of efforts to develop such a method is strongly recommended.

## IX GEOGRAPHY–CARTOGRAPHY

- Relevant maps and cartographic procedures should be standardized to fit the needs of geomedical research. Comparison of spatial distributions shown on maps may yield important clues to possible cause-and-effect relationships between geochemical phenomena and human pathology, but such efforts are hindered by the existing variety of map projections, map scales, methods of data classification, and methods of cartographic representation.
- Files of relevant maps and remote-sensing imagery should be assembled and made available for use in geomedical research. The enormous number and diffuse character of such aids is at present a serious obstacle to their effective utilization.
- A cartographic data bank should be created and continuously updated so that relevant maps and remote-sensing imagery may be easily referenced.
- Files should be maintained of consultants who would be available to advise geomedical researchers concerning technical aspects of cartography and remote sensing.
- The mapping of food crops should be intensified, with a view to finding relationships among spatial patterns of crops, geochemical phenomena, and human pathological conditions.
- A thorough exploration should be made of the possibilities for capitalizing on the rapidly developing applications of using satellite data to map landscapes, soils, geological formations, and other features with geometric correctness and with a resolution of 1.1 acres or better.
- Researchers seeking an effective format for presentation of their data or those seeking ways to apply multivariate considerations to geographic distributions should familiarize themselves with the wide range of cartographic innovations available.

## X DATA AND INFORMATION SYSTEMS

- An enthusiastic and interested group (e.g., those interested in geochemistry and health at the University of Missouri) should implement a project to seek out, collate, and adequately analyze the existing data relevant to the relations between disease and the geochemical environment. Such an ambitious and arduous project would require considerable funds and sufficient personnel appropriate to retrieve and analyze the data. However, there have been and still are in existence, several equally ambitious and heavily funded projects of similar nature in ecology, certain areas of environmental pollution, and certain health areas; hence, such large projects are feasible. These projects all heavily exploit high-speed computing, but, in general, they have not made use of the powerful statistical methodology that is available. In some instances, the analytical approaches are very simplistic and there is great risk that results will be relatively uninformative, if not misleading. A project to study the relations of disease to the geochemical environment could and should be planned and conducted to take full advantage of sophisticated statistical concepts and algorithms.

HOWARD C. HOPPS
*Workshop Chairman*

## KEYNOTE ADDRESS: CANCER, GEOGRAPHY, AND GEOLOGY—A PROBLEM FOR INTERDISCIPLINARY CROSS-FERTILIZATION

The classical epidemiologist, if he is to do his job well, has to be nearly a Renaissance man, if not a Leonardo, then at least a Jefferson. As we move farther away in time from Leonardo (and Jefferson) we also seem to move farther away from knowing enough in enough fields to be Renaissance men. The epidemiologists and statisticians know that they need to separate things by age, by sex, by race, perhaps, but then we are sometimes lost at the end of the road. That is why it is good that this Workshop brings us together with the geologists, the soil scientists, and lots of other people who know a great many things that we do not know. If individually we cannot be Renaissance men, perhaps collectively we can. We may look at a map of disease distribution and see no underlying uniformities, but a person who carries in his head a map of drainage patterns, or rainfall, or population density, or areas of mountains and plains, may see important patterns.

We work with cancer, and that disease, or group of diseases, has some added difficulties that may lead us at times to see trees and not forests. Sometimes knowing too much leads us to see only the details and not the large patterns. We hope that the association here with people who know fewer details about the disease will help force the patterns to the surface. Some of the details we think important, which unwisely may have been allowed to overwhelm us, relate to the time scale of cancer. Most cancers are diseases of long latent periods. Haenszel and his colleagues have argued that the patterns for stomach cancer are set before the age of 10 or 15 but get expressed at the age of 50 or 60 (Haenszel and Correa, 1975). Correa will have more to say about this later in the Workshop.

Americans are very mobile people. In the last decade, people have moved out of the central United States to the coasts, so that patterns of incidence and mortality at the coasts, at least, reflect both persons who have lived there all their lives and the in-migrants. What this means in

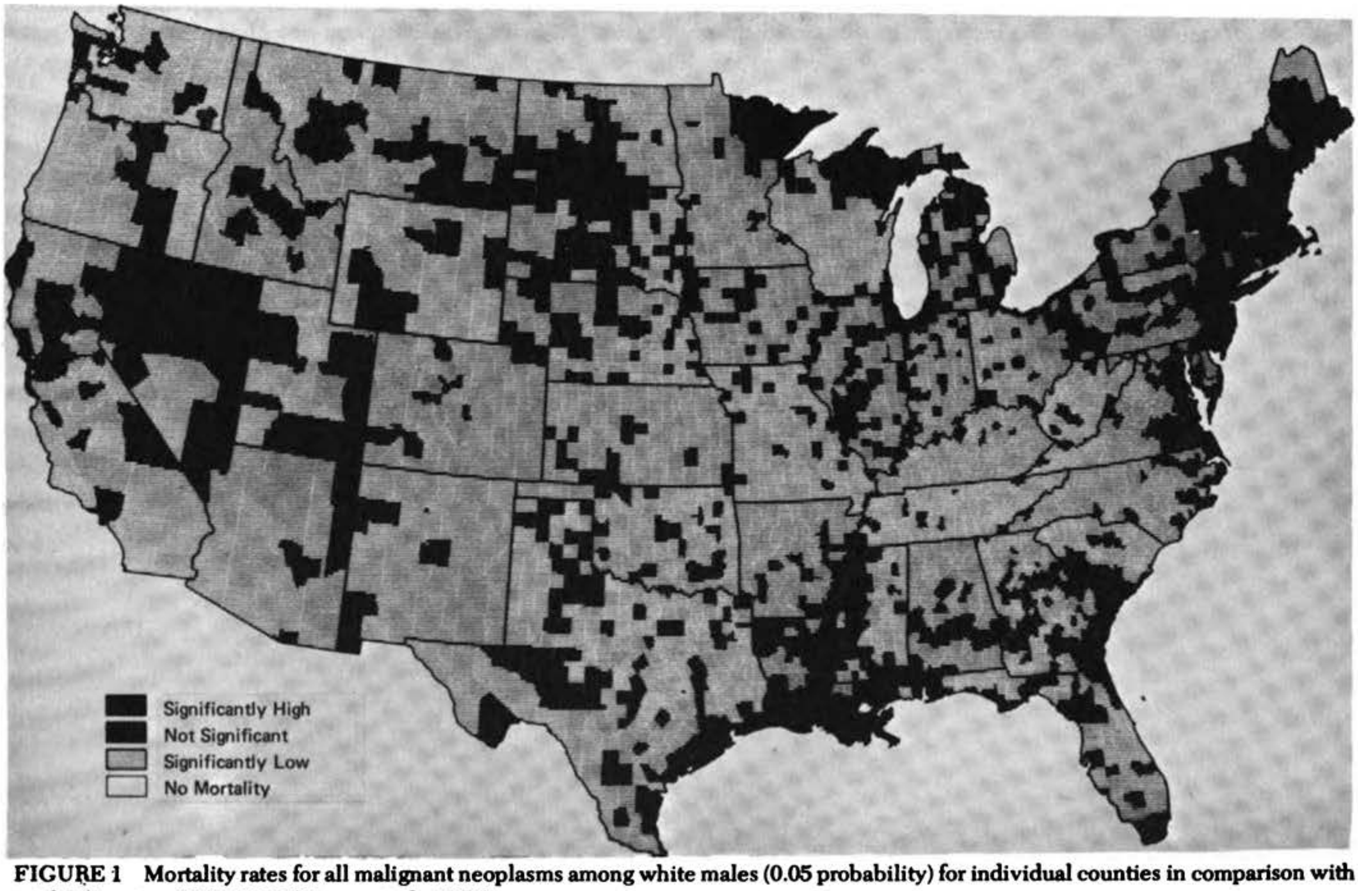


FIGURE 1 Mortality rates for all malignant neoplasms among white males (0.05 probability) for individual counties in comparison with total U.S. rates, 1950–1969 (Mason *et al.*, 1975).

connection with relating permanent features of our geochemical environment to transient features of our population, still needs to be resolved. Similarly, the U.S. population is now over 70 percent urban (U.S. Bureau of the Census, 1973), with food coming from other parts of the country to all or most of the urban areas. What does the composition of local soils mean for city dwellers?

Rather than get caught up in hypothetical questions, however, it might be better to look at some cancer maps to see what relations they may suggest. Figure 1 shows cancer mortality, by county, for white males in the United States, 1950–1969 (Mason *et al.*, 1975). The first impression from this map is that cancer is a disease of cities, of population density. For example, notice the northeastern states. The area around Boston is darkly shaded. So is the area around New York. New Jersey is almost solidly dark. So are the Philadelphia, Pittsburgh, Baltimore, and Washington areas. In the South, Dade County (Miami), Florida, is darkly shaded. In other areas of the country we can easily pick out Detroit and Chicago in the Midwest. In the Far West, Seattle, San Francisco, and Los Angeles stand out. (Appendix A describes methods used by the National Cancer Institute to prepare cancer mortality maps.)

There are also some areas that are not strictly urban that are darkly shaded, and perhaps information about river-flow patterns and geology may help here. Along the Texas Gulf coast and again in West Texas there are high-incidence areas. Is there some underlying geological influence at work, or does the geology enter indirectly, for example, through the petrochemical industry?

There are some things on this map that look like artifacts to us. Why is Nevada so dark? What big cities have we there? And North and South Dakota? And northern Minnesota and Wisconsin?

The presence of large cities leads to the development of an artificial environment, and we should like to think of the geochemical environment as a natural environment. We are aware of those philosophers who argue that any product of man is natural, because man himself is a natural product, and man's products are, in this sense, also natural. Figure 2, nonetheless, deals with a cancer that may be largely a product of the natural environment in the commonly accepted sense. The cancer is melanoma of the skin, and the natural factor is sunlight. Latitude stands as a surrogate for ultraviolet light: the higher the latitude, the lower the ultraviolet.

In this figure, we see more light shading in the northern counties, and more dark in the south, just as we expect, but with a few exceptions. There are light-shaded areas in southern Texas, in Arizona, and in New Mexico, so exposure to sunlight is not the only factor. Looking more closely at those southern counties, we find with the help of the Bureau of the Census that they have many people with Spanish surnames. People with Spanish surnames usually have dark skin. People with dark skin have rela-

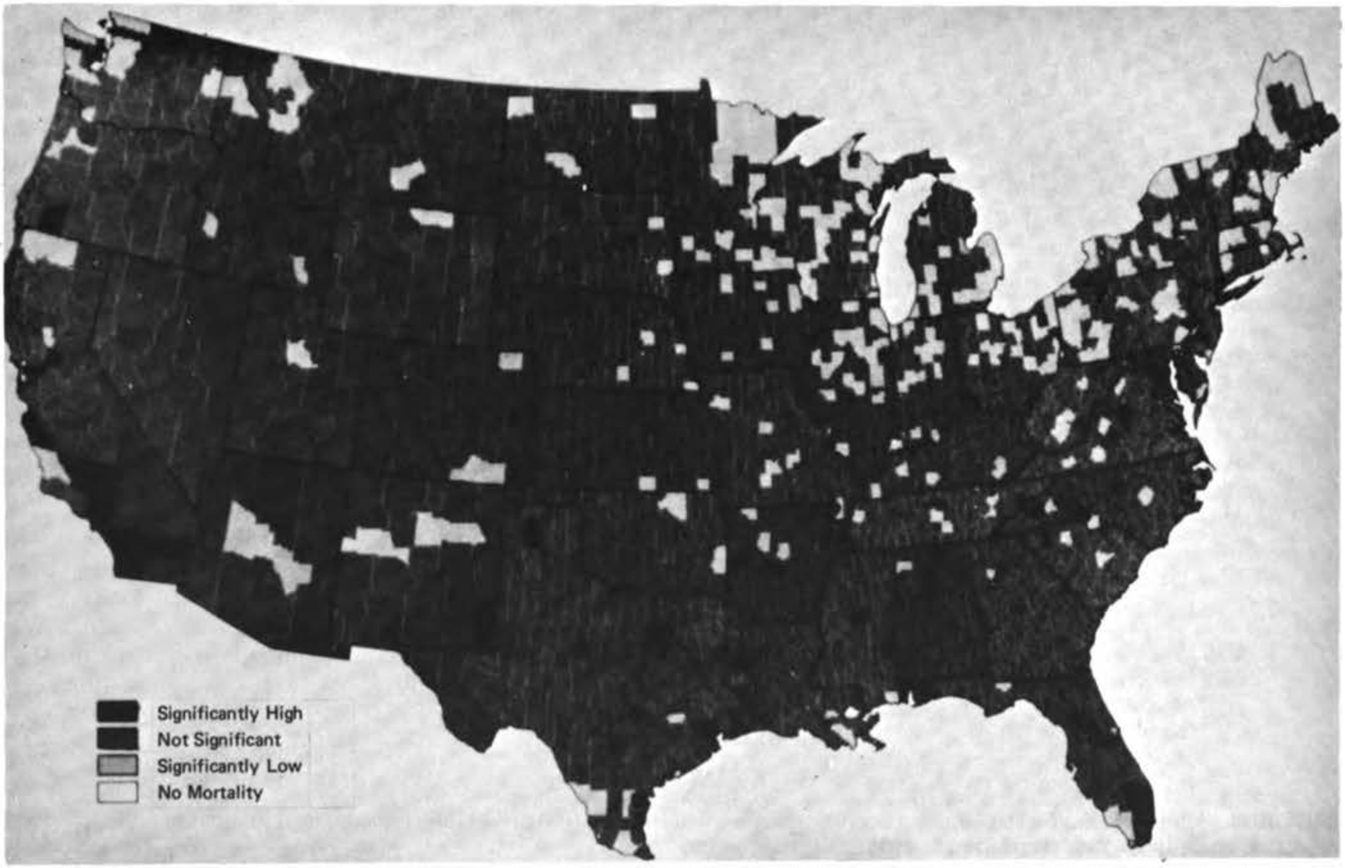


FIGURE 2 Malignant melanoma mortality for white males (0.05 probability) by county, 1950–1969 (Mason *et al.*, 1975).

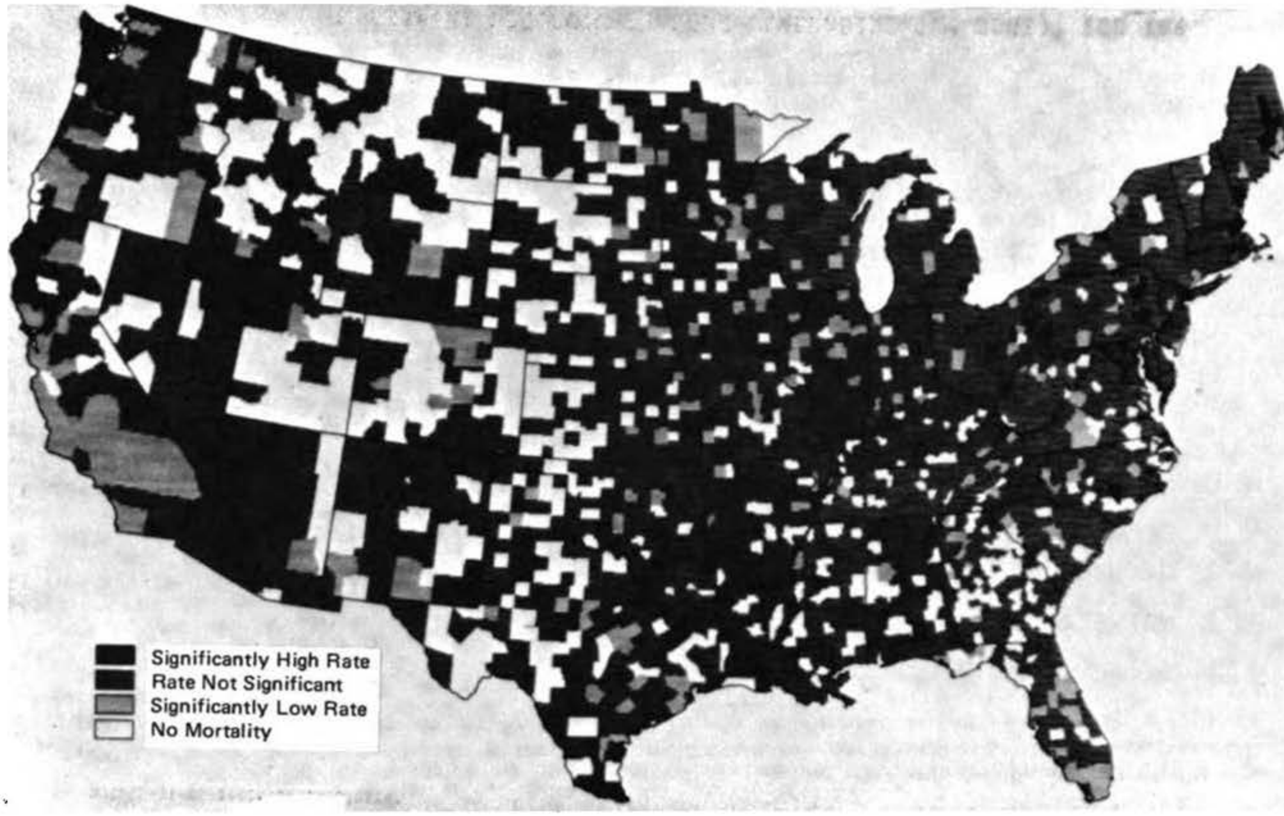


**FIGURE 3** Patterns in mortality in the United States, 1950–1969, white males (0.05 probability). Malignant neoplasm of bone (including jaw bone), International Classification of Disease (ICD 196) (Mason *et al.*, 1975).

tive immunity to skin cancers. So, even with a clear-cut case of a natural cause with an obvious consequence, confounding factors may enter, sometimes with overwhelming consequences.

Figure 3 deals with bone cancer. This is a cancer that might be related to the underlying geology. Other work has shown some bone cancers to be related to radiation (Loutit, 1970). Can we find a similar pattern here? Can we overlay it with a geological map showing areas underlain by radioactive rock formations? Do we need to modify the cancer map and show only bone cancers in children to perhaps reduce the "noise" generated by migration? In the Third National Cancer Survey (National Cancer Institute, 1973) 35 percent of all bone cancers reported were in persons under 20. Have the other 65 percent confused the issue? Preliminary work at the National Cancer Institute has not shown any relation between the mortality from bone cancer, as shown in Figure 3, and information we have been able to put together about radiation in the United States. This, of course, is rather discouraging. On the other hand, it may be rather reassuring. Perhaps the levels of radiation we are naturally exposed to are so low as not to constitute an observable hazard. Or, perhaps, other confounding variables have made the noise level so high that we cannot hear the signal, if there is one.

Berg (1974), in a report on cancer in Iowa, mentions a "belt of leukemia" that seems to go down through the Midwest. Figure 4 shows some older data, assembled by Gilliam (1960) and published in the textbook on epidemiology by MacMahon and Pugh (1970) that show high rates compared with the U.S. average in Wisconsin, Minnesota, Iowa, Nebraska, and Kansas—Berg's Midwest belt. There are also high rates in New York, in California, and somewhat surprisingly in Idaho and Montana. Looking at some more recent data (Mason and McKay, 1973), we found, for white males, that the Midwest belt does remain among the high-rate states, now adding North and South Dakota, Arkansas, Oklahoma, and a few surprise entries—Louisiana, Mississippi, Texas, Oregon, and Washington. Idaho remains high, as does Montana. New York and California both slipped a little. So the Midwest belt now extends down to the Gulf of Mexico and spreads east a little. In the north it now covers the northern states from Wisconsin to the Upper Northwest—Washington and Oregon. When we first looked at the Gilliam maps we were under the impression that Idaho and Montana might be showing artifacts of the sparsely settled areas type. Now we are not so sure.

Looking at these more recent data on a county-by-county basis gives us Figure 5. There the detail is overwhelming. This is a map in which the forest eludes us. Gilliam, with the earlier data, had a suggestion, which is carried out in Figure 6. Here, rather than combining the data by state, which is too gross a classification, or by county, which gives too fine a classification, the data are put together by economic subregions. These have natural

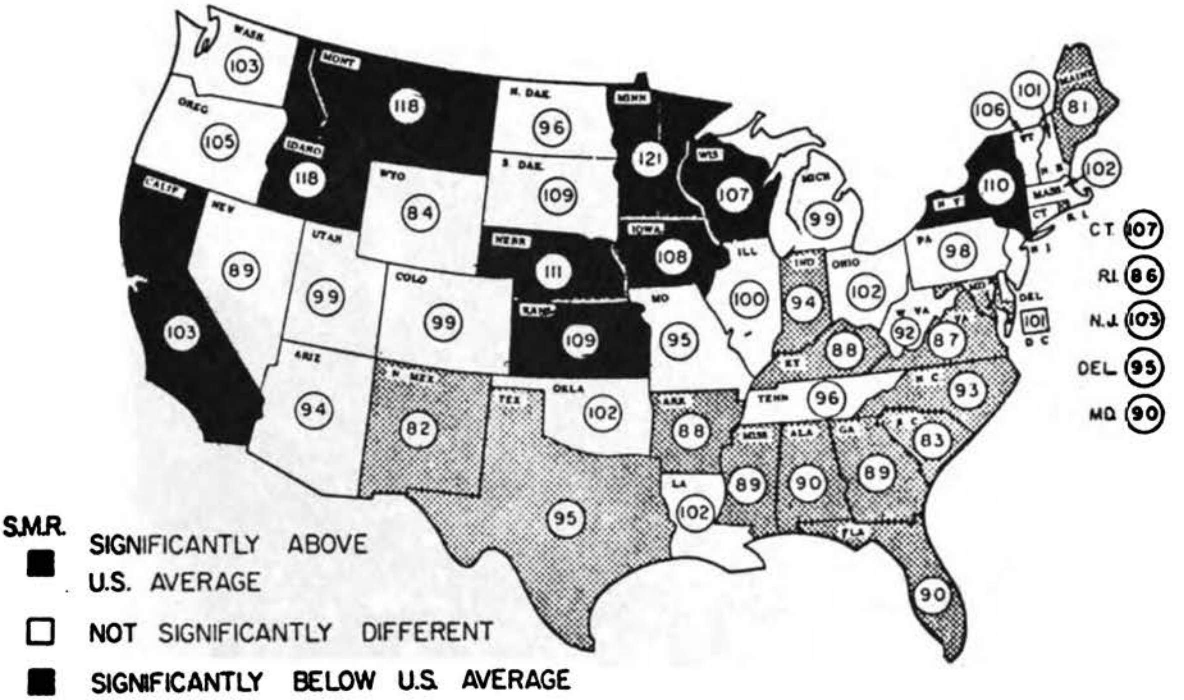


FIGURE 4 Standard mortality ratios (SMR's) for deaths from leukemia (0.05 probability) in 48 states, 1949–1955 (reprinted from Gilliam, 1960). (SMR of 100 = expected, given the age–sex–race composition of the state; <100 = less than expected; >100 = greater than expected.)

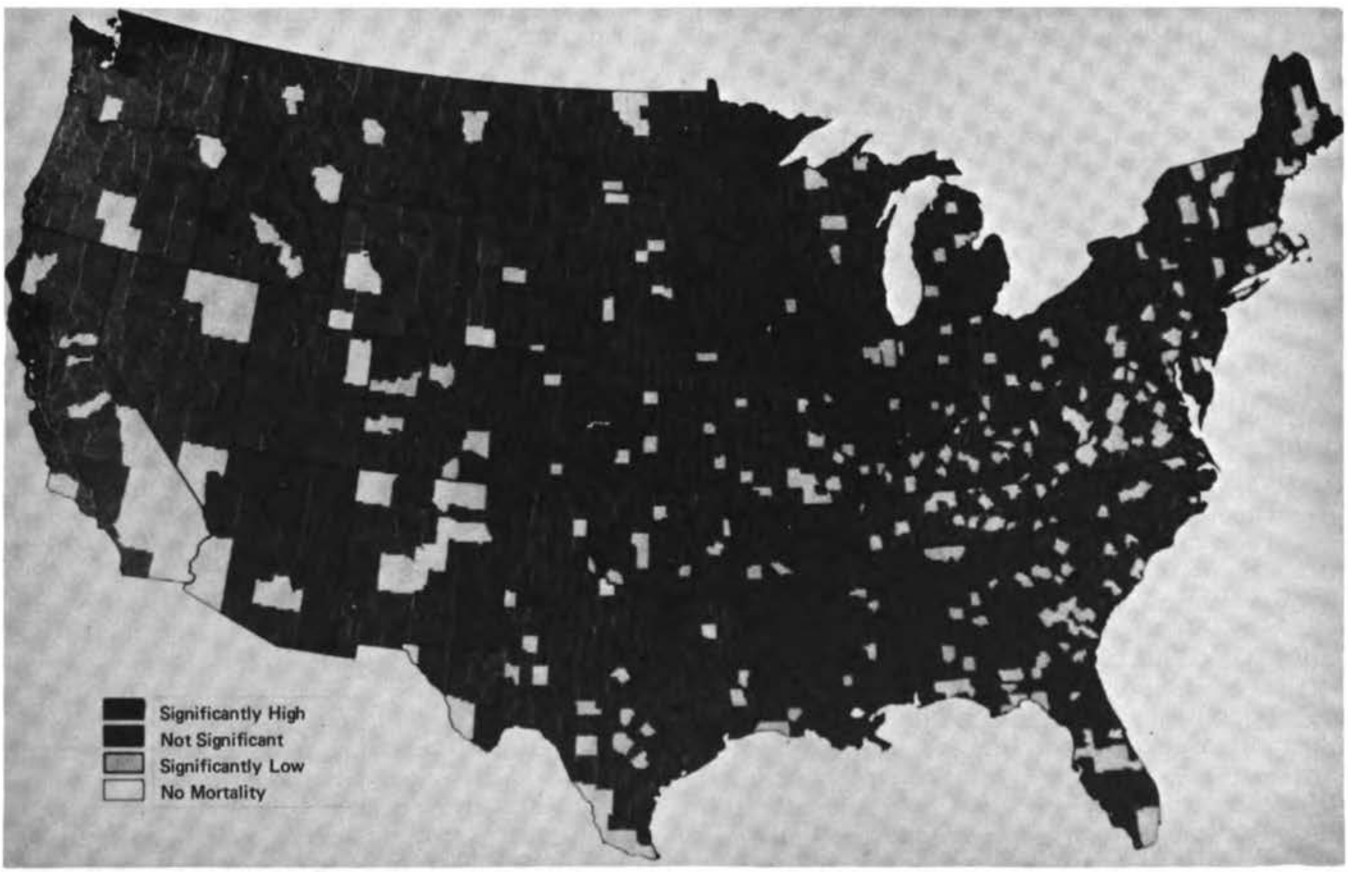


FIGURE 5 Leukemia mortality for white males (0.05 probability) by county, 1950–1969 (Mason *et al.*, 1975).

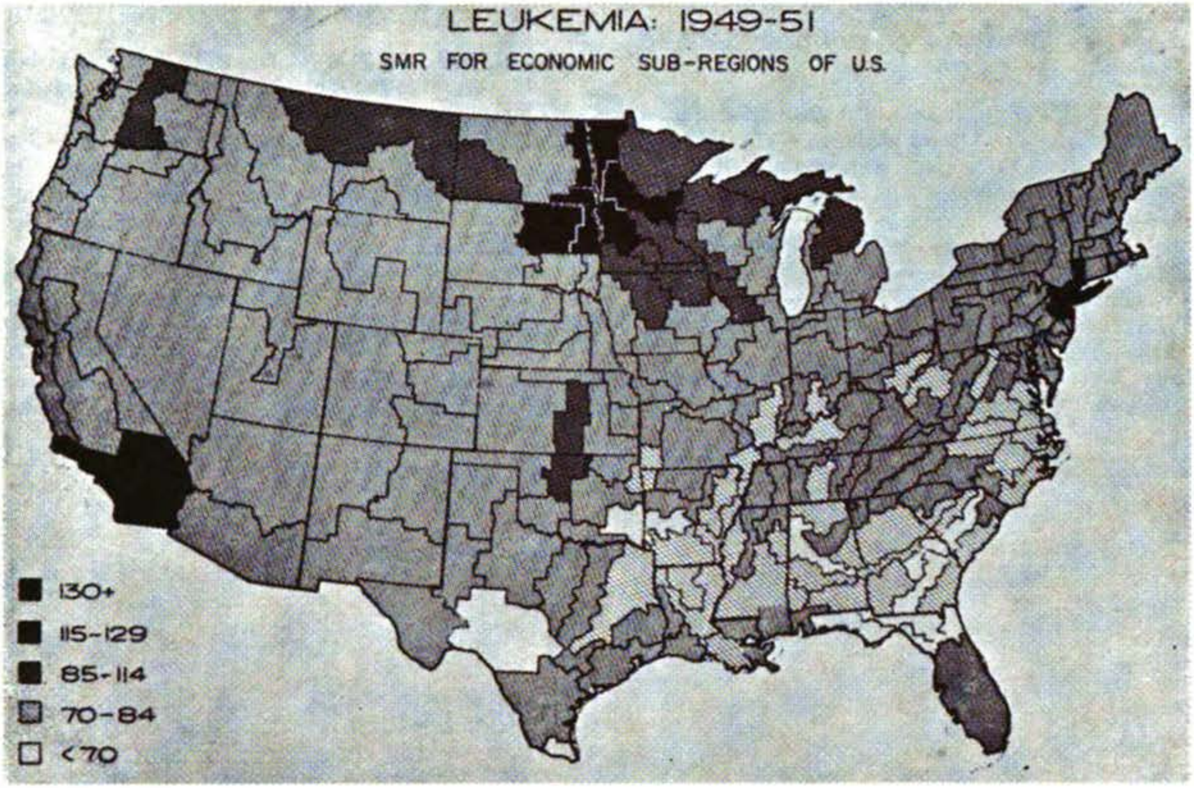


**FIGURE 6** Standard mortality ratios for deaths from leukemia (0.05 probability) for economic subregions of the United States, 1949–1951 (reprinted from Gilliam, 1960). (SMR of 100 expected, given age–sex–race composition of area.)

economic boundaries, rather than purely political boundaries. Of course, political boundaries are not always unnatural. They often follow rivers, or mountains, which are usually natural enough to suit most people.

What does Gilliam's economic-area map show? The upper Midwest high is still there, but it looks as if it has shifted. We now see dark areas in the Dakotas, in Minnesota, and in Iowa. There is a belt across the south-central states, the effect we finally saw with more extensive data on a statewide basis. What is now needed, of course, is a remapping of the more recent data on an area basis—like Gilliam's. This will soon be done at the National Cancer Institute, and perhaps this remapping will allow us to compare our patterns with some the geologists and the soil scientists can create.

One last caution is in order. We spoke of not letting details obscure the whole. This is not the same as neglecting what we know and not using it. Thus, if our bone-cancer maps, or our leukemia maps, when remade on an economic area basis still suggest nothing to us, we may still be able to learn something by redoing them on an age basis. Bone cancer in young people may have a different etiology than bone cancer in older people. Surely leukemia in children is a different disease than is leukemia in adults. Most of the maps we have shown are for white males. Obviously, if the major causes of the disease are the general environment, we should see the same patterns for nonwhites, both male and female, and for white females.

Things we look upon as general environmental natural phenomena may not be so immutable as the nonspecialist may think. Chemicals in our soils come from the underlying rocks and the rainfall and the nearby rivers and the man-applied fertilizers and pesticides, and the pollutants from the air and perhaps the decay of radioactive fallout. It will take all of our knowledge, sometimes looked at through highly selective filters, to lead to a proper cross-fertilization that will yield a viable and fertile product. This Workshop holds promise of being a good place to start, even if it does nothing more than help us select the right filters. Maybe one of the things we will find is that the filter that has us look at only the United States is inappropriate. We can learn more when the contrasts are greater and that should mean drawing on the whole world for data and ideas, especially ideas.

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# PART ONE

# *Trace-Element Pathways to Animals and Man*

# II

# *Rocks: The Geologic Source of Most Trace Elements*

HELEN L. CANNON, *Chairman*

*G. Gordon Connally, Jack B. Epstein, John G. Parker, Iain Thornton, Bobby G. Wixson*

The distribution and geochemical character of the various kinds of rock that are exposed at the surface, and the manner in which these parent materials might affect the disease patterns of man, were the primary concern of the Work Group on Rocks at the Captiva Island Workshop. Emphasis was placed on the relation of rocks and surficial material to subsurface water carried within them, the mineral content of surface water, and the mineral content of soils. The contribution of man-made pollution to the geochemical background was also discussed.

Attempts to correlate selected disease patterns or trends with rock-type distribution reveal no significant correlations because of complexities related to map scale and geologic detail, which of necessity make the geologic maps at the agreed-upon scale for publication in this report too generalized.

Rocks are the primary natural source of most elements that enter the human system. Most undisturbed rock does not directly affect man; radioactivity is the main exception. When airborne, volcanic dust and mining products (such as asbestos) or wastes may be absorbed through inhalation. A direct and relatively unbuffered pathway from rocks to man is water, the chemical composition of which may be closely related to the rock aquifer, long associated with the health of man. The quantity and effects of inorganic elements are appreciably reduced during weathering from rock to soil. At this interface, some elements are concentrated and some are removed by solution. Later changes in concentrations occur when plants absorb or reject these elements, and finally they may or may not be absorbed in quantity by the human gut. It is also obvious that large-scale food-delivery systems in developed countries may furnish, to a large segment of the population, produce that has been grown in areas actually deficient in trace elements.

Much more information is needed about trace-element availability along the food chain before predictions can be made about relations between the geochemical character of the rock substrate and the diseases under consideration. However, a start should be made, and two compromise approaches were suggested at the Workshop. One approach was that the rock, water, and soil geochemists furnish information on the distribution of trace elements that were implicated in the diseases under study. A second approach was for the disease groups to furnish the geochemists with mortality data that identify high- and low-incidence areas for which the source groups could provide existing geochemical data. A problem common to both compromises is that general geochemical distribution information is sparse because geochemical studies have concentrated on mineralized areas. Until recently, analytical methods have not been available for low-level trace-element analysis, necessary for defining areas of deficiency. The second approach offers more promise, because considerable data may already be available for a number of small target areas, and it is easier to fund a program to complete the collection of geochemical data in these areas than to fund a nationwide survey for a necessarily limited number of elements.

TABLE 1 Relative Abundance of Major Rock Types in the Physiographic Provinces of the Conterminous United States[a,b]

| Rock Type | Physiographic Province: Pacific Border | Cascade Sierra Mts. | Columbia Plateaus | Basin and Range | Colorado Plateaus | Rocky Mts. | Great Plains | Superior Uplands | Central Lowlands | Interior Low Plateaus | Coastal Plain | Appalachian Plateaus | Valley and Ridge | Blue Ridge | Piedmont | Adirondack | New England | St. Lawrence Valley |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ultramafic | C | R | R | R | — | R | R | — | — | — | — | R | R | C | C | R | R | — |
| Basaltic—extrusive and intrusive[c] | C | C | A | A | C | C | R | C | — | — | — | R | R | C | C | R | C | R |
| Granitic—intrusive and extrusive | C | A | R | C | R | C | R | C | R | — | — | — | — | A | A | A | A | R |
| Shales and clays | A | C | C | C | A | C | A | C | A | C | A | A | A | R | A | R | A | A |
| Black shales | R | R | — | R | R | C | C | — | R | C | R | C | C | — | R | — | R | C |
| Limestones | R | R | R | C | C | C | C | R | A | A | C | C | A | R | R | C | C | A |
| Sandstones and sands | A | C | A | A | A | C | A | C | A | C | A | A | A | A | C | C | A | A |
| Phosphorites | R | — | — | — | R | C | R | — | — | — | R | — | — | — | — | — | — | R |
| Coal | R | — | R | R | C | C | C | — | A | C | C | A | C | — | — | — | R | — |

[a]Source: Physiographic Divisions of the United States (Fenneman, 1928). Rock-type data in part from G. W. Colton, U.S. Geological Survey (personal communication, 1977).
[b]A, Abundant; C, common; R, rare; —, absent.

## ROCK TYPES IN THE UNITED STATES AND THEIR GEOCHEMISTRY

The number of rock types in the United States is relatively large, and their geographic distribution within the various physiographic provinces is complex (Fenneman, 1928) (Table 1). Furthermore the elemental composition of the various rock types differs greatly, and the composition of a single rock type may show significant variation (Table 2). Rocks are the parent materials from which soils of varying elemental composition and surficial deposits are derived and from which groundwater obtains most of its mineral matter. In general, variations in composition are small as a given rock type is traced laterally across an area (although there are notable exceptions), whereas marked variations are common in composition between rocks that are vertically superimposed. Rock outcrops may be exposed at the surface in widely separated small patches, in straight narrow bands, in dendritic patterns, or they may uniformly cover large, broad areas, depending on their thickness, their inclination, the topographic relief of the area, and the thickness of alluvium, colluvium, or residual or glacial soil cover. Some homogeneous rock units cover many thousands of square miles, for example, the volcanic rocks of the Columbia Plateau and the flat-lying shales of the Great Plains. In other areas, the distribution of rock types, especially where thin units of widely different types are superimposed or have been deformed structurally, may be so complex as to defy definition on small-scale maps, such as might be used by epidemiologists for comparative purposes.

The general composition of most common rock types is predictable. Limestones and associated dolomites are largely calcium and magnesium carbonates accompanied by relatively high levels of strontium and available phosphorus and may contain zinc, cadmium, and lead deposits. Chalks and marls are also high in calcium carbonate and may be associated with lignite or phosphate deposits. Shales and clays are rich in aluminum silicates and have a complex trace-element chemistry because of the wide range of metal substitutions that are possible. Some shales, such as those in the Great Plains, are high in selenium, molybdenum, or vanadium, and others, such as the Chattanooga Shale in Tennessee, are high in uranium. Sandstones are rich in silica and, because of their relatively high permeability, commonly have low abundances of trace elements because of low content originally and leaching by percolating waters. A striking example of this relation occurs on the Coastal Plain, where the highly porous sands are deficient in many elements. Granites and related igneous rocks are likewise rich in aluminum silicates but are commonly more homogeneous over wide areas than sandstones; some, like those in New Hampshire, may be radioactive. Serpentine, a type of altered ultramafic rock (dark, very rich in iron and magnesium, rather than light colored and high in silica and aluminum), contains an average of 1800 ppm chromium and 2000 ppm nickel; groundwaters from serpentine rocks may be a health hazard. In addition to having high levels of nickel and chromium, they have an anomalously high magnesium:calcium ratio (200,000:15) compared with the crustal average and relatively low levels of silica. Some types of rock, originally deposited under unusual physicochemical conditions, have unique compositions. These include coals, which generally have selenium and germanium contents greater than average crustal concentrations, while some individual coals are reported to have relatively high fluorine, boron, and mercury; phosphatic shales and phosphorites with abundant phosphorus, vanadium, uranium, and chromium; and evaporite deposits of halite (rock salt), borax, or gypsum, which may also contain large concentrations of lithium, strontium, and fluorine.

Table 1 and the accompanying map (Figure 7) outlining the physiographic provinces of the United States show the generalized distribution of some of these rock types (Fenneman, 1928). Within the next few years, the U.S. Geological Survey plans to complete a more detailed map (1:2,500,000), which will show the distribution of rock types that are exposed on the surface of the earth. It is important to understand that rock at various depths may differ markedly in composition and may yield different elements to groundwater than would be expected from the surface geology.

### *Surficial Deposits*

Deposits of rock detritus of relatively recent age cover the hard rock surface in much of the United States. These deposits are shown in a generalized map (Figure 8) prepared by Hunt (1967). They may result from weathering in place, evaporation of lakes or arms of the sea, glacial movement, wind action, streams at flood, gravity along mountain fronts (talus), biogenic activity in lakes, or volcanic ash.

One important attribute of young deposits, such as glacial drift, is interrupted or poor drainage, which may increase the possibility of high nitrate in the groundwater. Peat bogs may concentrate metals such as cadmium, zinc, and lead, which become highly available when the bogs are drained for muck farming, or organic complexes may tie up manganese and associated ions so as to make them unavailable. Evaporite basins in the Southwest are very high in potassium, lithium, magnesium, boron, and common salt. Sands are generally low in trace elements but may be high in $CaSO_4 \cdot nH_2O$ in arid areas. Volcanic ash is commonly high in nickel, copper, vanadium, zinc, iron, and magnesium. Some volcanic-ash layers are minable for uranium and vanadium and contain associated selenium.

## GEOCHEMICAL RECONNAISSANCE SURVEYS IN THE UNITED STATES AND THE UNITED KINGDOM

Regional geochemical surveys of rocks, soils, plants, or water are useful in outlining areas of excess or deficiency for prospecting and also for comparison with areas of disease. Several regional geochemical surveys have been

**TABLE 2 Concentrations of Some Elements in Various Natural Materials (ppm)[a]**

| Elements | Ultramafic Igneous | Basaltic Igneous | Granitic Igneous | Shales and Clays | Black Shales | Deep-Sea Clays | Limestones | Sandstones | Phosphorites | Coals (Ash) |
|---|---|---|---|---|---|---|---|---|---|---|
| Calcium | 2–100 | 30–160 | 4–30 | 18–120 | 20–200 | 0.02–2.0 | 0.01–0.22 | 0.001–0.3 | 10–100 | 2–40 |
| | 15 | 90 | 15 | 50 | 70 | 250 | 40 | 2 | 30 | 15 |
| Magnesium | 204,000 | 46,000 | 1,600–9,400 | 15,000 | 7,000 | 21,000 | 47,000 | 7,000 | 1,800 | 5,670 |
| Phosphorus | 220 | 1,100 | 600–920 | 700 | [b] | 1,500 | 400 | 170 | 133,000 | 400 |
| Arsenic | 0.3–16 | 0.2–10 | 0.2–13.8 | [b] | [b] | [b] | 0.1–8.1 | 0.6–9.7 | 0.4–188 | 0–2,000 |
| | 3.0 | 2.0 | 2.0 | 10 | | 13 | 1.7 | 2 | 22 | 13? |
| Barium | 0.2–40 | 20–400 | 300–1,800 | 460–1,700 | 70–1,000 | [b] | 10 | [b] | 50–300 | 10–440 |
| | 1 | 300 | 700 | 700 | 300 | 2,300 | [b] | 20 | 100 | 40 |
| Beryllium | 0.x[c] | 1.0 | 2–3 | 3 | [b] | 2.6 | 0.x[c] | 0.x[c] | [b] | 5 |
| Cadmium | 0–0.2 | 0.006–0.6 | 0.003–0.18 | 0–11 | <0.3–8.4 | 0.1–1 | [b] | [b] | 0–170 | [b] |
| | 0.05 | 0.2 | 0.15 | 1.4 | 1.0 | 0.5 | 0.05 | 0.05 | 30 | 2 |
| Chromium | 1,000–3,400 | 40–600 | 2–90 | 30–590 | 26–1,000 | [b] | [b] | [b] | 30–3,000 | 10–1,000 |
| | 1,800 | 220 | 20 | 120 | 100 | 90 | 10 | 35 | 300 | 20 |
| Cobalt | 90–270 | 24–90 | 1–15 | 5–25 | 7–100 | [b] | [b] | [b] | <10–30 | 2–200 |
| | 150 | 50 | 5 | 20 | 10 | 74 | 0.1 | 0.3 | 5? | 10 |
| Copper | 2–100 | 30–160 | 4–30 | 18–120 | 20–200 | [b] | [b] | [b] | 10–100 | 2–40 |
| | 15 | 90 | 15 | 50 | 70 | 250 | 4 | 2 | 30 | 15 |
| Fluorine | [b] | 20–1,060 | 20–2,700 | 10–7,600 | [b] | [b] | 0–1,200 | 10–880 | 2.0–4.15% | 40–480 |
| | | 360 | 870 | 800 | | 1,300 | 220 | 180 | 3.1% | 80 |
| Iodine | 0.6–0.3 | [b] | [b] | 2.2–38 | [b] | 11–50 | 0.4–29 | [b] | [b] | 1–11 |
| | 0.1 | 0.5 | 0.5 | 5? | | 35? | 5 | 1.7 | | 4 |
| Iron | 94,000 | 86,500 | 14,000–30,000 | 47,200 | 20,000 | 65,000 | 3,800 | 9,800 | 7,000 | 3,500 |
| Lead | [b] | 2–18 | 6–30 | 16–50 | 7–150 | [b] | [b] | <1–31 | 1–150 | 2–50 |
| | 1 | 6 | 18 | 20 | 30 | 80 | 9 | 12 | 10 | 15 |
| Lithium | [b] | 3–50 | 10–120 | 4–400 | [b] | [b] | 5–10 | 7–90 | [b] | 2–300 |
| | 0.5 | 20 | 35 | 80 | | 57 | 7 | 30 | | 50 |
| Mercury | 0.004–0.5 | 0.002–0.5 | 0.005–0.4 | 0.005–0.51 | 0.03–2.8 | 0.02–2.0 | 0.01–0.22 | 0.001–0.3 | 0.001–0.5 | 0.05–13.3 |
| | 0.1? | 0.05[d] | 0.06[d] | 0.09[d] | 0.5 | 0.4 | 0.04[d] | 0.05[d] | 0.05[d] | 0.3[d] |
| Molybdenum | [b] | 0.9–7 | 1–6 | [b] | 1–300 | [b] | [b] | [b] | 3–300 | 0.2–16 |
| | 0.3 | 1.5 | 1.4 | 2.5 | 10 | 27 | 0.4 | 0.2 | 30 | 5 |
| Nickel | 270–3,600 | 45–410 | 2–20 | 20–250 | 10–500 | [b] | [b] | [b] | 10–1,000 | 3–100 |
| | 2,000 | 140 | 8 | 68 | 50 | 225 | 20 | 2 | 100 | 20 |
| Selenium | [b] | [b] | [b] | [b] | [b] | [b] | [b] | [b] | 1–100 | 0.40–3.9 |
| | 0.05 | 0.05 | 0.05 | 0.6 | | 0.17 | 0.08 | 0.05 | 18 | |
| Vanadium | 17–300 | 50–360 | 9–90 | 30–200 | 50–1,000 | [b] | [b] | [b] | 10–100 | 0–700 |
| | 40 | 250 | 60 | 130 | 150 | 120 | 20 | 20 | 300 | 40? |
| Zinc | [b] | 48–240 | 5–140 | 18–180 | 34–1,500 | [b] | [b] | 2–41 | 20–300 | 7–108 |
| | 40 | 110 | 40 | 90 | 100? | 165 | 20 | 16 | 50 | 50 |

[a] The upper figure is the usually reported range, the lower figure the average.
[b] Not available.
[c] Early single-step spectrographic reporting.
[d] Not including anomalies with contents 10–1,000 times the average, particularly those from the Donets Basin, Kerch-Taman, and Crimea, USSR.
Compiled by M. Fleischer and H. L. Cannon.

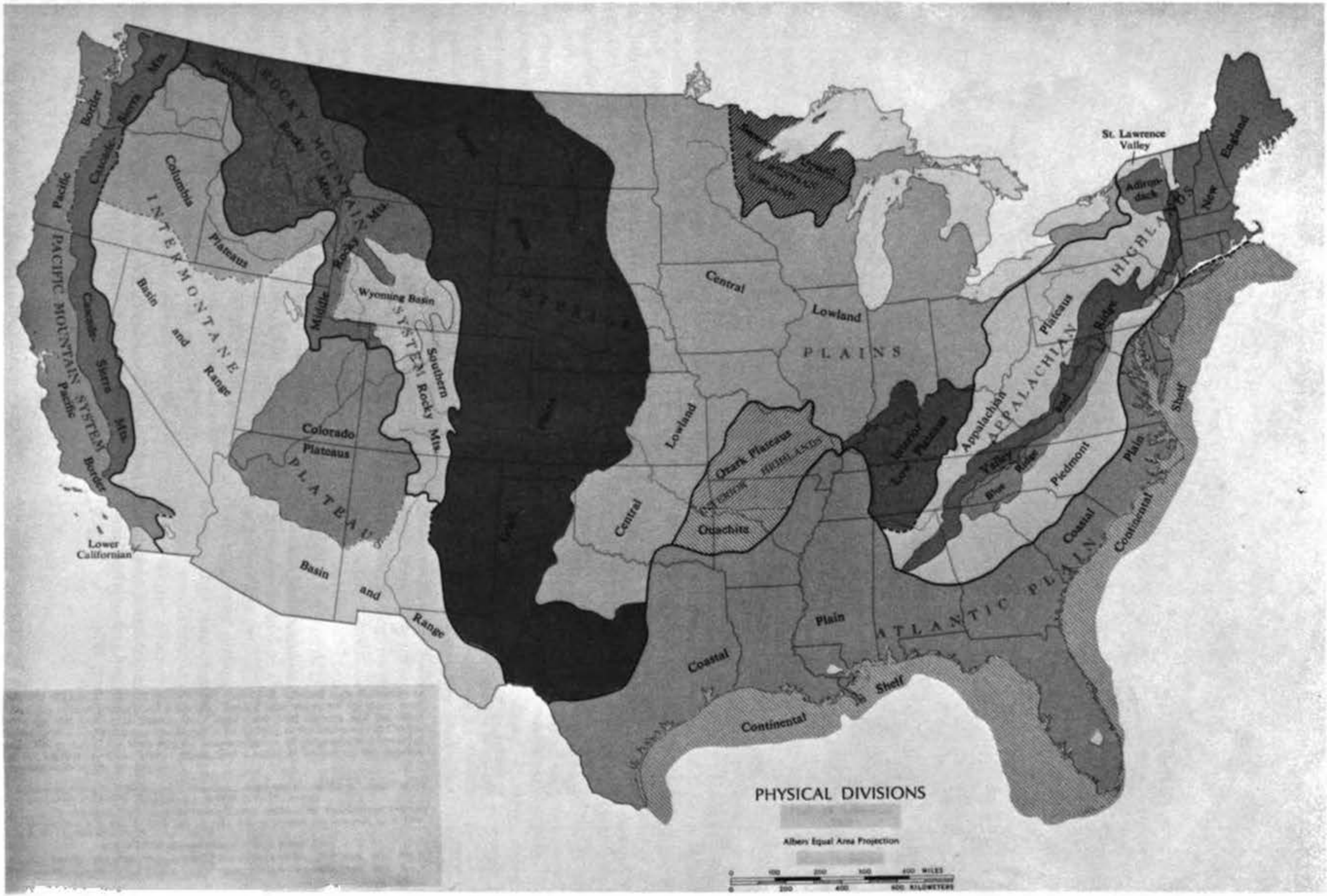


**FIGURE 7** Physiographic divisions of the United States (Fenneman, 1928). U.S. Department of the Interior, Geological Survey, *National Atlas*, 1970, p. 60.

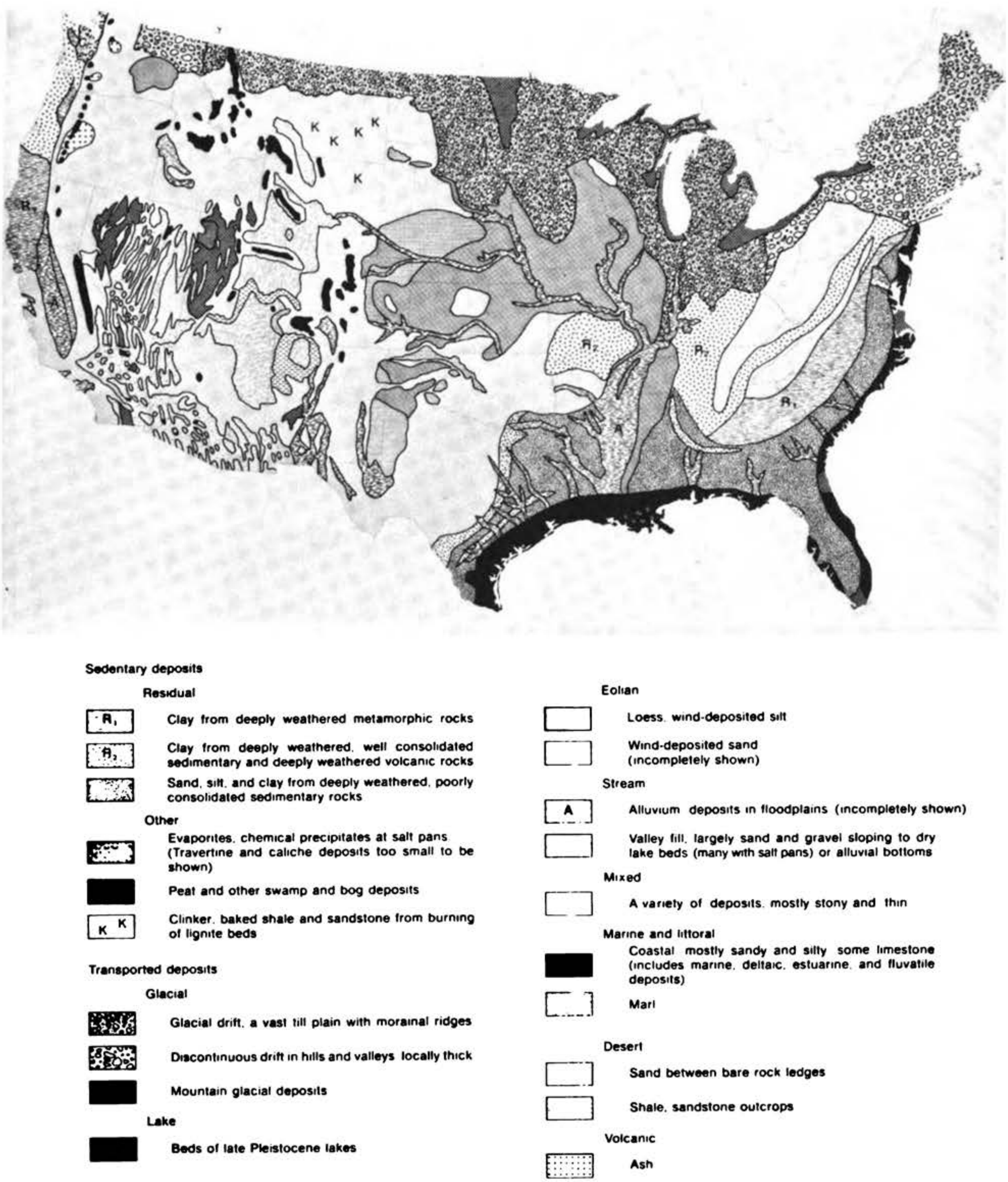


**FIGURE 8** Surface deposits in the United States, except Alaska and Hawaii. These are the parent materials of the agriculturalist's soils; most are late Pleistocene or Holocene and ages overlap (Hunt, 1967). From *Natural Regions of the United States and Canada* by Charles B. Hunt, W. H. Freeman and Company, 1974.

made in the United States. The most comprehensive of these was a U.S. Geological Survey team effort, in cooperation with the University of Missouri, to map geochemical differences in rocks, soils, plants, and water of Missouri. The first four of a series of reports have been published (Erdman *et al.*, 1976a, 1976b; Miesch *et al.*, 1976; Tidball, 1976); the others are in preparation.

Soils collected at 50-mi intervals in the United States have been analyzed for 41 elements and the resulting values plotted on maps, which have been published by Shacklette *et al.* (1971a; 1971b; 1973; 1974). Soils and vegetables were also analyzed from nine counties in Georgia with high cardiovascular death rates and from nine counties in Georgia with low cardiovascular death rates. The results suggested a correlation with deficiency rather than excess; cadmium was not reported (Shacklette *et al.*, 1970).

Geochemical surveys consisting of stream-sediment analyses have been most successful in delineating areas of anomalous metal content in the British Isles. Geochemical surveys based on multielement analysis of stream-sediment samples have been completed for 5000 mi$^2$ of Northern Ireland and 64,000 mi$^2$ of England and Wales. Samples were taken from tributary drainage at an approximate density of 1 per mi$^2$. Data showing the distribution of some 26 elements have been presented by computer as gray-scale line-printer maps at scales ranging from 4 mi per 1 in. to 1:1,000,000 and again as lasergraphic plots printed on diazo film (Webb *et al.*, 1973). These national maps show numerous geochemical patterns relating to bedrock lithology and geochemical facies on the one hand and regional contamination from past and present industry on the other (Thornton and Webb, 1973).

Research over the past 10 years by the Applied Geochemistry Research Group, Imperial College, London, has successfully demonstrated the application of these primary reconnaissance geochemical surveys in agriculture, pollution studies, estuarine fisheries, and, to a degree, public health. Parallel research has been carried out into computerized geostatistical techniques for processing and interpreting the results of regional surveys. In particular, pattern-recognition techniques based on discriminant and cluster analysis have proved promising in identifying and mapping the extent of specific geochemical features (Howarth, 1973).

Regional trace-element maps of this kind do not provide point-source information but rather focus attention on particular areas of geochemical relief wherein more detailed, time-consuming, and costly studies on rocks, soils, plants, waters, and animal tissue may then be concentrated. At the same time, they provide a useful basis for comparison with epidemiological data on human and animal health and disease.

## GEOCHEMISTRY AND DISEASE IN THE UNITED STATES

A number of trace elements, as well as nitrate, water hardness, and radiation have been associated with the incidence of various diseases. In several instances, sufficient data are available to permit geographic comparisons and the construction of causal hypotheses. For example, although attention is focused logically on calcium and on water pH as possible controls in the kidney-stone belt, in the southeastern United States, its coincidence with an area of zinc deficiency might bear investigation. Geographic patterns of water hardness and lithium have been compared with those for certain kinds of heart disease; maps showing concentrations of the various constituents of hard water can be prepared. Protective effects of selenium against cancer are being demonstrated in the laboratory (Shamberger, 1970), a positive correlation between cancer and the zinc–copper ratio in the soil (extractable with acetic acid) has been reported by Stocks and Davies (1960; 1964), and the deleterious effects of nitrosamines and high levels of radiation on the development of cancer (Furth and Lorenz, 1954) are well known. The geographic distribution of several of these substances is known and can be compared with that of the diseases under study (Cannon, 1974). A more detailed discussion of a few of these relations follows.

### *Trace Metals Correlated with Cancer Experience*

A study by the U.S. Geological Survey, in cooperation with the National Cancer Institute, of cancer incidence related to the geochemical environment in Washington County, Maryland (Cannon, 1977) suggests several possible causal factors. The soils and vegetation in the area of study are deficient in selenium compared with average soils, which has been suggested as causally related to cancer. A comparison of cancer incidence in 665 houses with the geologic substrate and also the proximity to highways showed unusually high cancer occurrence in houses located on the Catoctin Metabasalt, the Rockdale Run Formation, the Harpers Phyllite, along which the major state highways followed the strike of the outcrop, and the Martinsburg Shale, which is crossed by a major county road. The town with the highest incidence of cancer is in a synclinal valley where five highways converge. Vegetables from about 90 associated gardens were significantly higher in chromium, copper, and lead at index houses (with cancer experience and >20 years of residence) than at houses of similar years of residence but no cancer experience. Soils near roads were significantly higher in these metals. Houses with gardens less than 100 ft from the road had three times more cancer experience (largely of the gastrointestinal tract) than houses with gardens at greater distances from road traffic. These results suggest that man-created hazards superimposed on the existing geochemical environment may be an important factor. Walter Blumer, a general practitioner of Netstal, Switzerland, is reported to have also found a higher rate of cancer where people live near busy highways (Burk, 1974).

### *Radioactivity*

Geologic sources of radioactivity and their distribution are shown in Figure 9. Concentrations of uranium and

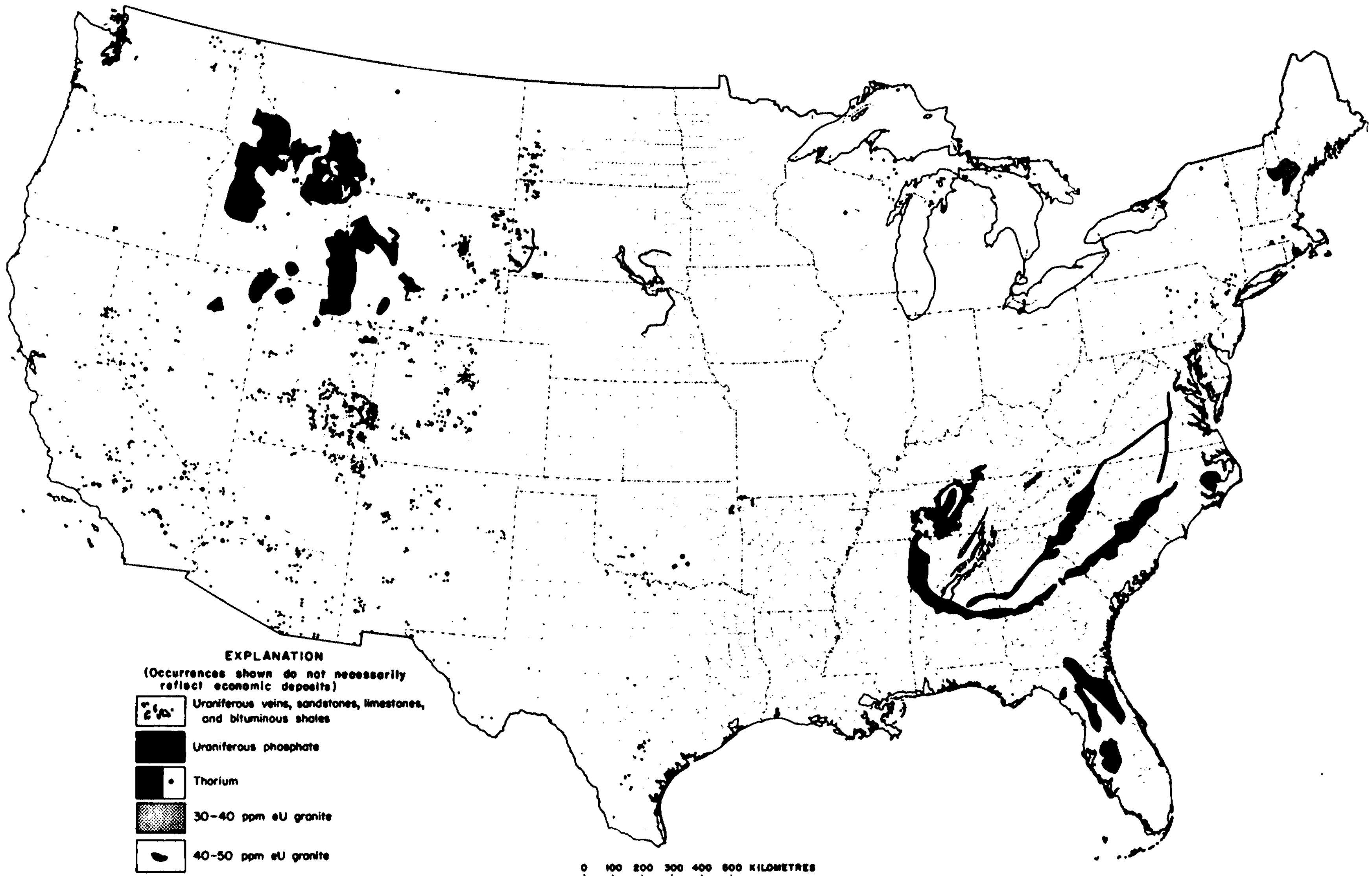


FIGURE 9 Map of geologic sources of radioactivity in the United States (Strobell and Cannon, 1975). Sources of data: Butler *et al.*, 1962; Conant and Swanson, 1961; Finch, 1957; Finch *et al.*, 1959; Olson and Adams, 1962; and Segall, 1963. U.S. Geological Survey Map.

thorium occur in various types of material including sandstones, limestones, black shales, phosphorites, and granite. In general, they occur in a wide band extending from southern California, Arizona, and New Mexico, northeasterly to the Canadian border, and in curved bands along the coastal plain and piedmont in Florida and New England. The largest highly populated areas of flat-lying radioactive rocks are in New England, Tennessee, and Florida.

Studies of radioactivity in groundwater in Maine and New Hampshire by Grune *et al.* (1960) showed an average of 10,690 and a maximum of 176,000 pCi/liter (picocuries per liter) of $^{222}$Rn (disintegrating to $^{214}$Po) in 21 drilled wells in New Hampshire, and an average of 65 and a maximum of 730 pCi/liter of $^{226}$Ra in 224 wells and springs in Maine. In both states, water from drilled wells (in metamorphic and igneous rocks) was more radioactive than that from dug wells in glacial drift. Highly radioactive water from a well in Raymond, Maine, contained 860 ppb uranium. In both states, 99 percent of the drilled wells tested had more radioactivity than the maximum permissible 2000 pCi/liter.

In addition to exposure to radiation from the natural environment, man has contributed by shipping phosphate containing uranium to various parts of the country as fertilizer and thorium-bearing granite as grit for poultry farming. Tailings from uranium mills have been dumped into rivers and used as fill in urban development. However, the patterns shown on the map do not appear to coincide with those of most types of cancer but resemble those of congenital malformations in the United States (Kratchman and Grahn, 1959).

### *Selenium*

Areas of seleniferous rocks and of selenium deficiency and toxicity are given in Figure 10. Shamberger and Willis (1971), who studied selenium distribution and human cancer mortality, reported that 10 normal males and females, ages 30–71, had average whole-blood selenium levels of $21.71 \pm 1.05$ $\mu$g/100 ml with a range of 17.0–27.3, and that 12 male and female cancer patients, ages 50–71, had average whole-blood selenium levels of $16.20 \pm 0.7$ with a range of 13.7–21.1. Selenium blood levels in 19 cities reported by Allaway *et al.* (1968) and cancer deaths per 100,000 had a correlation coefficient of −0.434. These data suggest that selenium, where it is available in the environment for human consumption, may exert a protective effect against cancer.

## THE GEOCHEMICAL ENVIRONMENT AS RELATED TO HUMAN DISEASE IN THE UNITED KINGDOM

### *Trace Elements Correlated with Cancer in North Wales and Southwest England*

Examination of garden soils from houses with stomach-cancer experience (10-year residence), compared with those from control houses, showed positive but empirical correlation of disease with the extractable zinc:copper ratio in the soil, when the zinc was extracted with *N*/2 (half strength) acetic acid. This relationship was stronger with 20 years of residence (Stocks and Davies, 1964).

Following observations by Allen-Price (1960) on the unusual occurrence of cancer deaths in certain villages in southwest England, the Royal College of General Practitioners compiled the data from exploratory stream-sediment studies (Applied Geochemistry Research Group, Imperial College, London), soil (Geography Department, University College of Wales, Aberystwyth), and vegetable analysis (Harry Warren, University of British Columbia) (Pinsent, 1968). Anomalously high levels of arsenic, copper, lead, and zinc in both sediment and soil in the area do not fully explain geochemical differences between high cancer-incidence villages and controls. High lead contents were found in lettuce. Recently, the Royal College of General Practitioners has introduced a diagnostic index to improve the standard and uniformity of diagnosis by general practitioners; participating doctors will make returns to the College. The Geography Department, University College of Wales, Aberystwyth, is also carrying out more detailed studies on heavy metals in soils and domestic water supplies, and a survey of lead in human blood is under consideration.

### *Lead in Garden Soils and the Human Lead Burden*

A collaborative study between St. Mary's Hospital Medical School and the Applied Geochemistry Research Group has shown that significant differences occur in the lead content of the blood and hair of 2- to 3-year-old children, grouped according to contents of $<1000$ ppm, 1000–10,000 ppm, and $>10,000$ ppm lead in garden soil. Target areas of high- and low-lead soil in central England were selected on the basis of geochemical data. The high lead levels reflect contamination from past mining and smelting activities (Barltrop *et al.*, 1974; Strehlow and Barltrop, 1974). A program has been initiated to determine the form and bioavailability of lead in soils from these areas. The study will include feeding trials with rats in which soil will be incorporated in the diet.

### *Cardiovascular Disease in Relation to the Hardness of Water Supplies*

The incidence of cardiovascular disease has been negatively correlated with water hardness in 61 large county boroughs of England and Wales, which have populations of $>80,000$. Cardiovascular disease (CVD) rates are about 40 percent higher in the very-soft-water towns compared with the very-hard-water towns. The correlations of CVD with water calcium and carbonate were the highest ($r = -0.7$ and $-0.6$, respectively, based on death rates at ages 45–64) (Crawford *et al.*, 1968). Further studies in three soft-water and three hard-water towns have shown the lead content of ribs from necropsies to be higher in the soft-water towns (Crawford and Clayton, 1973). Currently, a proposal is under discussion to extend the study

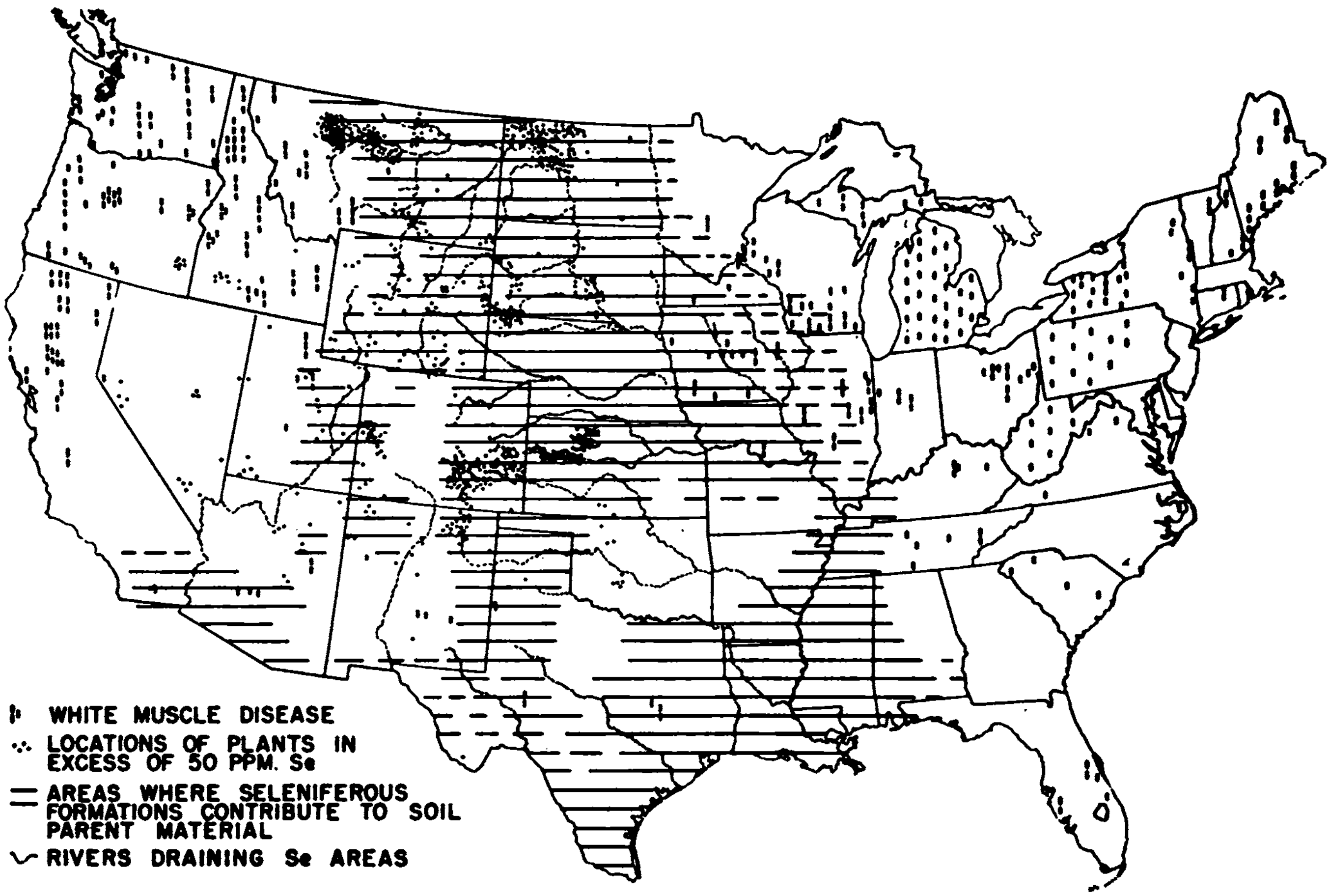


FIGURE 10 The relation of white muscle disease to the distribution of naturally occurring selenium in the United States (Muth and Allaway, 1963). Reproduced with permission from the *Journal of the American Veterinary Medical Association*.

on CVD and waters to 145 towns with populations >50,000 and later to follow this up with clinical studies in selected towns.

## POLLUTION SOURCES OF METALS IN THE UNITED STATES

Man's activities provide a major contribution to the concentration and distribution of metals and other substances in the environment. The biologic effects of some of the atmospheric pollutants have been reported by the National Research Council's Committee on Biologic Effects of Atmospheric Pollutants (1972), since renamed the Committee on Medical and Biologic Effects of Environmental Pollutants. In early 1978, it completed its series of reports on some 20 important pollutants for the Environmental Protection Agency. Automobile emissions are the major source of air pollution, comprising over 60 percent of all emissions (U.S. Public Health Service, 1966). Industry contributes 17 percent of the air pollution, and electric power plants, space heating, and refuse disposal contribute the remaining amount. This material, especially in the form of particulate matter, may be deposited on vegetation, soil, and surface rock or in streams, rivers, lakes, and oceans, thereby increasing the normal mineral or metal concentrations.

Considerable research has been conducted on the amounts of lead and other emissions from automobile sources (Edwards *et al.*, 1973; University of Illinois, 1972). Such emissions are, of course, not confined locally. Patterson *et al.* (1973) found that a 2½-mi-long area of Thompson Canyon in Yosemite Park, some 275 mi distant from Los Angeles, received approximately 195 lb of automotive lead per year.

### *Smelters and Associated Refineries*

One nonautomotive source that has recently received attention has been the metal-smelting industries. The locations of copper, zinc, and lead smelters in the United States are shown in Figure 11.

Thirteen of the 15 copper smelters are located in the West, with nine of them in the Southwest (two are at Hayden, Arizona). Five electrolytic copper refineries are located at Tacoma, Washington; Garfield, Utah; Miami, Arizona; San Manuel, Arizona; and El Paso, Texas; and two fire refineries are located at El Paso, Texas, and Hurley, New Mexico.


*Copper Smelters*
*Tacoma, Washington (ASARCO)
Anaconda, Montana (AC)
McGill, Nevada (KCC)
*Garfield, Utah (KCC)
Ajo, Arizona (PDC)
Hayden, Arizona (ASARCO)
Hayden, Arizona (KCC)
*Miami, Arizona (ICCC)
Morenci, Arizona (PDC)
*San Manuel, Arizona (MCC)
Douglas, Arizona (PDC)
+Hurley, New Mexico (KCC)
+*El Paso, Texas (ASARCO and PDC)
Copperhill, Tennessee (CSC)
White Pine, Michigan (WPCC)

*Lead Smelters*
#Kellogg, Idaho (BHC)
East Helena, Montana (ASARCO)
Tooele, Utah (ISARC)—*closed 1971*
El Paso, Texas (ASARCO)
Boss, Missouri (ALC)
Herculaneum, Missouri (SJMC)
Glover, Missouri (ASARCO)

*Zinc Smelters*
Amarillo, Texas (ASARCO)—*closed 1975*
Dumas, Texas (AZ)—*closed 1971*
Blackwell, Oklahoma (BZC)—*closed 1973*
#Bartlesville, Oklahoma (NZC)
Monaca, Pennsylvania (SJMC)
Palmerton, Pennsylvania (NJZC)

*Associated Refineries, as Indicated*
*, Electrolytic Refinery
+, Fire Refinery
#, Electrolytic Zinc Plant

*Key to Corporate Ownership*

| | |
|---|---|
| AC | The Anaconda Company (a subsidiary of Atlantic Richfield) |
| ALC | Amax Lead Company (a subsidiary of AMAX) |
| ASARCO | American Smelting and Refining Company |
| AZ | American Zinc |
| BHC | Bunker Hill Company (a subsidiary of Gulf Resources and Chemical Corporation) |
| BZC | The Blackwell Zinc Company (a subsidiary of AMAX) |
| CSC | Cities Service Company |
| ICCC | Inspiration Consolidated Copper Company |
| ISARC | International Smelting & Refining Company (was a subsidiary of Anaconda Company) |
| KCC | Kennecott Copper Corporation |
| MCC | Magma Copper Company (a subsidiary of Newmont Mining Corporation) |
| NJZC | The New Jersey Zinc Company |
| NZC | National Zinc Company (a subsidiary of Engelhard Minerals & Chemicals Corporation) |
| PDC | Phelps Dodge Corporation |
| SJMC | St. Joe Minerals Corporation |
| WPCC | White Pine Copper Company (a subsidiary of Copper Range Company) |

FIGURE 11 Locations of present and recently closed copper, lead, and zinc smelters in the United States.

Only six lead smelters are currently operating, three in southeast Missouri, and one each in El Paso, Texas; East Helena, Montana; and Kellogg, Idaho; an outmoded seventh plant at Tooele, Utah, closed at the end of 1971. Foreign concentrates used at custom lead smelters usually contain more arsenic than those of domestic origin. At one custom plant, Honduran and Peruvian lead concentrates appear to be relatively high in cadmium and are an important source of that metal.

In the northeastern United States, two zinc smelters are located at Monaca and Palmerton, Pennsylvania; both use domestic and foreign concentrates, and, although information is available on materials going through the plant, data by state and area are withheld because of proprietary restrictions. A similar situation exists regarding processes and products at the only other operating zinc smelter in the United States at Bartlesville, Oklahoma. Three other zinc smelters in Oklahoma and Texas were closed in the early to mid 1970's—those at Dumas, Texas (1971); Blackwell, Oklahoma (1973); and Amarillo, Texas (1975). Two zinc electrolytic refining plants also at Kellogg, Idaho, and Bartlesville, Oklahoma, are not shown on the map.

Smelter emissions are affected to various degrees by such factors as composition of the feed, recycling of dusts, slags, and sinter and efficiencies of fume and dust collectors.

Arsenic, cadmium, and selenium all occur as minor constituents in various concentrations in ore concentrates fed to smelters. Cadmium is a companion metal in zinc ore and is commonly a major by-product of zinc smelters; cadmium also occurs in lead ores. While quantitative input data, particularly for concentrates, are available or have been derived for lead and zinc plants, it is virtually impossible to assess the input and output of minor metals in various processing stages because of the difficulty of determining quantities and assays of fume and dust generated and the reluctance or inability of the company to provide data on gaseous emissions.

Because of the companies' reluctance, the concentrations that are released can only be estimated by analyzing soils and vegetation near smelters and other processing plants. Such information has been accumulating in recent years in government, university, and Environmental Protection Agency (EPA) files as environmental projects are funded. The high rate of deaths from all causes in counties where some processing plants occur makes it imperative that such existing data be assessed. Some information has been made available. A comprehensive study by the EPA has been conducted in the Helena Valley of Montana to determine the effects on vegetation of pollutants from the American Smelting and Refining Company (ASARCO) smelter (Gordon, 1972). A detailed geochemical study of zoning of metals in the Coeur d'Alene district by Gott *et al.* (1969) showed contamination with metals of the Coeur d'Alene River Valley east from the smelter and an increase in cadmium:zinc ratio near the smelter.

The lead industry as a potential source of trace metals in the environment has been described by Wixson *et al.* (1972) with emphasis on the "Viburnum Trend" or "New Lead Belt" in southeast Missouri. This area is the world's largest lead-producing district and produced more than 80 percent of the total U.S. lead production in 1973. Also in 1973, the annual production of Missouri's three lead smelters was more than 455,000 short tons (Missouri Geological Survey and Water Resources, 1974). The amounts and distribution of metals around these smelters have been studied to determine the efficiency of emission controls and to delineate areas of high metal concentrations where livestock should not be allowed to graze. Studies by Purushothaman *et al.* (1973) were used by lead industries to refine pollution-control monitoring through the construction of remote air-monitoring systems, with the monitored data telemetered to a smelter for use in averting serious air-pollution episodes.

Dorn *et al.* (1973) also studied cattle on a farm in the lead-producing district of southeast Missouri during 1971–1972. They found an increased body burden of cadmium and lead, although none of the animals had developed signs of toxicity. Further work on the distribution of heavy metals in soils near an active lead smelter was done by Bolter *et al.* (1974), who indicated that lead deposited in a forest around a new lead smelter showed that most (50–90 percent) of the lead was retained in the leaf litter. These amounts decreased from 5000 μg/g of lead in the litter within 1 mi of the smelter to 100 μg/g of lead in the litter 10–30 mi away.

Similar studies have been made by other investigators. Roberts and Goodman (1973) have indicated that the surface soil around one zinc–lead smelter in South Wales returned to background concentration within 5 years after the plant closed. Cannon and Anderson (1971), however, found that piñon branches, collected 0.6 mi from the Leadville smelter 13 years after the plant had closed, contained 18,000 ppm lead in the ash (342 ppm by dry weight) and 140 ppm cadmium in the ash (2.7 ppm by dry weight). Thornton and Webb (1973) also studied the environmental geochemical effects of old smelting and mining activities in the United Kingdom. Hutchinson and Whitby (1973) pointed out that nickel smelters in the Sudbury Basin of Canada had caused severe soil contamination by nickel and copper. Mercury is also a possible contaminant from smelters.

These problems associated with contamination from smelting activities illustrate the need for valid geochemical maps that show normal background concentrations of metals prior to the start of man-made activities. From this information, optimal sampling plans could be developed by industries, agencies, and researchers. A good example of this concept has been presented by Tranter and Sandvos (1974), who suggest a plan for estimating the required number and distribution of sampling sites necessary to assess accurately metal concentrations in soil and vegetation.

Maps of natural metal concentrations in the environment and the levels of environmental contamination, which are superimposed on the natural concentrations, are necessary to evaluate the impact of metals in the environment on the incidence of disease in man.

## RECOMMENDATIONS

### *Long-Range Plan for Comparing Geochemical and Disease Data*

A long-range plan for action by rock geochemists should include the following:

• Preliminary compilation of computerized maps of geochemical provinces in the United States showing existing data on elemental distribution, carefully assessed as to its source and anomalous character in view of the reason for collection.

• Additional surveys at appropriate densities to gather meaningful information about bedrock/overburden geochemistry to provide systematic data in areas of present insufficiency and to disclose regional facies variations within the geologic units.

• Production of general maps by automated procedures, which lend themselves to the superimposing of multielement patterns of elemental distribution, to permit comparison of disease incidence with more than one element at a time. Elemental data based on rock, stream sediment, and soil analysis should be supplemented by interpretive notes on the source and mode of dispersion of those elements of prime interest.

• Comparison of these maps with maps of disease incidence by medical epidemiologists.

• Performance of closed-spaced sampling and epidemiological studies in target areas that emerge from the overall study as being particularly anomalous, i.e., high or low.

### *Short-Term Plan for Immediate Implementation*

• Because geochemical and disease data for the three diseases in question are not available for all parts of the country and the acquisition of total coverage will be time-consuming and expensive, a compromise for immediate implementation is suggested. Epidemiologists who have access to such data for stomach cancer and heart disease should furnish rock and water geochemists with lists of 100 highest-incidence counties and 100 lowest-incidence counties in the United States for the specific diseases on which they work. From these, ten or more counties from each group for which pertinent elemental information exists should be chosen for comparative study. Rock, water, and disease data should then be sent to soil and plant specialists for further study and then to the epidemiologists for final evaluation. It is also recommended that a group be formed from Workshop participants, from interested government agencies, such as the Bureau of Mines and the Environmental Protection Agency, and from private industry, such as sanitary engineering firms, to assess the effect of industrial pollution in these particular counties.

• Information is also available to permit a study of trace-element distribution and availability of metals in peats of the United States from existing U.S. Geological Survey files.

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# III

# Water: Trace Elements in Solution

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## GENERAL CONSIDERATIONS

Documented outbreaks of acute waterborne disease in the United States during the period 1946–1972 show 405 outbreaks involving 79,000 cases of illness, of which 19 involving 279 illnesses were caused by chemical poisoning. This chemical contamination of drinking water resulted both from man's activities and from natural geochemical effects. The influence of chemical constituents of water on the development of certain chronic diseases, however, still remains controversial and unresolved. Studies have shown a relation between water hardness and cardiovascular diseases. Data have also been presented that suggest a link between selected trace elements in water and certain cancers and between calcium and magnesium and urolithiasis. Further study of these relations is desirable from a public-health standpoint.

To conduct meaningful studies in relation to health and disease, one must be cognizant of the mechanics of drinking-water delivery systems in the United States. Water used for drinking is essentially a local product, that is, it is normally consumed within a reasonable distance of its source. Exceptions, such as Los Angeles, of course, exist. A distinction needs to be made between raw and finished (treated) water and between community and individual water systems. Data must be obtained on raw-water sources, the treatment of water, the chemical composition of tap water, and the nature of the chemical species present in the water. Of additional concern is the use of untreated, undivided water systems, bottled water, and additional treatment (water softening) within a water-distribution system. These differences have not generally been recognized or considered in most epidemiological studies. They are of overriding concern in any epidemiological study of the relation of drinking water and chronic diseases.

Few reliable data exist on the chemical composition of most bottled water sold in the United States. Other than self-imposed standards, little control on the quality of this water is evident. This is also true of water that has been subjected to additional treatment. Little or no data are available on the resulting chemistry of water that has undergone this added treatment. Clearly, chemical studies of these relatively common sources of water are in order.

In most nonrural areas, water is generally treated to some degree before it is consumed, and attention paid only to natural surface-water or groundwater composition may be misleading if we ignore the changes effected by treatment on the chemistry of a particular water source. Trace-element chemistry of surface water, for example, varies greatly in composition on a seasonal basis (Angino *et al.*, 1969). Groundwater from a given source or aquifer, however, tends to be of reasonably constant composition over time. Also, some of the trace elements of concern may be almost completely removed by treatment processes. Iron, nickel, cobalt, cadmium, lead, zinc, and copper are most likely to be removed by lime softening, whereas lithium, selenium, molybdenum, and arsenic are most likely to be passed into the delivery system (pipes) relatively untouched. For these components, knowledge of natural concentrations in raw waters may be of value. In addition, it is possible that the water as it emerges from a tap may have been changed considerably from what was sent into the delivery system, because of interaction with the pipes making up the delivery system.

To put the problem in better perspective, let us examine in more detail the problems related to (1) collecting useful water-quality data, (2) changes in water quality resulting from the water-supply system, (3) data reliability, (4) elemental speciation, and (5) production of reliable maps relating water chemistry to health and disease.

## COLLECTION OF RELIABLE WATER-QUALITY DATA

A great deal of surface-water and groundwater information exists in the United States that can be used by the epidemiologist. However, if the chemical character of the water that is consumed is to be related more accurately to the occurrence of specified diseases, the data on water quality will have to be more reliable than currently existing data, which unfortunately vary both in accuracy and precision. The reasons for this lack of reliable information are many, but the most important are the following:

### *Sampling*

It is particularly important to establish a reliable range of values for surface-water supplies, because water quality varies considerably. A literature search indicates no uniform sampling or sample storage procedures used prior to analysis by all health-research groups. This lack leads to collecting procedures for various research groups that are redundant or incompatible to the point of being almost useless. National guidelines on sampling, storage, and preservation procedures are urgently needed. We strongly recommend that studies on this subject be made as soon as possible.

Consider, for example, sample preservation. The water sample may be altered by the method of collection, fixation by chemical means, and type of container in which it is transported or stored. Research by Struempler (1973) on the adsorption of five heavy metals onto glass, polyethylene, and polypropylene containers indicated that no single container was satisfactory for all metals. It was found that polyethylene would not adsorb cadmium and zinc; however, new containers could not be cleaned satisfactorily for these metals. A similar problem was found when acidification with nitric acid to pH 2 prevented sorption of metals onto glass, but this method was effective for lead for only a few days. The problem with storage of water samples has been noted previously, and further study on improved storage methods has been suggested by Wixson *et al.* (1977) for the development of a National Environmental Specimen Indexing System advocated at the Subcommittee on the Geochemical Environment in Relation to Health and Disease Workshop on Geochemistry and the Environment held at Capon Springs, West Virginia, in 1973.

### *Analytical Data*

In a survey conducted by the Trace Elements and Toxicity Subcommittee of the Committee on Water Quality, Environmental Engineering Division, American Society of Civil Engineers (ASCE), preliminary data indicate that only four of the fifty states and four possessions of the United States have criteria for evaluating or accrediting their testing laboratories (Jennett, 1974). Virtually no programs exist for sample exchange and for analytical cross-checking in any state. Only the largest cities can afford their own analytical facilities. Most small systems must use commercial laboratories, a practice that immediately raises problems, not only of laboratory quality but of sample collection and of the effectiveness, length, and conditions of storage.

### *Requirements for Reporting Data*

In practice, the frequency of reporting is erratic. More importantly, the only information sought is whether certain constituents exceed state or federal standards. As a result, the bulk of the data are being reported as a value of "less than" that required for a particular standard, and this does not provide usable information for the researcher. Another and perhaps equally important factor is that few states require or request information on elements other than those for which there are specific limitations or standards. Consequently, relatively little information is available on those trace elements for which there are currently no standards, and little information is accessible on anions at all, except for chlorides, nitrates, sulfates, biocarbonates, and possibly phosphates.

It should be emphasized that, with few exceptions, relatively little is known about the quality of water in individual water wells. Although data on individual wells and their water quality may be required by some states, the requirements are virtually unenforceable. It will, therefore, be difficult to equate health problems with the quality of water in the rural areas of the United States.

Reviews of waterborne diseases by Craun and McCabe (1973) indicated that over 92 percent of the cases associated with public systems were associated with the water source and treatment deficiencies. They also pointed out that most disease outbreaks associated with private water systems were due primarily to the use of untreated groundwater.

### *Treatment Plant Operators*

The role that these individuals play in the sampling and testing of water is probably one of the most important factors determining the reliability of the data. Until recently, few states had minimum standards for the employment of treatment-plant operators, but the situation is rapidly changing. Currently, 36 states have some type of program that requires mandatory certification of water-treatment plant operators (W. C. Ford, Missouri Department of Natural Resources, Jefferson City, personal communication, 1974). The quality of these programs varies from stringent examination to adherence to general formalities. The trend, however, is toward the examination procedure. Because most current certification regulations carry a clause exempting those currently employed, the upgrading process will take time, but the end result will be that the treatment plants will be run more efficiently and the data on water quality will be more reliable. Certification alone, however, does not assure a competent qualified work force, but it does provide a mechanism and standard through which state agencies can improve their programs (Warrington, 1973).

It is ironic that the people who are directly associated with public health rarely have backgrounds that qualify them for their positions. Because of the low salaries associated with water utilities work, the requirements for education and skills have been minimal. Mandatory licensing will help materially to alleviate these conditions, if the requirements are stringent enough. However, there is a shortage of private and public funds for training professional and technical personnel in the water-treatment field.

### *Tap Water*

Except for those health studies conducted when pollution of water sources has been suspected, virtually no nationwide data exist on the quality of the water as it comes from user taps. The Environmental Protection Agency's Interstate Carrier Water Supply study unfortunately covers a large population but a small geographical area. These data, however, are primarily from treatment-plant taps (i.e., finished water sources). Although water-plant analyses may be well performed, little is known about the changes in the chemical quality of the water as it moves through the distribution system. Such changes can appreciably affect the heavy-metal content of the water. The metals may either precipitate in the distribution system or be added to the water as a result of corrosion. Many large cities probably possess such data in unpublished form, and these data would be valuable to epidemiologists, who could use them to facilitate study of urban populations large enough for reliable statistical analysis. Most medical data are collected in large regions.

### *Drinking Water*

A major problem exists in drinking-water research because of a lack of funds for training professional and technical personnel in the water-treatment field. Funds for this purpose have, in fact, declined decidedly in the last 5 years, and the money available for research in water treatment and quality has decreased to the extent that more is known about waste than about drinking water.

## CONTAMINATION OF WATER DURING TREATMENT AND DISTRIBUTION

A major source of metal contamination of drinking water is the water-supply system itself, beginning with the chemicals used in the water treatment. Copper is often added for algae control in reservoirs. Treatment chemicals very likely contribute to trace-metal concentration levels found in water. Corrosion of the distribution system and household plumbing add to the metal content of drinking water.

Water samples collected as part of an industrial health survey conducted in Chicago in 1968 (L. J. McCabe, EPA, Cincinnati, and J. C. Vaughn, Miami University, Oxford, Ohio, unpublished data, presented at meeting of American Chemical Society, Minneapolis, 1969; McCabe, 1974), provided an opportunity to determine the metal content of a large number of samples from a single system. Composite samples were collected at the treatment plants, and these results were compared with 550 grab samples collected from the distribution system to give an indication of metal pickup. The percentage of grab samples having trace metal pickup were as follows: cadmium, 15; chromium, 17; cobalt, 10; copper, 28; iron, 39; lead, 20; manganese, 32; nickel, 34; silver, 15; and zinc, 67. Except for lead, this pickup did not result in samples exceeding the drinking-water standards. For the lead, 0.7 percent exceeded the limit. However, when corrosive water is distributed, the problem can be more serious. Distribution studies conducted in Seattle (Dangel, 1975) and Boston illustrate the effect of corrosive water on tap-water quality (Craun and McCabe, 1974). Both Boston and Seattle use impounded surface water and provide chlorination as the only treatment, except that Seattle also fluoridates with fluorosilicic acid ($H_2SiF_6$). The hardness and alkalinity of these waters are remarkably low, and the pH is on the acidic side. The dissolved oxygen content of Seattle's water approaches saturation. The distributed waters are excellent solvents and exhibit aggressive corrosion tendencies. The water-quality parameters shown in Table 3 were measured on treated water at the source.

In Seattle, that part of the distribution system served by the Tolt River was sampled. Samples were collected from 31 points in the distribution system, primarily from household taps, although some samples were collected from major transmission mains. Two types of sample were collected early in the morning for comparison: *standing* and *running* samples. The *standing* samples, as the first water to run out of the faucet, normally represented the water that had been standing in the household plumbing and service line overnight. *Running* samples were collected after the house lines were well flushed, and they represented water from the mains. This same procedure was followed in Boston, where *running* and *standing* samples that had a higher concentration of trace metals than the *running* sample collected at the same point (after considering analytical variability) are used as evidence of trace metal pickup. The percentage of samples with trace metal pickup is shown in Table 4.

TABLE 3 Water-Quality Parameters Measured on Treated Water at the Source[a]

| Parameter | Boston (MDC)[b] | Seattle |
|---|---|---|
| pH | 6.7 | 5.5 |
| Hardness ($CaCO_3$) | 14 ppm | — |
| Total dissolved solids (TDS) | 50 ppm | — |
| Alkalinity ($CaCO_3$) | 8 ppm | 2 ppm |
| Chlorides | 12 ppm | 1.7 ppm |
| Calcium | — | 2.1 ppm |
| Magnesium | — | 0.3 ppm |
| Specific conductance | — | 20 mho/cm (25°C)[c] |

[a]Sources: Dangel (1975); Craun and McCabe (1974).
[b]MDC, mean daily concentration.
[c]mho, reciprocal ohm.

TABLE 4 Percentage of Samples with Trace Metal Pickup[a]

| Trace Metal | Boston | Seattle |
|---|---|---|
| Cadmium | 13 | 61 |
| Chromium | 39 | — |
| Copper | 44 | 73 |
| Iron | 52 | 86 |
| Lead | 30 | 95 |
| Manganese | 11 | 82 |
| Zinc | 35 | 95 |

[a]Sources: Dangel (1975); Craun and McCabe (1974).

TABLE 5 Percentage of Homes with the Trace Metal Content of a Sample Exceeding the Drinking Water Standard (DWS)[a]

| Trace Metal | Boston | Seattle |
|---|---|---|
| Cadmium | 0 | 7 |
| Chromium | 0 | — |
| Copper | 19 | 24 |
| Iron | 9 | 76 |
| Lead | 65 | 24 |
| Manganese | 0 | 5 |
| Zinc | 0 | 10 |

[a]Sources: Dangel (1975); Craun and McCabe (1974).

The levels of trace metals in these systems exceed drinking-water standards, as shown in Table 5.

The difference in trace-metal pickup between these systems is probably related to the type of plumbing material and service lines in use. In Boston, a high percentage of homes sampled had lead service pipes; whereas in Seattle, copper and galvanized iron were more commonly used. No lead pipes were reported in Seattle; the presumed source of lead there is the solder used to join copper piping.

### *Human Intake of Trace Metals*

Although other sources of human metal intake may predominate, water seems to offer the most direct means of studying the effects and relations between trace-metal intake and the environment. Most investigators feel that food is the major source of many of man's trace metals. A more recent study of intake from food used institutional total diets for children 9 to 12 years of age (Murthy *et al.*, 1971). If a comparison is made between this study and the Community Water Supply Survey (CWSS), it is found that the largest proportion of intake from water compared with food is for zinc; but this is only 4.3 percent. Next is cadmium at 3.3 percent, and then manganese at 2.8 percent. The water cobalt intake was only 0.4 percent; the chromium intake was 0.8 percent; however, chromium does not commonly occur in water, except under unusual conditions. It is possible, however, that the physiological availability of metals in food and water may be different, and if water is to provide a significant contribution to body burden of trace metals, the metal must be more readily available in water than in food.

The CWSS collected water samples at the consumer's tap and covered 969 water systems in 9 geographic areas around the country (McCabe *et al.*, 1970). It was not a totally representative sample of the United States, but its wide coverage should provide an estimate of the metal intake from water of consumers of water supplies (Table 6).

Metal contamination in drinking-water supply systems in rural areas utilizing individual water sources will continue to be a problem to the epidemiologist. Many incidences of metal toxicity have been reported connected with the pH of the water supply and the type of storage or distribution system utilized. Walker-Smith and Blomfield (1973) reported the case history of a 14-month-old child in Australia that exhibited evidence of Wilson's disease. The child subsequently died, and elevated copper levels were found in his liver. Because of the severity of the case, the possibility of copper poisoning was investigated. The family had moved to the farm in question when the mother was four months pregnant. An investigation of the drinking water, which came from a well and passed through copper pipes in the house, indicated that the water pH of 4.4 give a copper concentration of 675 $\mu g$/100 ml in the cold-water supply. Gallery *et al.* (1972) traced the history of a patient on home dialysis who suffered acute nausea, vomiting, and fever, which were found to be caused by zinc concentration of 625 $\mu g$/100 ml contained in the home water supply used. The water had been stored in a galvanized tank.

### *Data Reliability*

Research scientists must have confidence in the reliability of their data if studies relating water chemistry to health and disease are to have meaning. Two important aspects of the reliability of water-quality data are the

TABLE 6 Estimated Average Intake of Metals from Water by Consumers[a]

| | Community Water Supplies | | |
|---|---|---|---|
| Metal | Average Concentration, μg/liter | Intake in μg at 2 liters/ day | Percentage of Samples with 1 μg/ liter or More |
| Cadmium | 1.3 | 3 | 63 |
| Chromium | 2.3 | 5 | 11 |
| Cobalt | 2.2 | 4 | 62 |
| Copper | 134.5 | 270 | 99 |
| Iron | 166.5 | 440 | 99 |
| Lead | 13.1 | 26 | 74 |
| Manganese | 22.2 | 44 | 78 |
| Nickel | 4.8 | 10 | 78 |
| Silver | 0.8 | 2 | 23 |
| Zinc | 193.8 | 390 | 100 |

[a]Source: McCabe (1974).

capability of the analytical methods or techniques to generate valid data and the capability of the analyst to apply them appropriately to produce analytical results with a high degree of confidence.

To produce reliable water-quality data, the laboratory must use methods of proven adequacy for the purpose intended. Collections of acceptable methods are available (American Public Health Association, 1971; American Society for Testing and Materials, 1975; U.S. Environmental Protection Agency, 1971; Brown *et al.*, 1970). Generally, the methods included in these publications represent the consensus of analysts and researchers of extensive experience in the development and use of the best available methods for analyzing water from different sources, of various types, and used for various purposes.

The techniques of analytical chemistry change; new instruments and methods are constantly being developed. It is not uncommon for methods published in one of the above-referenced manuals to be out of date and superseded by an improved method almost by the time the manual is published. The American Society for Testing and Materials manual of standard methods is probably the least objectionable in this regard, inasmuch as the volume is revised annually.

Any method proposed as a standard acceptable method for water analysis should, as a minimum requirement, be accompanied by a statement giving the accuracy and precision of the method. This precision statement expresses the degree of reliability of the analysis, provided that the method is used by an experienced analyst working in a properly equipped laboratory. Such a statement assures the data user that the data should have at least this degree of reliability. The data user should satisfy himself that adequate methods of a satisfactory degree of reliability were used to obtain the data of interest.

Despite the use of standard analytical methods, data may be unacceptable because the analyses were performed in a careless manner or in an improperly equipped or managed laboratory. Good analytical data can consistently be generated only by a conscientious and experienced analyst working in a well-equipped and properly maintained and managed laboratory. Personnel, equipment, and laboratory operation and management, therefore, are also necessary factors to consider when striving for the acquisition of water-quality data in which the data user may have full confidence. Evidence of sustained proper laboratory management and operation can be obtained only by an adequate analytical quality-control program, incorporating a completely objective evaluation of overall laboratory performance in the analysis of reference control samples. Such a program must be fully documented, and the data user has every right to insist that such evidence of laboratory analytical reliability be demonstrated.

Concentration of trace or minor constituents frequently approach the limit of detection of the analytical method. However, the standard deviation of the method may be found to be as great as or greater than the concentration of the constituent being measured. When it is determined that such very low concentrations are significant, special analytical techniques must be used, the analytical costs increase appreciably, and the accumulation of sufficient data that can lead to valid statistical treatment is severely limited. Most often a compromise must be achieved whereby a statistically significant amount of data must be obtained at a reasonable cost, usually with some sacrifice of data reliability.

One final factor in connection with reliance on a single analysis is that water quality is a constantly changing factor, especially in the case of surface waters. Consequently, reliance on a single analysis is risky. Samples should be collected over a sufficient period of time to identify the ranges of concentration that may be expected for the several constituents of interest. Data reporting the mean concentration over a period of time will in general be more useful to the epidemiologist than data based on the analysis of a single sample.

The several factors that we have mentioned are the most critical in terms of cautioning the data user concerning hazards inherent in the blind acceptance of data as being of unquestioned reliability. The design of any data-survey program must include an adequate plan for the full documentation of data reliability.

## METAL SPECIATION IN WATER—ITS EFFECT ON HUMAN HEALTH

The importance of chemical speciation on body assimilation of metals has been demonstrated by comparative studies that have shown high uptake of methyl mercury ($CH_3Hg^+$) from the intestinal tract as compared with the uptake of inorganic mercury. In addition, numerous studies have been conducted that document variations in the availability of trace metals in water as a function of other dietary components such as phytates, hemicelluloses, amino acids, and carbohydrate complexes.

The chemical form of substances in natural water or in water entering a treatment plant affects the efficiency of removal. For example, stable, water-soluble complexes of metals with either organic or inorganic ligands can pass through a treatment plant unaffected. Sand filters are generally less effective for metal removal than treatments involving coagulation. Chlorination of water will often degrade organic complexes of metals and again alter removal characteristics.

As water leaves the plant and enters the distribution system, it is again subject to concentration and species variation through interaction with other water constituents and reactions with the elements of the distribution system. Calcium and magnesium salts associated with water hardness are excellent coprecipitators of divalent ions such as zinc, cadmium, and lead and often accumulate on the wall of pipes in the distribution system. A home water softener will eliminate nearly all divalent elements in water if the unit is operated efficiently.

Observation and experimental evidence presented by H. Mitchell Perry, Jr. (Washington University, St. Louis, Missouri, personal communication, 1974) suggest a relation between cadmium concentration and hypertension and an inhibition of the cadmium effect by water hardness. The effect of water hardness on cadmium availability can be logically attributed to the tendency of carbonate and phosphate, the anions often associated with water hardness, to precipitate cadmium, thus either effectively removing it or converting it to an unavailable chemical form. Calculations by Morel *et al.* (1973) show that $10^{-6}$ molar cadmium in $10^{-3}$ molar carbonates will exhibit a theoretical free cadmium ion concentration of about $5 \times 10^{-11}$ molar. Both experimental and additional theoretical studies are needed to prove this point.

### *Mercury Speciation and Human Health*

Mercury provides an excellent example of chemical changes that can occur in nature that have dramatic effects on bioavailability and toxicity. Mercurous salts are relatively insoluble in aquatic systems, form weak complexes with organic ligands, and are relatively nontoxic. Calomel (mercurous chloride) has been used as a diuretic. The mercurous ion is easily oxidized in nature to the divalent mercuric ion, which is highly toxic. Mercuric ions adsorb strongly on both organic and inorganic materials, form extremely strong complexes with sulfide-containing organic materials, and typically concentrate in anaerobic sediments as the insoluble mercuric sulfide.

Various inorganic forms of mercury can be transformed into methylmercury or dimethylmercury in natural aqueous systems by microbiological processes (Wood *et al.*, 1968; Jenson and Jernelov, 1969). Spangler *et al.* (1973a, 1973b) have found organisms capable of methylating mercury in sediment. Methylmercury anion is readily absorbed in animal tissue, is both water and lipid soluble, is retained in the body for relatively long periods, and is extremely toxic. Dimethylmercury is also readily absorbed by animal tissue, is lipid soluble, but is rapidly excreted by the body and is much less toxic than methylmercury. Toxicity attributed to dimethylmercury may actually be due to partial acid hydrolysis or biodegradation to the very toxic methylmercury anion.

Variations in toxicity of these different mercury compounds can be at least partially explained by considering their physiochemical properties and chemical changes that can occur when they are ingested.

Mercurous salts, being relatively water and lipid insoluble and weak complexing agents, will pass through both the acidic conditions of the stomach and the slightly alkaline conditions of the intestine unaltered although some oxidation to the mercuric ion may occur, particularly in the more alkaline conditions of the intestine.

Ingested mercuric ions will exist primarily as the hydrated ion or as a mercuric chloride complex at the acid pH of the stomach. However, as this ion encounters the alkaline conditions of the intestine it will adsorb strongly on fibrous materials or react with amino acids, peptides, and proteins to form very stable complexes (Bjerrum *et al.*, 1957; Jonasson, 1970). Internists have for many years recognized milk, egg whites, and other high-protein foods as effective antidotes for ingested heavy metals (Merck Index, 1968). In addition, British anti-lewisite (BAL) and ethylenediaminetetraacetic acid (EDTA), strong metal-chelating agents, have been used as an effective treatment for excessive body burdens of heavy metals. Typically about 5 to 10 percent of an ingested heavy metal (depending on the metal and the homeostatic mechanism) will be absorbed into the body from the intestinal tract. However, these metals are probably absorbed as complexes of amino acids or small peptides and not as the free-metal ion, because metal–amino acid complexes generally exhibit stability constants in the range of $10^6$ to $10^{10}$, and peptides in the range of $10^4$ to $10^5$. Therefore less than 0.01 mole percent of the metal would be expected to be present as the free ion.

Amino acid and peptide complexes of the mercuric ion have properties that would allow them to pass through the lipoprotein network of cell membranes. Once inside the body, however, the complexes can be exchanged by stronger complexing agents or other biological processes that release the metal; it can then interfere with a variety of metabolic reactions.

Although mercury has been studied extensively, little is known about the lifetime and routes of the toxic methylated species through the food chain, whether these compounds are being formed in the intestinal tract of aquatic species, and whether water-treatment processes remove or degrade these toxic compounds.

Other metals, such as lead, tin, and cadmium, can also be alkylated. However, it is not known whether microbiological processes will readily produce such species in the natural environment. For example, the information needed to assess the hazards or benefits of metals in water include the following:

- What are the chemical forms of metals in natural aquatic systems?
- How does chemical form influence environmental transport and bioaccumulation?
- Are water-treatment processes effective in removing metals, and is metal removal dependent on the chemical form of the metal?
- Are there metals other than mercury that can be converted to highly toxic metallo-organic compounds in the natural environment?
- What chemical reactions can metals undergo in the stomach and intestine that would alter their absorption and toxicity?
- What are the relations between chemical form, absorption, tissue burden, rate of excretion, and toxicity?

### *Effects of Hard Water*

Various investigators have indicated that the amount of hardness of surface-water or groundwater supplies has some type of effect that will decrease the toxicity of certain trace substances and influence the growth of aquatic life. For example, mountain streams in Kentucky have been classified by Neel (1973) into two distinct categories based on hardness: Type A streams with hardness (expressed as $CaCO_3$) exceeding 50 mg/liter, which contained abundant flowering plants or algae and well-developed mollusk populations; and Type B streams, with hardness values of up to 30 mg/liter, no vegetation, sparse algal growth, and few mollusks.

Yongue *et al.* (1973) reported on differences in freshwater protozoan communities studied in chemically dissimilar bodies of water with emphasis on a bog pond (pH 5.8–6.0, hardness 17.1–34.2 ppm) and a pit pond with pH 8.0–9.0 and hardness 102–154 ppm.

In his studies on acid mine-drainage problems in the Canadian Province of Ontario, Hawley (1972) reported a general trend noted by investigators working with water-pollution problems in the metal-mining industries, namely, the toxic effects of metals decrease with increased pH and increased water hardness. Jennett and Wixson (1972), Wixson (1975), and Wixson and Jennett (1974) reported the same effect for slightly alkaline hard waters associated with the development of the world's largest lead-mining district in southeast Missouri. This apparent buffering effect of water hardness continues to be of interest and may play an important role in protecting livestock and other forms of life that utilize surface-water or groundwater resources for drinking purposes.

Kobayashi (1972) showed good correlation between cerebrovascular mortality and the acidity of water supplies in Japan, which are soft. On the basis of his work, a number of other investigators (e.g., Malpas, 1973) are attempting to define more clearly the role of drinking water in cardiovascular diseases (see section on Cardiovascular Disease in Relation to the Hardness of Water Supplies in Chapter II).

## RESEARCH NEEDS FOR CORRELATING WATER QUALITY WITH HUMAN HEALTH

### *Water-Quality Maps*

Numerous problems are associated with producing reliable nationwide maps representing water-quality parameters. Among these are the availability and quality of the data, the relevance of the data to the purpose at hand, and the representation of the three-dimensional aspect of water sources on a two-dimensional map.

For many trace elements of interest, the availability and quality of the data are the most important constraints on map production. Though the amount of trace-element data has increased rapidly in the past several years, there are still large areas in the United States with little or no available data. Also there exists no standard group of trace elements that are routinely determined by all laboratories. Laboratories vary in their analytical capability, and investigations vary in their trace-element data needs. The general result is a further reduction in the amount of trace-element data available for a trace element of interest.

In addition to poor analytical accuracy and precision, large variations occur between laboratories in detection limits for specific elements. Most of the variations in detection limits do not reflect present-day analytical capabilities but rather are in response to differences in the use of the data. Most laboratories interested in determining whether a trace element exceeds a mandatory or suggested limit of concentration will report all values below the limit as a "less than" value, whereas geochemical or other studies might seek and report values one or more orders of magnitude below these limits. Most data-storage systems that combine data from numerous sources provide no means of evaluating the quality of the data, and as much consideration is often given to interpretations based on poor data as on excellent data.

The importance of proper sampling procedures for waters and other environmental components to obtain data of known reliability is discussed in detail by Miesch *et al.* (1976). A study of the distribution of trace elements in

Missouri groundwaters by Feder (1972) using the principles outlined by Miesch provides trace-element data of known reliability for the State of Missouri. At present it is the only study of its kind in the United States.

Other trace-element data can be useful for constructing maps of trace-element distributions in waters; however, care must be exercised in choosing the data. Water supplies in many areas can be obtained from either streams or subsurface aquifers. In addition, many areas are underlain by two or more groundwater aquifers, each capable of furnishing adequate water supplies to municipalities. Many areas, in fact, use multiple sources; thus we have to define the populations using each.

Where each of these sources of water has a different chemical composition, it is difficult to represent this essentially vertical variation on a two-dimensional map, especially on a small-scale map of the entire United States. Where extrapolations from point data are required to regionalize the data, the regionalized data can best be represented by using several maps with each map representing one vertical layer of water supply.

### *Relation between Water Quality and Health and Disease*

For useful comparisons, water should be taken from a source whose chemical composition remains relatively uniform with time (e.g., groundwater). To define better the relation between water hardness and chronic disease, an area taking its water supply from a uniform aquifer would be preferable. For example, the Florida hard-water aquifers (Biscayne and Floridian systems) all underlie an area of sufficiently large population to be considered for this purpose. Such maps as those showing hardness of surface and subsurface waters can be useful in this regard; see Figures 12–14 (Geraghty *et al.*, 1973). These data can be coupled to knowledge of distribution of groundwater aquifers in the United States, Figures 15 and 16 (Geraghty *et al.*, 1973), for maximum utility.

Considerable useful geochemical information pertaining to groundwater quality is available and should be used. For example, one would not expect a high chromium value in hard waters of the south Florida aquifers but might expect it in waters draining the Sweetwater Complex in Montana. These areas might be used to identify relations between chromium (if any) and cardiovascular diseases.

It is possible by use of hardness maps already available, Figures 12–14, 17, and 18 (Geraghty *et al.*, 1973), to delineate those areas of the United States that should be of concern medically.

Concluding, a reasonable body of reliable data clearly exists on the quality of both surface water and groundwater and can be obtained from cities, rural water cooperatives, private utilities, state geological surveys, federal agencies, and many other sources. As a result of the problems previously mentioned, the quality of these data must be evaluated on a case-by-case basis. All these data should be assembled in central data-storage systems together with information on how, when, and where the samples were collected, stored, and analyzed so that they could be more effectively used by epidemiologists to establish criteria for making judgments. Initially, it would be of considerable help for epidemiologists to know what data sources can be tapped. Similarly, if information from physicians were made more readily available, it would be of great value not only to those interested in the geochemical environment and health but also to professionals in the fields of water treatment and distribution.

## RECOMMENDATIONS

- Increase the usefulness of existing data on both surface-water and groundwater geochemistry (mostly major-element data—calcium, magnesium, sodium, potassium, $HCO_3^-$, and chlorine) by developing maps of water-quality data on a distribution-system basis using low-, medium-, and high-order streams, terms that stream morphologists use to classify streams according to their number of tributaries.
- More information on concentrations in water of all the trace elements mentioned in this study is needed. Except for iron, manganese, nitrate, and phosphate, insufficient effort is routinely directed toward determination of trace elements in water.
- Water-quality maps that separate concentrations of calcium and magnesium, rather than combining them on a hardness map, might be of considerable value. Maps of trace-element speciation in natural water systems would be even more valuable. Further refinement is needed in the manner of reporting data. Large amounts of data reported as "less than" are of little value to those attempting to make comparisons between incidence or absence of a particular health problem.
- Until the water-quality data situation improves, physicians and epidemiologists should select small study areas with high- and low-incidence rates for a given disease to permit evaluation of available water-quality data for the area. This procedure would provide better balanced data for statistical evaluation. Alternatively, areas of high or low concentration may be identified for correlation with available morbidity or mortality data.
- Additional support should be made available for training people for the water-treatment industry to permit establishment of reliable information on water quality and the effects of water treatment on trace elements. The development of uniform standards for sampling and analysis is also in need of support. State agencies charged with the collection of data concerning the quality of water consumed at the tap should be given more assistance, so that the information needed by epidemiologists may be made available.
- A system must be developed for collecting an accurate data base on specific aquifers and for determining the quality of the tap water derived from these aquifers. Such data on groundwater would generally be more reliable for epidemiological work, because its quality normally varies

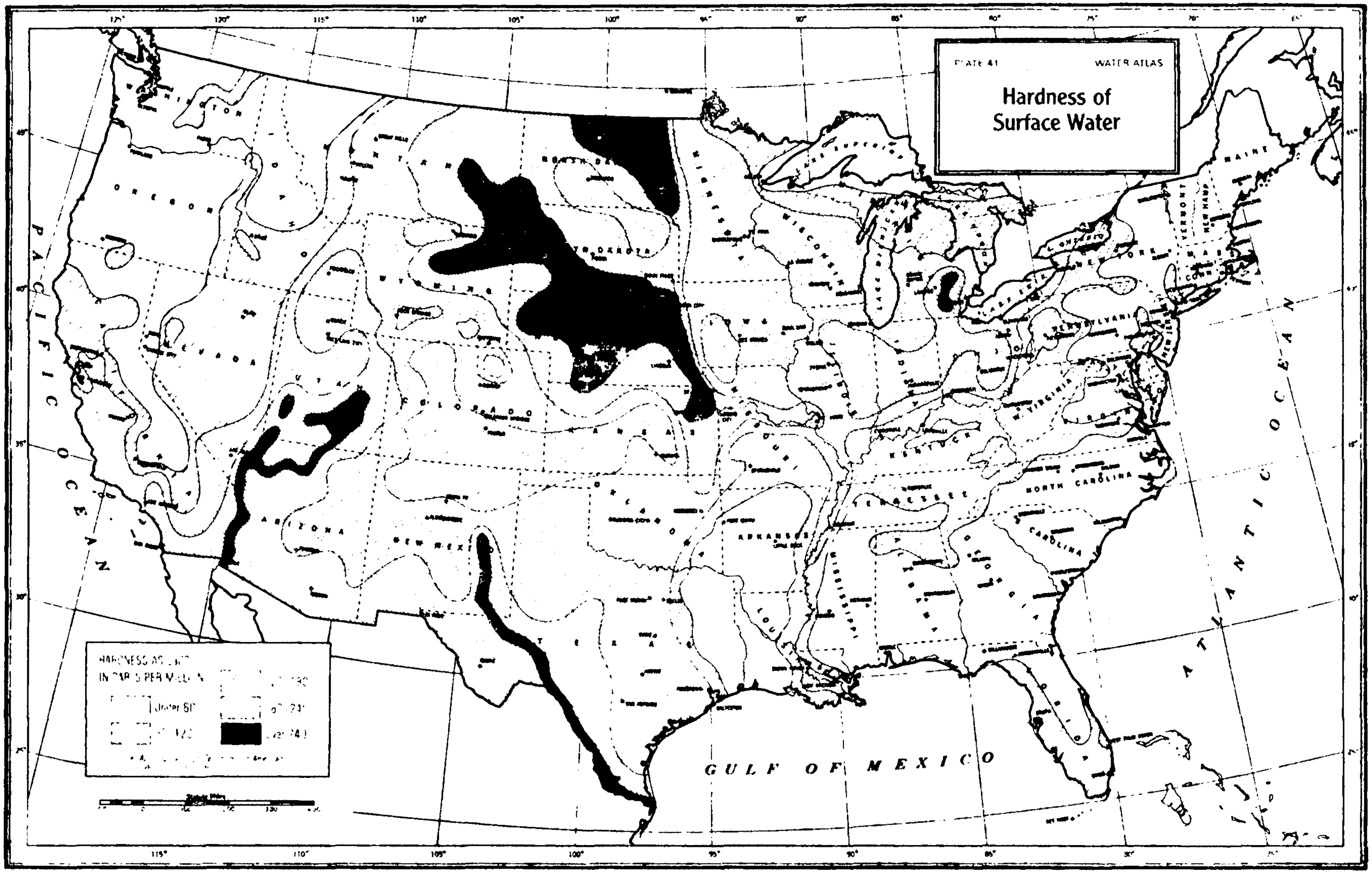


**FIGURE 12** Hardness of surface water (Geraghty *et al.*, 1973).
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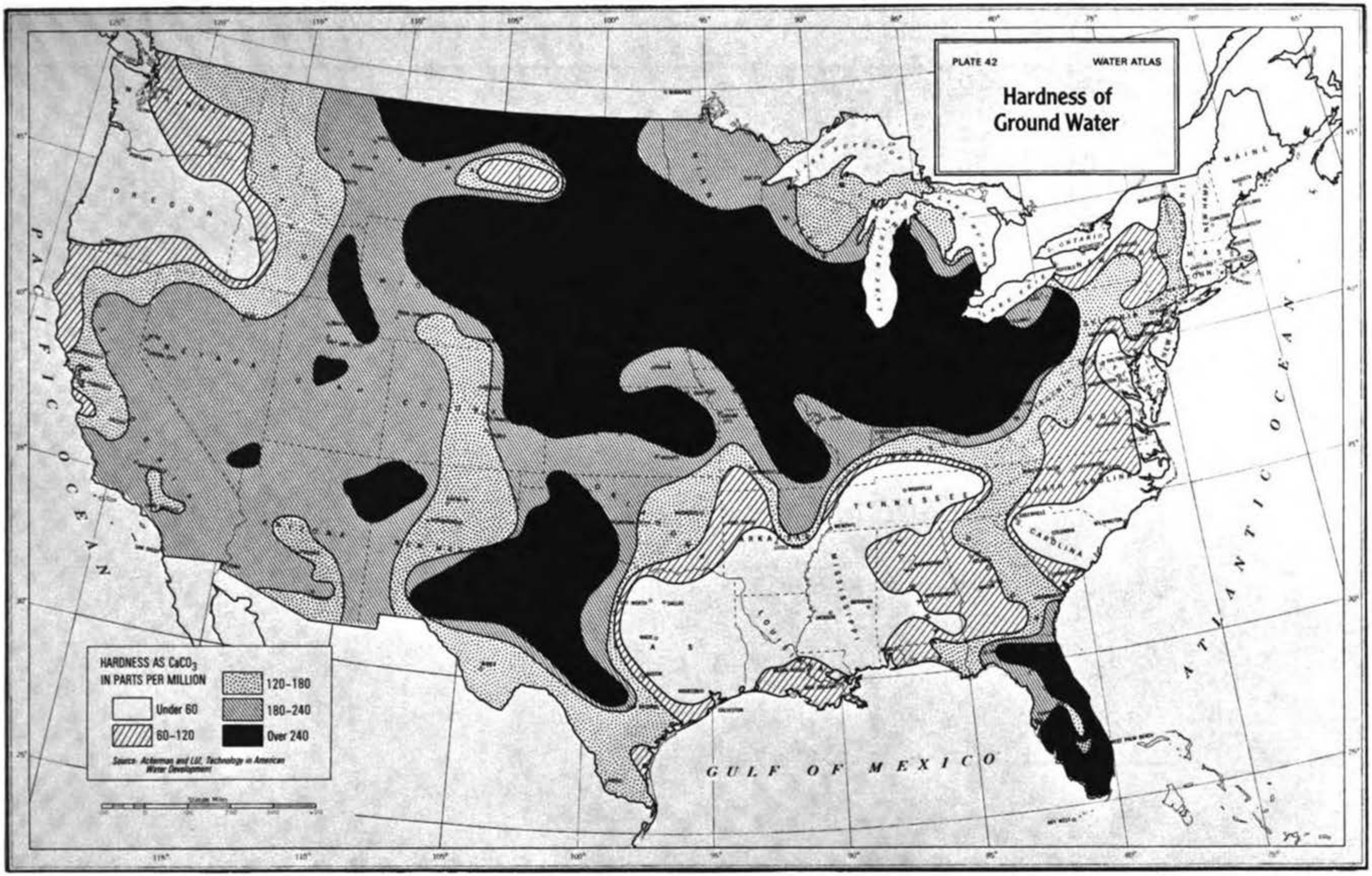


**FIGURE 13** Hardness of groundwater (Geraghty *et al.*, 1973).
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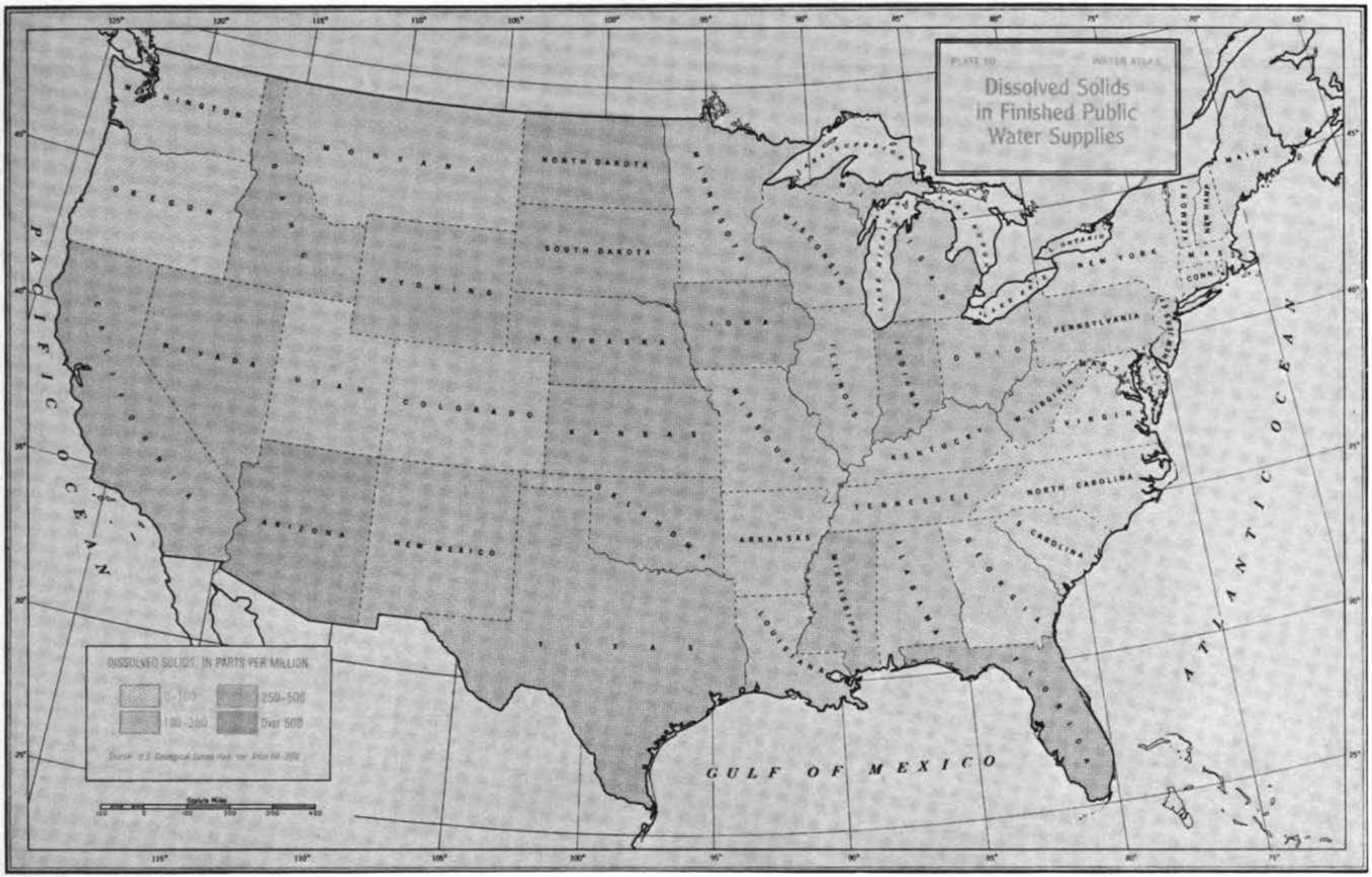


**FIGURE 14** Dissolved solids in finished public water supplies (Geraghty *et al.*, 1973).
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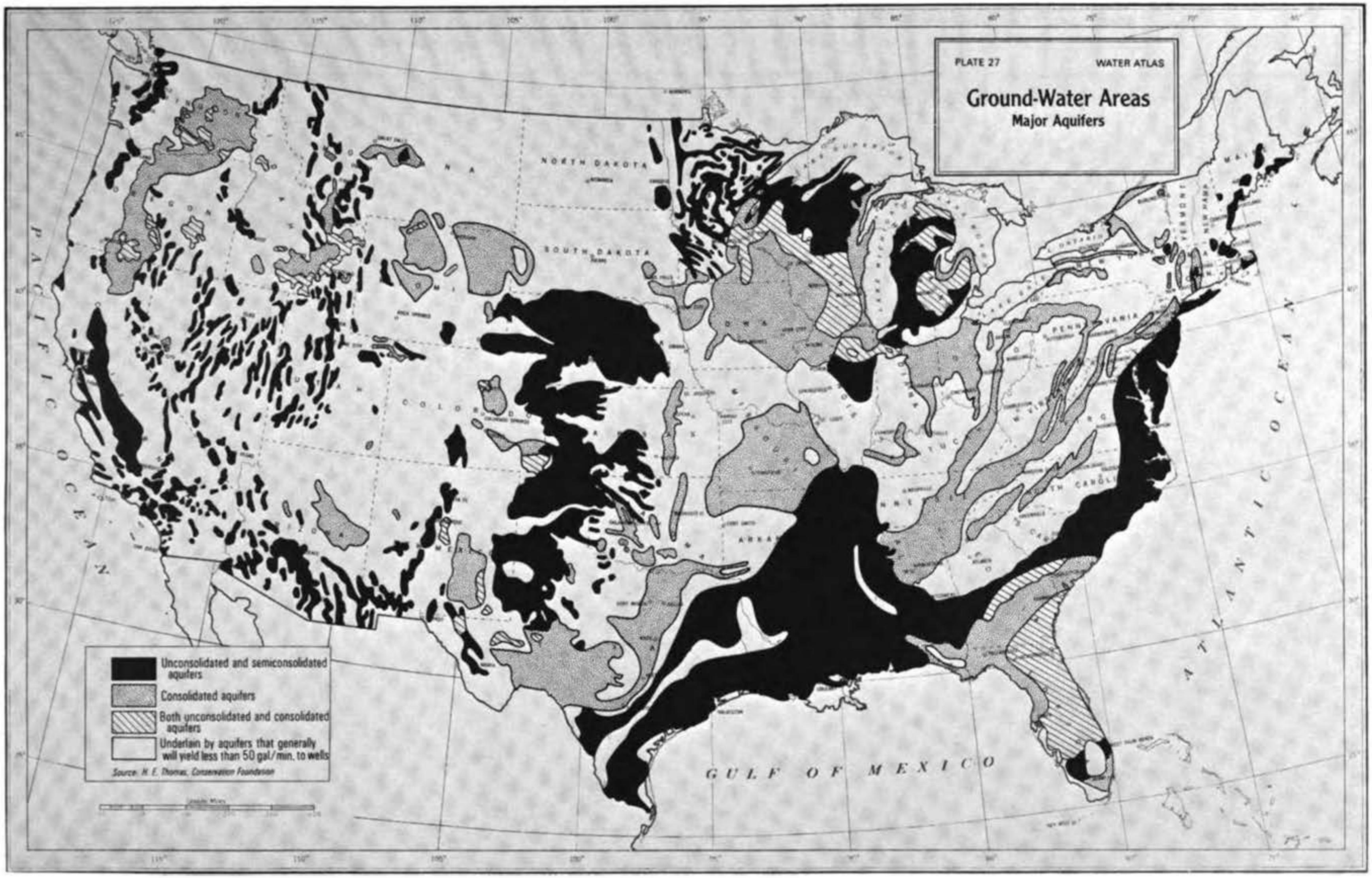


**FIGURE 15** Groundwater areas—major aquifers (Geraghty *et al.*, 1973).
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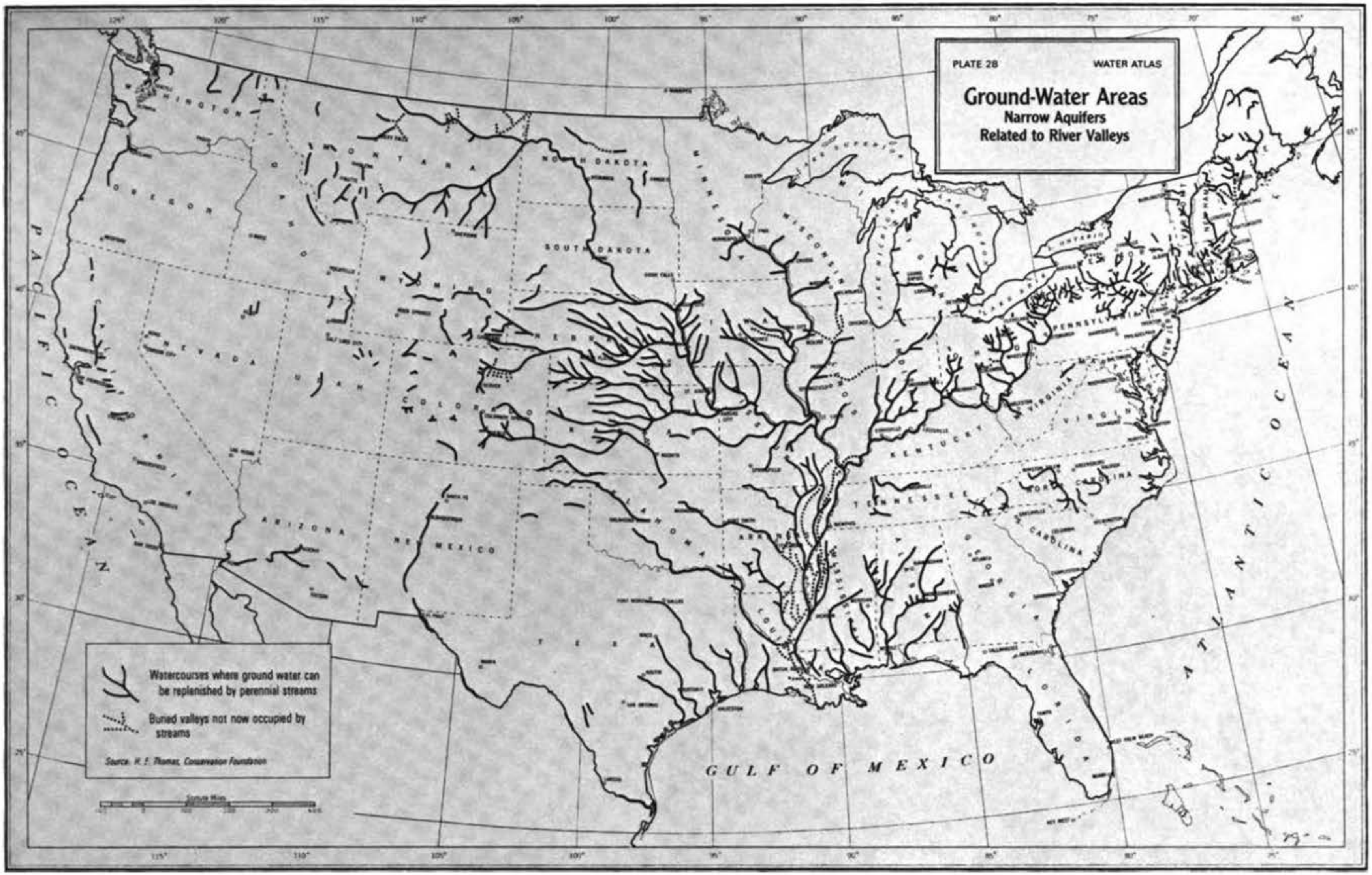


**FIGURE 16** Groundwater areas—narrow aquifers related to river valleys (Geraghty *et al.*, 1973). Reproduced with permission from ***Water Atlas of the United States***, Water Information Center, Inc., Huntington, New York.

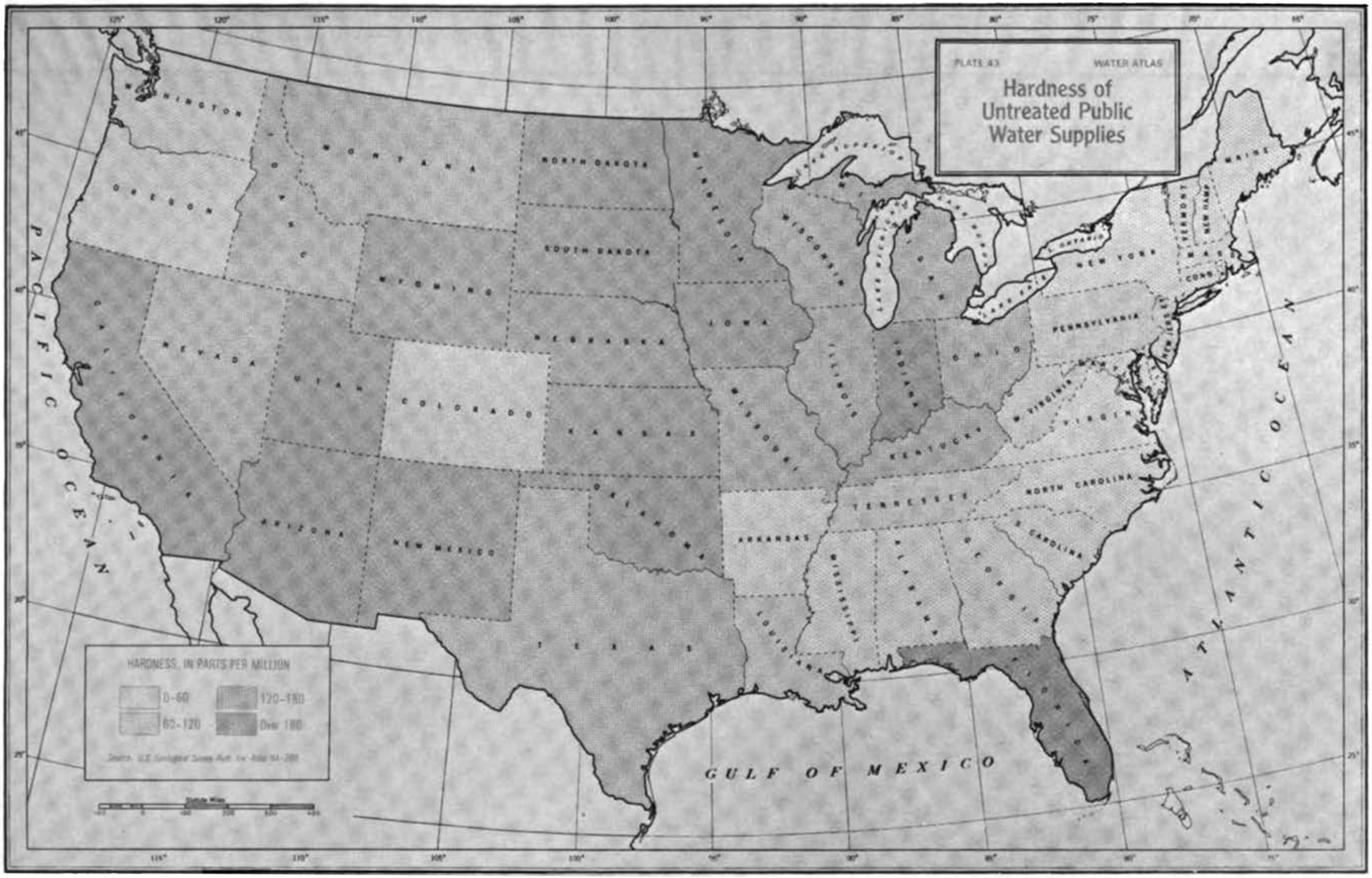


**FIGURE 17** Hardness of untreated public water supplies (Geraghty *et al.*, 1973).
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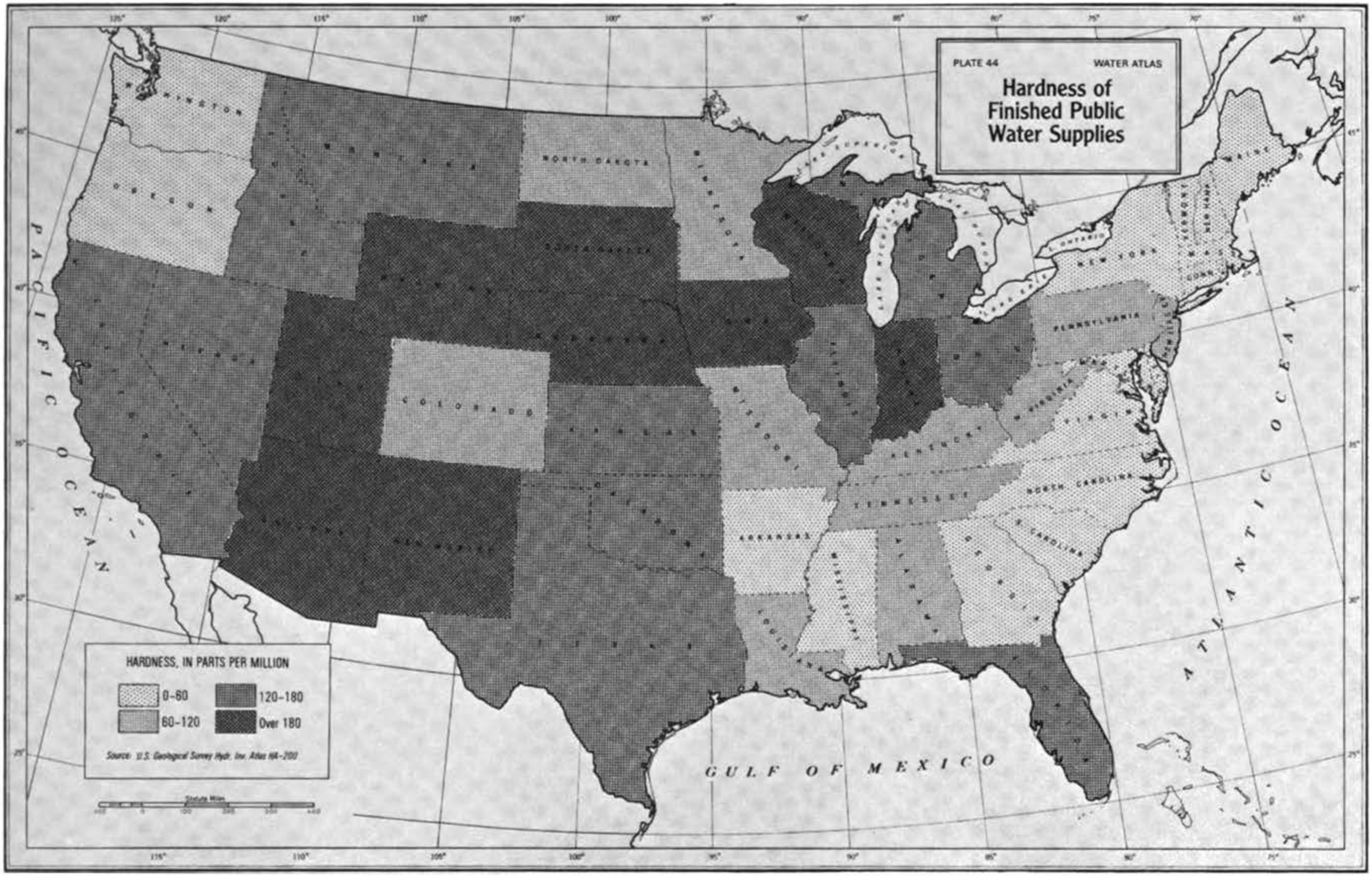


FIGURE 18 Hardness of finished public water supplies (Geraghty *et al.*, 1973).
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within a smaller range than does the quality of surface water.

- More data are needed on the concentration of those waterborne trace metals that may be associated with specific diseases. These data should be based on the chemistry of the water at the tap.
- There should be a concomitant development of uniform standards for collecting, storing, and analyzing water collected at the tap. It is absolutely necessary that the many disciplines involved in research on water quality use compatible techniques to permit valid comparisons.
- Initially, a data-source information system should be developed so that epidemiologists may select prime study areas. Ultimately, however, a completely compatible information storage and retrieval system should be established to allow researchers of various disciplines to retrieve data and maps quickly. For information to be truly effective, it must be current, multidisciplinary, and available on a demand basis.
- There is a need to develop a data base and analytical procedures on the chemical form of the metals associated with disease. In particular, it is necessary to know what anions are associated with the metals in high- and low-risk areas and whether organometallics are a major problem. Singer (1973), has reported clear evidence that organic compounds materially increase the mobility of metals in an aqueous environment. Perhaps the same phenomenon also makes these metals more available to biological systems.
- More chemical data are needed to characterize the surface-water and groundwater supplies that are used in the United States, particularly for areas with very high and very low incidences of disease.
- Long-term multidisciplinary studies should be made of the relation between the geochemical environment and disease, particularly in areas where the existing data base is reliable. The studies should receive stable funding of sufficient duration so that complete data collection and analysis can be made without the constant stress of fund seeking.

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# IV

# *Soils: Their Distribution, Uses, and Trace-Element Concentration*

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## GENERAL CONSIDERATIONS

Consistent with the objective of the Workshop, the Work Group on Soils assessed basic soil maps, interpretative soil maps, and maps of trace elements in soils for their usefulness in evaluating the geographic incidence of human diseases. How soils are used in the production of food for humans was also considered because of their effect on the movement of trace elements in a food chain.

## BASIC SOIL MAPS

Soil maps depict the geographic distribution of soils as a collection of natural bodies on the earth's surface. In places these bodies, which are modified or even made by man, consist of earthy materials containing living matter that is supporting or capable of supporting plants (Soil Conservation Service, 1951, 1975). Through weathering, soils develop properties that reflect the integrated effects of climate and living matter acting on parent material as conditioned by relief. Regional patterns of soil distribution generally parallel regional changes in climate and vegetation. For example, soils in humid regions are acidic, whereas those of arid regions are mostly alkaline and often calcareous. Stable landscapes may have soils with properties acquired from an earlier environment that may be merged with those of the current environment. Locally, soils on recent geologic deposits may have many properties inherited from surficial materials, but under conditions of intense weathering, their rock origin may be completely obliterated as in many tropical soils.

Soil development may have a pronounced effect on the distribution and behavior of trace elements in soils. Although the distribution of trace elements in a relatively unweathered soil (Table 7) is essentially uniform with depth, marked changes may result under intense weathering, as in the sandy (Haplaquod) soil of New York (Table 8). The leaching of cobalt beyond rooting depth of common plants is a contributing factor in the production of low-cobalt forage plants grown on the sandy soil. Measurements of trace elements in surface horizons of relatively unweathered soils are good indicators of their amounts in the subsoil, but poor indicators in strongly weathered soils.

Soil morphology, together with physical and chemical properties, provides a basis for soil classification. Various categorical levels of generalizations—soil series, soil families, great groups, orders, and suborders—are recognized, as they are in the classification schemes of plants and animals. The most homogeneous soil unit is that of the soil series.

Soil mapping units are based on taxonomic soil classes. Field observations supported by laboratory investigations are used to define soils that soil scientists in the field can consistently recognize and map. Because mapping units are applied to landscapes, they include some geographically associated soils. On complex landscapes, where soils differ markedly within short distances, soil associations are shown to depict their intricate distribution pattern.

TABLE 7 Distribution of Selected Trace Elements in a Nevada Soil (Aquic Xerofluvent) Formed in Recent Alluvium[a]

| Soil Horizon[b] | Depth (inches) | pH | Organic Carbon (%) | Clay (%) | Trace Elements, Total Fe (%) | Co (ppm) | Se (ppm) |
|---|---|---|---|---|---|---|---|
| $A_p$ | 0–5 | 8.0 | 1.05 | 21.6 | — | 8.5 | 0.32 |
| $C_1$ | 5–14 | 7.8 | 0.70 | 21.7 | 2.90 | 10.6 | 0.32 |
| $C_2$ | 14–25 | 8.0 | 0.52 | 20.5 | 2.85 | 10.6 | 0.32 |
| $C_3$ | 25–31 | 8.0 | 0.45 | 18.6 | 2.80 | 10.4 | 0.28 |
| $C_4$ | 31–41 | 8.0 | 0.25 | 12.8 | 2.70 | 9.2 | 0.23 |

[a]Source: Kubota (1972).
[b]$A_p$ is surface horizon, plow layer; C is unconsolidated material.

In the United States, the distribution of different kinds of soil is mapped using a standard procedure outlined for soil surveys made under the National Cooperative Soil Survey. This is a cooperative program that involves the Soil Conservation Service, the U.S. Department of Agriculture, other federal agencies, state agricultural experiment stations, and many state and local government agencies. The distribution of the soil series is depicted in field mapping on aerial photographs with scales between 1:15,840 and 1:24,000. A process of soil correlation is used to recognize similar soils with the same series name, where they occur in adjoining counties and states.

Detailed maps of soil series are especially useful in recognizing trace-element-related nutritional problem areas for grazing animals. Wet swales and wet parts of narrow floodplains and alluvial fans associated with molybdenum-toxic areas for grazing animals can be depicted in upland areas, where well-drained soils are dominant (Kubota *et al.*, 1961, 1967). Similarly, soils with calcareous subsoils that enhance the uptake of selenium by plants through subsoil feeding can be distinguished from those with noncalcareous subsoils that produce forage plants with inadequate selenium to meet the dietary needs of browsing animals. The distribution of Aquods (wet sandy soils with an organic subsoil pan) associated with cobalt deficiency in animals can be distinguished from other geographically associated wet soils (Aquults) on the southeastern coastal plain. Broad distribution patterns of problem areas can be shown on generalized schematic maps.

TABLE 8 Distribution of Selected Trace Elements in a Highly Weathered, Sandy Soil (Aeric Haplaquod) of New York[a]

| Soil Horizon[b] | Depth (inches) | pH | Organic Carbon (%) | Clay (%) | Trace Elements, Total Fe (%) | Co (ppm) | Se (ppm) |
|---|---|---|---|---|---|---|---|
| $A_0$ | 4–0 | 4.1 | 13.1 | — | 0.46 | 1.1 | 0.22 |
| $A_2$ | 0–12 | 4.4 | 0.17 | 0.4 | 0.68 | 0.9 | <0.01 |
| $B_h$ | 12–14 | 4.3 | 1.13 | 2.8 | 1.31 | 1.8 | 0.13 |
| Birm | 14–18 | 5.2 | 1.33 | 1.2 | 1.83 | 2.3 | 0.13 |
| Bir | 18–24 | 5.8 | 0.22 | 1.2 | 1.63 | 4.0 | 0.09 |
| $B_3$ | 24–40 | 5.8 | 0.14 | 0.6 | 1.72 | 4.0 | 0.07 |
| $C_1$ | 40–58 | 5.6 | 0.08 | 0.7 | 0.91 | 2.8 | — |
| $C_2$ | 58–65 | 5.4 | 0.05 | 1.3 | 1.02 | 3.1 | 0.06 |

[a]Source: Kubota (1972).
[b]$A_0$ is surface horizon, undisturbed organic-rich surface; $A_2$ is surface horizon, of eluviation; $B_h$ is subsoil horizon of organic matter accumulation; Bir is subsoil horizon of iron accumulation (*m* designates indurated layer); $B_3$ is transitional horizon; and C is unconsolidated material.

Soil maps of states and multistate regions provide broad geographic coverage and may be more useful for some purposes than detailed maps prepared on a county-by-county basis. A broader geographic coverage sacrifices some detail because generalized taxonomic groupings of soils or associations of soils are us^d. State and regional maps are essentially compilations of information from detailed soil maps and other sources of information. Soil maps of New York (Cline, 1957), North Carolina (Lee, 1955), Minnesota (McMiller, 1954), and Maryland (Miller, 1967) illustrate the kind of state soil maps that are available. Regional maps are available for the North Central Region (University of Wisconsin, 1960), the western states (Washington State University, 1964), the southern states (Buol, 1973), and the New England states (Soil Conservation Service, undated).

A National Soil Map at a scale of 1:7,500,000 is presented in the National Atlas (U.S. Geological Survey, 1970), which shows the geographic distribution of soil suborders or their associations. A generalized version of the national map with legend is presented in Figure 19.

The current National Soil Map reflects our state of knowledge of soils in the United States. Although the focus of soil maps is not on trace elements, they are, however, especially useful for selecting soils for studies of trace-element behavior.

## INTERPRETATIVE SOIL MAPS

Interpretative maps, which depict the suitability and limitations of certain soils for specific purposes, are compiled by grouping together soils with similar features that affect their use: soils that have similar responses to management practices or soils that have certain limitations when used for specific purposes. For example, interpretative maps are available that show areas where detailed on-site investigations are needed to locate suitable soils for septic systems or sites for solid-waste disposal. The presence of a high water table or firm, slowly permeable subsoil is a common feature among soils that may be reflected on suc^h interpretative maps. Interpretative maps are compiled by counties, states, regions, or on a nationwide basis. Much of the information, including supporting laboratory data needed to construct such maps, is routinely collected when soil surveys are made.

Interpretative maps, such as Land Resource Regions and Major Land Resource Areas Map of the United States (Soil Conservation Service, 1963), are also available that show the uses made of soils for the production of food and feed crops consumed directly or indirectly by humans. Assessments of such maps provide insights into geographic sources and possible pathways of trace elements in a food chain. Major areas of food crops consumed directly by humans are distinguished from those having a soil–plant–animal pathway (areas of forage crop production), a distinction useful in evaluating possible associations of geochemical environment in relation to human health and disease.

The Land Resource Regions and Major Land Resource Areas Map, in particular, shows a strong interrelationship of land use with climate. Major production areas of food plants consumed directly by humans occur predominantly in regions where the climate is mild and the growing season is long. For example, an absence of killing frost, the development of irrigation systems, and adaptability of land to mechanization are features common to soils that are intensively cultivated. Good soil tilth (tilling or cultivation) over a wide range of moisture is also a feature common to soils in these major production areas. Physical limitations of soils, such as presence of hardpan and poor soil tilth, are major obstacles to growth of most human food plants. A summary of the interplay of soils and climate in the geographic distribution of agriculturally productive areas is presented in Table 9.

Sandy soils that are responsive to intensive soil- and crop-management practices are most used in growing vegetable crops. Areas of organic soils, where reclaimed by drainage, are also important vegetable production areas particularly in Florida and California. Sensitive vegetable crops exhibit a wide range of nutritional problems when grown on such soils, many of which are traceable to trace-element deficiencies. Trace-element problems associated with the use of these soils have been observed in California (Bradford *et al.*, 1967); New Jersey (Prince, 1957); and Florida (Peech and Young, 1948; Gammon *et al.*, 1953). Use of trace-element fertilizers and sprays is a common crop-management practice on these kinds of soil (see Figure 21 in Chapter V on plants). Trace elements applied to meet the nutritional requirements for plant growth may be reflected in the mineral composition of food crops.

Most of the fruit-production areas in this country also reflect a strong interplay of soils and favorable climate for plant growth. Common features of highly productive fruit-growing areas are good air drainage that minimizes frost damage and good soil drainage within rooting depth of fruit trees. Many fruit trees are sensitive to trace-element imbalances in soils, and trace-element fertilization is commonly practiced. Intensive management practices, including sprays to control insects and plant diseases, are also sources of trace elements in orchards.

Broad areas of inherently fertile soils of the Great Plains states are used in the production of such field crops as corn and soybeans. Although some of the products, after processing, are consumed directly by humans, most of these crops are fed to animals. Like corn and soybeans, most of the wheat is produced on inherently fertile soils. Inadequate soil moisture is the primary factor limiting wheat production.

Among the various kinds of crops, the widest range of soils is used to grow forage plants for animals. Improved varieties of grasses and legumes have extended the yield and range of forage-crop production. Where soil-related nutritional problems in farm animals occur, mineral supplements, including trace elements, are fed both to prevent and to correct their suffering from such deficiencies.

## TRACE-ELEMENT MAPS OF SOILS

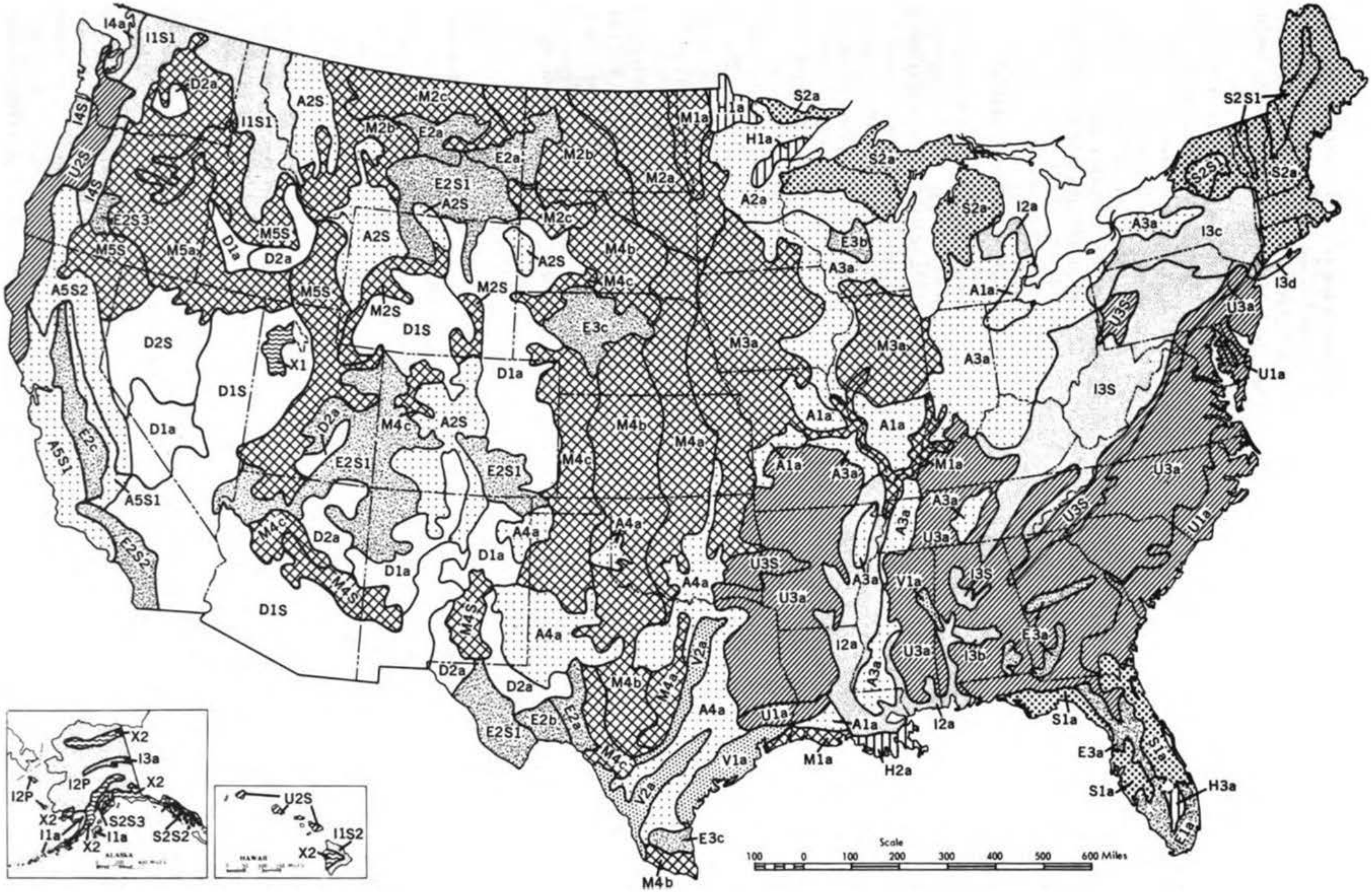
The third group of maps of importance to soils is essentially a summary of work by the U.S. Geological Survey (Shacklette *et al.*, 1971a, 1971b, 1973, 1974). Their results appear in a series of maps, each devoted to an individual mineral element. Concentrations in surficial materials are shown by symbols according to sampling locations in the United States. The lack of defined boundaries for the symbols leaves their placement open to interpretation.

The maps are based on 863 sample sites, at a sampling intensity of about one sample every 50 linear miles throughout the conterminous United States. The samples represent the collection by 25 individual geologists working with a common set of sampling directives. Samples were taken to a depth of approximately 8 inches.

The concentrations of the 35 elements listed below were determined on the samples from all 863 sites in a single laboratory under carefully controlled conditions. The elements determined were aluminum, arsenic, barium, beryllium, boron, calcium, cerium, chromium, cobalt, copper, fluorine, gallium, iron, lanthanum, lead, lithium, magnesium, manganese, mercury, molybdenum, neodymium, nickel, niobium, phosphorus, potassium, scandium, selenium, sodium, strontium, titanium, vanadium, ytterbium, yttrium, zinc, and zirconium.

The geometric means and concentration ranges for 26 of the less abundant elements reported by these and other authors are summarized in Table 10 and are in reasonable agreement with summaries of selected elements compiled at the Subcommittee's Asilomar Workshop in February 1972 (NRC Subcommittee on the Geochemical Environment in Relation to Health and Disease, 1974). An average of 280 ppm and a range of 10 to 1000 ppm of fluorine in soils were reported by the Work Group on Fluorine; an average of 40 ppm and a range of 10 to 150 ppm for chromium; and an average of 20 ppm and a range of 1 to 50 ppm for copper.

Maps showing ranges of trace-element concentrations by symbols and by location are also available for all or parts of Colorado, Maine, and Missouri in a series of open-file (unpublished, but available at cost) reports and in recently published reports of the U.S. Geological Survey (U.S. Geological Survey, 1972a, 1972b, 1972c, 1972d, 1972e, 1972f, 1973; Erdman *et al.*, 1976). Concentrations


I4a
I1S1
D2a
I4S
U2S
I1S1
A2S
M2c
M1a
H1a
S2a
M2b
E2a
E2a
M2b
H1a
S2a
S2S1
E2S1
M2a
A2a
S2a
I2a
S2S
S2a
I4S
E2S3
D1a
M5S
A2S
A2S
M2c
E3b
A3a
I3c
M5S
M5a
D2a
A2S
M4b
A3a
I3d
A5S2
M5S
M2S
M4c
A1a
M2S
D1S
E3c
U3S
U3a
D2S
X1
M3a
M3a
A3a
U1a
D1S
D1a
I3S
D1a
E2c
A5S1
D2a
M4c
A2S
M4b
A1a
A1a
E2S1
E2S1
M4c
M4a
A1a
A3a
M1a
U3a
A5S1
A3a
U3S
U1a
M4c
A4a
A4a
A3a
U3a
D2a
D1a
E2S2
M4S
D1a
A4a
U3S
A3a
V1a
I3S
D1S
M4S
U3a
A4a
V2a
E3a
I2a
U3a
I3b
A3a
D2a
D2a
M4b
M4a
A4a
E2S1
E2b
E2a
U1a
A1a
I2a
S1a
M4c
V1a
M1a
H2a
E3a
S1a
V2a
S1a
H3a
E3c
E1a
M4b
Scale
100
0
100
200
300
400
500
600 Miles
X2
I3a
I2P
X2
I2P
X2
S2S3
I1a
X2
I1a
S2S2
ALASKA
U2S
I1S2
X2
HAWAII

## LEGEND: KEY TO SOIL TYPES

### ALFISOLS

**AQUALFS**

A1a–Aqualfs with Udalfs, Haplaquepts, Udolls; gently sloping.

**BORALFS**

A2a–Boralfs with Udipsamments and Histosols; gently and moderately sloping.

A2S–Cryoboralfs with Borolls, Cryochrepts, Cryorthods, and rock outcrops; steep.

**UDALFS**

A3a–Udalfs with Aqualfs, Aquolls, Rendolls, Udolls, and Udults; gently or moderately sloping.

**USTALFS**

A4a–Ustalfs with Ustochrepts, Ustolls, Usterts, Ustipsamments, and Ustorthents; gently or moderately sloping.

**XERALFS**

A5S1–Xeralfs with Xerolls, Xerorthents, and Xererts; moderately sloping to steep.

A5S2–Ultic and lithic subgroups of Haploxeralfs with Andepts, Xerults, Xerolls, and Xerochrepts; steep.

### ARIDISOLS

**ARGIDS**

D1a–Argids with Orthids, Orthents, Psamments, and Ustolls; gently and moderately sloping.

D1S–Argids with Orthids, gently sloping; and Torriothents, gently sloping to steep.

**ORTHIDS**

D2a–Orthids with Argids, Orthents, and Xerolls; gently or moderately sloping.

D2S–Orthids, gently sloping to steep, with Argids, gently sloping; lithic subgroups of Torriorthents and Xerorthents, both steep.

### ENTISOLS

**AQUENTS**

E1a–Aquents with Quartzipsamments, Aquepts, Aquolls, and Aquods; gently sloping.

**ORTHENTS**

E2a–Torriorthents, steep, with borollic subgroups of Aridisols; Usterts and aridic and vertic subgroups of Borolls; gently or moderately sloping.

E2b–Torriorthents with Torrerts; gently or moderately sloping.

E2c–Xerorthents with Xeralfs, Orthids, and Argids; gently sloping.

E2S1–Torriorthents; steep, and Argids, Torrifluvents, Ustolls, and Borolls; gently sloping.

E2S2–Xerorthents with Xeralfs and Xerolls; steep.

E2S3–Cryorthents with Cryosamments and Cryandepts; gently sloping to steep.

**PSAMMENTS**

E3a–Quartzipsamments with Aquults and Udults; gently or moderately sloping.

E3b–Udipsamments with Aquolls and Udalfs; gently or moderately sloping.

E3c–Ustipsamments with Ustalfs and Aquolls; gently or moderately sloping.

### HISTOSOLS

**HISTOSOLS**

H1a–Hemists with Psammaquents and Udipsamments; gently sloping.

H2a–Hemists and Saprists with Fluvaquents and Haplaquepts; gently sloping.

H3a–Fibrists, Hemists, and Saprists with Psammaquents; gently sloping.

### INCEPTISOLS

**ANDEPTS**

I1a–Cryandepts with Cryaquepts, Histosols, and rock land; gently or moderately sloping.

I1S1–Cryandepts with Cryochrepts, Cryumbrepts, and Cryothods; steep.

I1S2–Andepts with Tropepts, Ustolls, and Tropofolists; moderately sloping to steep.

**AQUEPTS**

I2a–Haplaquepts with Aqualfs, Aquolls, Udalfs, and Fluvaquents; gently sloping.

I2P–Cryaquepts with cryic great groups of Orthents, Histosols, and Ochrepts; gently sloping to steep.

**OCHREPTS**

I3a–Cryochrepts with cryic great groups of Aquepts, Histosols, and Orthods; gently or moderately sloping.

I3b–Eutochrepts with Uderts; gently sloping.

I3c–Fragiochrepts with Fragioquepts, gently or moderately sloping; and Dystrochrepts, steep.

I3d–Dystrochrepts with Udipsamments and Haplorthods; gently sloping.

I3S–Dystrochrepts, steep, with Udalfs and Udults; gently or moderately sloping.

**UMBREPTS**

I4a–Haplumbrepts with Aquepts and Orthods; gently or moderately sloping.

I4S–Haplumbrepts and Orthods; steep, with Xerolls and Andepts; gently sloping.

### MOLLISOLS

**AQUOLLS**

M1a–Aquolls with Udalfs, Fluvents, Udipsamments, Ustipsamments, Aquepts, Eutrochrepts, and Borolls; gently sloping.

**BOROLLS**

M2a–Udic subgroups of Borolls with Aquolls and Ustorthents; gently sloping.

M2b–Typic subgroups of Borolls with Ustipsamments, Ustorthents, and Boralfs; gently sloping.

M2c–Aridic subgroups of Borolls with Borollic subgroups of Argids and Orthids, and Torriorthents; gently sloping.

M2S–Borolls with Boralfs, Argids, Torriorthents, and Ustolls; moderately sloping or steep.

**UDOLLS**

M3a–Udolls, with Aquolls, Udalfs, Aqualfs, Fluvents, Psamments, Ustorthents, Aquepts, and Albolls; gently or moderately sloping.

**USTOLLS**

M4a—Udic subgroups of Ustolls with Orthents, Ustochrepts, Usterts, Aquents, Fluvents, and Udolls; gently or moderately sloping.

M4b—Typic subgroups of Ustolls with Ustalfs, Ustipsamments, Ustorthents, Ustochrepts, Aquolls, and Usterts; gently or moderately sloping

M4c–Aridic subgroups of Ustolls with Ustalfs, Orthids, Ustipsamments, Ustorthents, Ustochrepts, Torriorthents, Borolls, Ustolls, and Usterts, gently or moderately sloping.

M4S–Ustolls with Argids and Torriorthents; moderately sloping or steep.

**XEROLLS**

M5a–Xerolls with Argids, Orthids, Fluvents, Cryoboralfs, Cryoborolls, and Xerorthents; gently or moderately sloping.

M5S–Xerolls with Cryoboralfs, Xeralfs, Xerorthents, and Xererts; moderately sloping or steep.

### SPODOSOLS

**AQUODS**

S1a–Aquods with Psammaquents, Aquolls, Humods, and Aquults; gently sloping.

**ORTHODS**

S2a–Orthods with Boralfs, Aquents, Orthents, Psamments, Histosols, Aquepts, Fragiochrepts, and Dystrochrepts; gently or moderately sloping.

S2S1–Orthods with Histosols, Aquents, and Aquepts; moderately sloping or steep.

S2S2–Cryorthods with Histosols; moderately sloping or steep.

S2S3–Cryorthods with Histosols, Andepts and Aquepts; gently sloping to steep.

### ULTISOLS

**AQUULTS**

U1a–Aquults with Aquents, Histosols, Quartzipsamments, and Udults; gently sloping.

**HUMULTS**

U2S–Humults with Andepts, Tropepts, Xerolls, Ustolls, Orthox, Torrox, and rock land; gently sloping to steep.

**UDULTS**

U3a–Udults with Udalfs, Fluvents, Aquents, Quartzipsamments, Aquepts, Dystrochrepts, and Aquults; gently or moderately sloping.

U3S–Udults with Dystrochrepts; moderately sloping or steep.

### VERTISOLS

**UDERTS**

V1a–Uderts with Aqualfs, Eutrochrepts, Aquolls, and Ustolls; gently sloping.

**USTERTS**

V2a–Usterts with Aqualfs, Orthids, Udifluvents, Aquolls, Ustolls, and Torrerts; gently sloping.

### Areas with little soil

X1–Salt flats.

X2–Rock land (plus permanent snow fields and glaciers).

### Slope classes

Gently sloping–Slopes mainly less than 10 percent, including nearly level.

Moderately sloping–Slopes mainly between 10 and 25 percent.

Steep–Slopes mainly steeper than 25 percent.

FIGURE 19 General soil map of the United States (Soil Conservation Service, 1975).

TABLE 9 Generalized Summary of Important Food and Feed Production Regions of the United States

| Crop | Climate | General Features of Soils | Essential Management Practices | Principal Areas |
|---|---|---|---|---|
| Vegetables | Seasonally mild | Nearly level to gently sloping land suited for land leveling, irrigation, and mechanization; mineral soils of sand to loam textures, peats and muck with good tilth over a wide range of soil moisture; responsive to fertilization and irrigation | Irrigation and fertilization, including trace elements on mineral soils | California, Gulf Coastal Plain, Florida, Atlantic Coastal Plain, including Long Island, New York |
| | | | Drainage, irrigation, and fertilization including trace elements on organic soils | California, Florida, Michigan, New York |
| Fruit crops | Generally mild winters | Nearly level to gently sloping bottomlands to footslopes of mountains; sands to loam soils with good subsoil drainage; areas with good air drainage | Irrigation, locally supplemental, and fertilization including trace elements | Southern United States, principally southern California, Gulf Coast, and Florida<br>Northern United States, north central lake states, Oregon, Washington |
| Feed grain (corn and soybean) mostly for livestock | Temperate with adequate rainfall during plant growing season | Inherently fertile, mostly loamy soils on level to gently undulating to rolling land suited for mechanized agriculture | Improved soil drainage locally | Great Plains states (corn belt) |
| Wheat and other small grains | Temperate; ranges to areas with marginal rainfall during plant growing season | Inherently fertile loam to clay soils on level to gently undulating to rolling land suited for mechanized agriculture | Summer fallow necessary locally where rainfall is marginal for production of crops | Central Belt: Texas, Oklahoma, Colorado, South Dakota, and North Dakota. Also, Palouse area in Washington and adjoining areas in Oregon |
| Forage plants, legumes, and grasses | Warm to cold | Slope limitations vary with intensity of forage-crop production, ranging from native-grass hay grown in wet meadows and hillsides to improved, intensively managed alfalfa fields, often irrigated. Nearly all kinds of soils used, some in permanent grasslands, others as part of crop rotation system | Variable, depending on region, soils, and periods when forage is needed | United States from California to Maine |

TABLE 10 Abundance in Soils of Some Trace Elements Commonly Present in Living Organisms, Listed in Order of Decreasing Abundance in the Continental Crust (All Values in Parts Per Million)

| Element | Continental Crustal Abundance[a] | Geometric Mean of Surface Soils of Conterminous United States[b] Western States | Eastern States | Range in Surface Soils[b] |
|---|---|---|---|---|
| F | 625 | 250 | 115 | <10–4000 |
| Ba | 425 | 560 | 300 | 15–5000 |
| Sr | 375 | 210 | 51 | <5–300 |
| S | 260 | [d] | [d] | 420–9600[c] |
| V | 135 | 66 | 46 | <7–500 |
| Cl | 130 | [d] | [d] | 20–900[c] |
| Cr | 100 | 38 | 36 | 1–1500 |
| Rb | 90 | [d] | [d] | 10–600[c] |
| Zn | 70 | 51 | 36 | <25–1700 |
| Cu | 55 | 21 | 14 | <1–300 |
| Co | 25 | 8 | 7 | <3–70 |
| Sc | 22 | 9 | 7 | <5–50 |
| Li | 20 | 23.3 | 17.3 | <5–120 |
| Ga | 15 | 18 | 10 | <5–70 |
| Pb | 12.5 | 18 | 14 | <10–700 |
| B | 10 | 22 | 32 | <20–300 |
| Be | 2.8 | 0.6 | 0.6 | <0.6–7 |
| U | 2.7 | [d] | [d] | 2.4–4[c] |
| Sn | 2 | [d] | [d] | 2–40[c] |
| As | 1.8 | 6.1 | 5.4 | <1–93 |
| Mo | 1.5 | <3 | <3 | <3–8 |
| I | 0.5 | [d] | [d] | 0.1–40[c] |
| Tl | 0.45 | [d] | [d] | [d] |
| Cd | 0.2 | [d] | [d] | <1–10 |
| Hg | 0.08 | 0.055 | 0.096 | <.01–5 |
| Se | 0.05 | 0.25 | 0.39 | <0.1–4 |

[a]Source: Taylor (1964).
[b]Source: Shacklette *et al.* (1971a, 1971b, 1973, 1974).
[c]Source: Vinogradov (1959).
[d]Not observed.

of 35 to 40 elements in over 1000 samples of Missouri soils selected by county are shown. As part of this study, soils of areas in fallow for about 30 years were compared with those of current agricultural areas. One open-file report (Chaffee *et al.*, 1972) presents concentrations of 55 elements for 6155 samples of stream sediments of southeastern Maine between latitudes 45° and 46° N. A report is also available on trace elements in surficial materials of the Front Range Urban Corridor between Fort Collins and Colorado Springs, Colorado (Tourtelot, 1973). The purpose of this study was to establish background levels of trace elements in surficial materials for evaluating changes with urbanization.

The trace-element maps of surficial materials in their present state have limitations when assessments are made for geographic associations with human health and disease. The significance of total soil concentrations, in the absence of corresponding concentrations in plants grown on the soils, is especially difficult to establish (see section on Soil–Plant Relations and Nutrient Supply in Chapter V on plants).

Plants, as bioassay tools, are effective for evaluating the availability of mineral elements in soils. We use cobalt to illustrate this point. A geometric mean of 7 ppm of cobalt is indicated for soils of the eastern United States (Table 10) and concentrations of 3 ppm are indicated for the Southeast (Figure 9, in Shacklette *et al.*, 1971b). Many soils of the Southeast and the Northeast have less than 3 ppm of cobalt (Table 11), and significant differences are evident in the cobalt concentration of forage plants grown on the soils. In the Southeast, soils with about 0.4 ppm of total cobalt or less are associated with the production of cobalt-deficient forage plants for animals, whereas in the Northeast, soils with 2 ppm or less are implicated (Kubota and Lazar, 1960). Many soils in the Southeast produce cobalt-sufficient forage plants, although they may have only about 2 ppm of total cobalt. They are strongly leached and acid, but they have a greater proportion of the cobalt present in reactive forms, as reflected by amounts extractable with dithionite and acetic acid (Kubota, 1965). A biopedologic cycling of soil cobalt appears to be a factor among soils that support growth of

TABLE 11 Comparison of Cobalt and Iron in Sandy Coastal Plain Soils of the Southeastern United States and Sandy Glacial Drift Soils of New England[a]

| Principal Kind of Soils | Characteristic of Soils | No. of Samples | Cobalt (ppm) | Iron (ppm) |
|---|---|---|---|---|
| *Sandy Coastal-Plain Deposits* | | | | |
| Haplaquods | Soils with distinct horizonation due to soil formation | 71 | 0.39 ± 0.04 | 0.15 ± 0.02 |
| Quartzipsamments | Soils without distinct effects of leaching | 34 | 1.71 ± 0.20 | 0.39 ± 0.06 |
| *Sandy Glacial-Drift Deposits* | | | | |
| Haplorthods | Soils with distinct horizonation due to soil formation | 24 | 2.13 ± 0.41 | 1.13 ± 0.21 |
| Udipsamments | Soils without distinct effects of leaching | 18 | 5.97 ± 0.47 | 1.75 ± 0.09 |

[a]Source: Data generalized from Kubota and Lazar (1960).

cobalt-sufficient plants for animals in the presence of relatively small amounts of total cobalt.

A further source of trace-element data, particularly for metals in soils, is the large number of geochemical surveys undertaken each year. Some of these are published, but many others are available, with some restrictions, from the files of mining companies. Such ripe possibilities for additional research data make eminently pursuable goals.

## GENERAL ASSESSMENT OF SOIL MAPS

The various kinds of soils maps have limitations when used individually to assess the role of soils on disease incidence. Pooling information from various map sources provides an insight into levels as well as probable trace-element behavior in soils and increases their usefulness. Total concentrations often strongly reflect amounts in solid-soil phases and consequently may be influenced by the nature of the soil's parent materials. Total amounts in soils, when tied to plant composition, are useful measures of the soil that supply power for various elements. Shallow-rooted plants often reflect total amounts in surface horizons, but deeply rooted plants may not.

Soluble forms of mineral elements are better indicators of reactive forms in soils than are total concentrations. Various chemical extractants are used to approximate forms and levels of nutrients available to plants. (In Chapter V on plants, see also sections on Soil–Plant Relations and Nutrient Supply and on Uptake of Heavy Metals by Plants.) Most extractants are directed toward problem soils and may not be universally applicable to a wide range of soils, e.g., calcareous to noncalcareous. Although soluble forms are available for uptake by plants, they also can be leached from soils. Leaching losses of soluble elements may sometimes result in mineral deficiencies of plants grown on soils that might otherwise be expected to have adequate amounts of the elements to meet plant-growth needs.

Interactions between soluble and solid phases affect the supply of biologically reactive forms of mineral elements in soils. The mechanisms of importance are organic complexes, surface sorption, ion exchange, oxidation–reduction, and pH. To facilitate their studies, mechanisms are usually studied as isolated systems, although they are complex, interrelated, and interdependent. Some systems are concentration dependent and specific for a mineral element.

While many cations have lower solubility with increasing pH, many anions (arsenic, selenium, molybdenum) increase in solubility with increasing soil pH. Mineral behavior in various soil systems differs so that specific elements or combinations of elements of importance to specific diseases need to be identified.

The usefulness of the trace-element maps for interpretative purposes would be increased if the maps were accompanied by expanded legends and text indicating kinds of soils sampled and studied. Identification of the soils provides access to voluminous information about the chemical behavior of mineral elements in soils in different regions and their uptake by plants.

Existing trace-element maps based on chance sampling may be adequate for some regions but totally inadequate for others. Summaries in charts and maps (U.S. Department of Agriculture, 1958) indicate that chance sampling (one sample in 50 miles) may be adequate in the Great Plains states, where 58 percent of the total land is used for crop production, but totally inadequate in the Rocky Mountain states, where only 8 percent of the land is under cultivation.

## RECOMMENDATIONS

Various kinds of soil maps may be useful in evaluating the role of soils in the incidence of the human diseases.

- An assessment of the role of soil in human health and disease may be greatly enhanced when evaluations are focused on specific elements or suites of elements. Deficiencies in existing information should serve as a stimulus for additional research.

• Greater use of the soil maps available in most countries should be made to evaluate disease incidence among people living in similar climates in different parts of the world, which will permit assessment of their different dietary habits.

• Soil surveys should be developed to help assess within-area differences in mortality rates. Their application may lead to the identification of important environmental factors, including soils that contribute to mortality rates. Current summaries by counties undoubtedly mask out important within-county differences in mortality rates that contribute to ill-defined patterns of disease incidence. Detailed soil surveys for high-incidence counties are available from local and state offices of the Soil Conservation Service, the State Agricultural Experiment Stations, and libraries of the land-grant colleges and universities.

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# V

# *Plants and Foods of Plant Origin*

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## THE ROLE OF PLANTS IN THE SOIL-NUTRITION COMPLEX

(Kenneth C. Beeson)

Plants have been used successfully as indicators of the occurrence of unusual concentrations of mineral elements in soils and in the underlying rock (Cannon, 1957, 1971; Brooks, 1972; Hawkes, 1957). Plants have also been used to establish direct connections between soils and mineral-element deficiencies or toxicities in grazing animals. Recently, broad regional relations between soils and the concentrations of selenium or cobalt in forage plants have been studied (Kubota *et al.*, 1967; Kubota, 1968), but the more complex relations between soils and man have been confined to specific crops in specific areas.

The relative importance of foods of plant origin compared with the other carriers of mineral elements to man is not completely known. Although it is generally agreed that water is an important source of some elements, e.g., iodine and fluorine, certain animal organs are considered to be better sources of iron, copper, and zinc for meeting man's needs than are plants. Limited data on heavy-metal uptake by plants have prevented an evaluation of the relative roles of airborne particulates, plants, and water as carriers of lead, mercury, and other toxic elements. In the final analysis, however, plants are recognized as a principal key to any consideration of carriers to man of significant quantities of most of the mineral elements.

Because of the complexities of plants, and their differences in uptake and translocation of mineral elements among the various species, few generalizations concerning the mineral components of a plant have been established, except to recognize their universal need for a select list of mineral elements known as plant nutrients.

The mineral composition of specific plants grown in a specific soil under normal seasonal and climatic conditions is the only precise measure of the quantity and nature of the mineral elements in that particular soil that will be transferable directly or indirectly to people in their food. Not even a primitive person is likely to obtain all of his or her food from one soil, and people in a developed country will, of necessity, consume food that is produced on many soils under different climates in widely different regions of the world. Nevertheless, many people may obtain a particular food from a limited number of locations where soil and climatic conditions are especially suited to a specific crop.

### *Soil Chemical Systems*

Soils comprise several dynamic systems in which numerous reactions occur simultaneously. The availability to plants of nutrients and other ions depends on their concentrations in the soil solution. This, in turn, depends on their presence in or on the exchange complex of the soil including decomposed organic sources. When the plant removes a nutrient from the soil solution, its concentration in the solution drops, but it is replaced by ions held on the exchange complex. Changes in this equilibrium trigger a change in the equilibrium between the crystalline forms of the element, that in the soil solution and that on the exchange complex. These interrelations are described diagrammatically in Figure 20 (Lindsay, 1972). Exchange complexes more significantly affect heavy metal behavior than such elements as selenium or molybdenum.

Lindsay (1972) points out that true equilibrium in soils probably never is obtained. Fortunately for plant growth, the environment of the soil is constantly changing as variations in climate, root growth, and soil microorganisms occur. Such changes assure a constantly renewed supply of nutrients for the plant. Clearly, the demands of an intensive agricultural program may not be met in all respects by these natural sources of the plant nutrients, and supplemental fertilizers will be necessary.

Hodgson (1963) has described the forms of the micronutrients in soils as follows: they may (a) be associated with soil surfaces, organic or inorganic; (b) be occluded during development of new solid phases in which they are principal constituents; (c) be precipitated with other soil components forming a new phase; (d) occupy sites in soil minerals either as an organic constituent or by entering the crystal lattice through solid-state diffusion; and (e) become incorporated in biological systems or their residues in the soil. The distinction between these forms is not always clear-cut. Sometimes the entrance of an ion into a structure or its adsorption on a surface is largely a matter of definition.

The ability of soil organic matter to form stable complexes with the metal ions and its important role in the availability of trace elements to higher plants have been well established. According to Stevenson and Ardekani (1972), these complexes may be divided into two main groups: (1) biochemicals of the type known to occur in living organisms and (2) a series of complex polymers formed by secondary synthesis reactions, bearing no resemblance to the natural products. Included in the first group are the organic acids, polyphenols, amino acids, peptides, proteins, and polysaccharides. The second group includes the humic and fulvic acids.

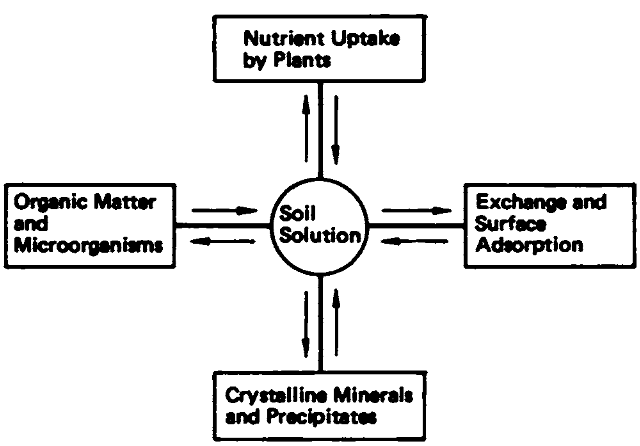


FIGURE 20 Diagrammatic representation of the dynamic equilibrium occurring in soils (Lindsay, 1972).

### *Soil–Plant Relations and Nutrient Supply*

Increased solubility and mobility of chelated metals have major effects on many aspects of the movement and availability of metal ions to plant roots (Brown, 1969; Lindsay and Norvell, 1969). Norvell (1972) warns that additions of chelates to soils for agronomic purposes, or those in effluents from waste-treatment systems, may greatly increase the hazards from heavy metal uptake by plants. Further research in this area is essential if the use of municipal wastes on arable soils is to be expanded.

The dynamics of trace-element movement in soils and its importance to the contact of those elements with the plant root has recently been discussed by Wilkinson (1972). He points out that the rates of nutrient absorption into plant roots in soils are governed both by the ionic environment at the root and the relation between the ionic environment and rate of absorption. Soil exploration by the root is, of course, an important adjunct to convection and diffusion of the mineral elements in the soil.

### *Uptake of Nutrients by Plants*

At least a portion of the total ion uptake by plants is under metabolic control, and it is highly selective. In a recent review of the subject, Moore (1972) pointed out that although evidence for the role of metabolism for the uptake of iron and manganese is fairly good, that for zinc and copper needs further investigation.

An important factor in ion uptake is, of course, the supply of the ion in the soil solution. Soil reaction has long been recognized as a factor. Except for iron and manganese in excessively acid and hence nonfertile soils, cation absorption reaches a maximum at pH 5 to 7, and it is reduced markedly at pH levels below 5. Effects of pH levels above 7 vary with different ions (Table 12). The chromium uptake in Table 13, for example, was greater at pH levels above 7, although little if any of the excess moved into the vegetative portion of the plant. Patterson (1971) found that less nickel is taken up by the plant at pH levels 5.5 and above compared with uptake under more acidic conditions (Table 14), and in this case most of the nickel is transported to the seed. More information is needed concerning the effect of soil reaction on others of the heavy metal group, such as mercury, lead, cadmium, and tin.

The interactions of the ions can have profound influences on their uptake and translocation in the plant. The early work of Somers and Shive (1942) on the iron–manganese interaction and of Parks and his co-workers (1944) on the effects of boron on ion uptake have been extended to include all the plant nutrients. Moore (1972), in his review, suggests that the wide variations encountered in iron concentrations are due to the sensitivity of iron absorption to the influence of other ions (Table 12).

TABLE 12 Interactions of Mineral Nutrients in Soils and in Plants[a]

| Element and Optimum pH Range | | Interactions at the Root Surface: Antagonistic Effects | Synergistic Effects |
|---|---|---|---|
| Ca | pH 6.5–8.5 | Mg, K, Toxic B[b] | B |
| Mg | pH 7.0–8.5 | Ca, Toxic B | B |
| P | pH 6.5–7.5 | | Mg |
| Cu | pH 5.0–7.0 | B, Zn, Mo | Toxic B |
| B | pH 5.0–7.0 | Ca, K | |
| Fe | pH 4.5–6.0 | Toxic B, Cu, Zn, Mo, Mn, Cd, Hg, Pb | B, Mo at high Fe levels |
| Mn | pH 5.0–6.5 | Fe, B | Toxic B |
| Mo | pH 6.0–8.0 | Cu, S | P |
| Zn | pH 5.0–7.0 | P, B, Fe, Cu | N, Toxic B |
| **Element** | | **Interactions within Plants** | |
| Fe | | Zn, Mo, P, Mn, S | |
| Mo | | S | P |
| Zn | | Fe, N (either a dilution effect or a translocation effect) | Fe, Mg |

[a]Source: Beeson *et al.* (1944), Parks *et al.* (1944); Olsen (1972).
[b]Toxic B is the minimum supply of boron in the nutrient medium that results in retarded yields.

Lee *et al.* (1969) reported, however, that although zinc appears to interfere with iron absorption, iron does not interfere with zinc uptake. Boawn *et al.* (1960) reported that high levels of nitrogenous fertilizers were related to lower pH levels in the soil and higher zinc uptake by plants. Boawn and Brown (1968) and Brown *et al.* (1970) reported that high levels of phosphorus induced a zinc deficiency in certain plants. The excellent review of this subject by Olsen (1972) and some very early reports are sources of the summary presented in Table 12. Boron, it will be noted, may have different effects on other element uptake depending on its physiological effects on the plant. Thus, a minimum concentration level that is toxic to plant growth may inhibit calcium uptake, whereas a nontoxic level will enhance calcium uptake. Likewise, the effect of molybdenum on iron uptake is somewhat dependent on iron concentration in the nutrient medium. At normal levels of iron, molybdenum may retard iron uptake, while at high levels of iron an opposite effect may be observed. Olsen states that the mechanisms of these interactions are not clearly understood. A few interactions within the plant are also summarized in Table 12.

*Soil–Weather Interaction and Its Effect on the Mineral Concentration in Plants*

Plant uptake of ions is also related to soil temperature and to the supply of oxygen, hence to climate (Richardson *et al.*, 1954). A comprehensive study of climate and its relation to the composition of vegetable crops was organized by workers in many fields of agriculture in the experiment stations of the Southeast and Puerto Rico.

During the first two years of this study, much effort went into the standardization of field and laboratory procedures and included studies of the diurnal variations in nutrient content of plants, losses of moisture at harvest, variations in composition from leaf to leaf and plant to plant, effects of washing leaves, and similar subjects (Peterson *et al.*, 1951).

The turnip leaf was used as the test vegetable, and spring and fall crops were grown in three plantings on two or more sites at each location for 4 years. Complete climate and soil records were kept during each growing season, and the turnip-leaf blades were analyzed for several vitamins and minerals, including calcium and iron (Speirs *et al.*, 1955). Some results are shown in Table 15 and briefly referred to here (Lucas, 1959).

*Phosphorus* Because acid soils are generally thought to depress phosphorus uptake, the negative phosphorus–pH correlation in this study suggests confounding factors.

TABLE 13 Effect of Soil pH on the Concentration of Chromium in the Barley Plant—Dry-Weight Basis[a]

| Soil pH | Chromium Added (ppm) | Leaves (ppm) | Roots (ppm) |
|---|---|---|---|
| 5.6 | 200A[b] | 2.1 | 46 |
| | 200D[c] | 2.2 | 137 |
| 6.4 | Control | 0.8 | 2.6 |
| | 200A | 2.7 | 78 |
| | 200D | 2.3 | 115 |
| 7.8 | Control | 0.5 | 1.9 |
| | 200A | 2.6 | 146 |
| | 200D | 3.2 | 168 |

[a]Source: Patterson (1971).
[b]A, chrome alum [$KCr(SO_4) \cdot 12H_2O$].
[c]D, potassium dichromate ($K_2Cr_2O_7$).

TABLE 14 Effect of Nickel Applied to Soils at Different pH Levels on the Concentration of Nickel in Wheat Plants—Dry-Weight Basis[a]

| Soil pH | Nickel Added to Soil (ppm): 0 | 5 | 10 | 20 | 40 | 80 |
|---|---|---|---|---|---|---|
| | Nickel in Dry Wheat Plants (ppm) | | | | | |
| 5.1 | 2.5 | 4.5 | 3.8 | 8.0[b] | 10.0[c] | 14.0[d] |
| 5.5 | 2.2 | 2.5 | 3.7 | 4.7 | 6.5 | 17.2 |
| 6.5 | 1.0 | 0.75 | 2.2 | 2.0 | 2.75 | 3.0 |
| 7.5 | 0.5 | 0.5 | 0.5 | 0.75 | 0.75 | 1.2 |

[a]Source: Patterson (1971).
[b]Slight toxicity.
[c]Moderately toxic.
[d]Toxic.

TABLE 15 Simple Product–Moment Correlations between Concentrations of Nutrient Elements in Turnip Greens and Various Soil Properties Using Crop Means (Only Values for Significant Correlations at the 5 Percent Level of Significance Are Given)[a]

| | Plant Measures | | | | | |
|---|---|---|---|---|---|---|
| Soil Measure | Phosphorus | Calcium | Potassium | Magnesium | Iron | Sodium |
| Organic matter | +[b] | −[c] | + | − | +0.48 | −0.34 |
| Cation-exchange capacity (C) | − | + | − | − | +0.27 | −0.52 |
| Anion-exchange capacity (A) | + | + | + | −0.25 | +0.56 | −0.43 |
| C/A | − | + | −0.32 | + | −0.32 | − |
| pH | −0.37 | −0.32 | − | − | 0[d] | −0.34 |
| $pH_e$ (Equilibrium pH) | + | − | + | −0.26 | +0.41 | + |
| Base saturation | − | +0.43 | − | − | − | −0.36 |
| Phosphate saturation | + | − | − | + | −0.59 | −0.34 |
| Base saturation × phosphorus saturation | − | +0.26 | − | + | −0.48 | + |
| pH/base saturation | + | −0.28 | + | + | + | +0.40 |
| Exchange phosphorus | + | − | +0.26 | + | − | + |
| Available phosphorus (Modified Truog)[e] | +0.43 | − | +0.26 | − | + | − |
| Exchange Ca | − | +0.39 | − | − | + | −0.42 |
| Exchange Mg | 0 | 0 | − | + | − | −0.28 |
| Exchange K | − | + | − | − | +0.27 | −0.42 |
| Exchange Na | 0 | − | − | − | +0.25 | −0.42 |

[a]Source: Lucas (1959).
[b]+, positive correlation.
[c]−, negative correlation.
[d]No effect either positive (+) or negative (−) was observed.
[e]This and other methods employed for soil measurements are described by Speirs *et al.* (1955).

*Calcium* Calcium uptake is increased in more basic soils with higher exchangeable calcium content. It seems likely that soils low in sand are conducive to higher calcium concentration in the plant, primarily because such soils can retain more calcium per unit volume than can those soils high in sand content.

*Magnesium* Magnesium uptake is conditioned, in part at least, by the amounts of other cations available and absorbed by the plant, particularly the amount of calcium.

*Iron* The mechanisms governing iron absorption by plants appear to be complex. Apparently, the greater the general exchange capacity of the soil, the more conducive are conditions to iron uptake. If, however, the exchange mechanism for anions is relatively saturated with phosphate ion, and if the ratio of cations to anions is high, iron uptake is depressed. Reducing conditions in the soil should presumably promote iron uptake.

*Weather Factors* Because of both the quantity and variety of weather measures, it was also possible to recognize some relations between weather and composition, as follows:

High solar radiation—low iron;
High soil temperature—high mineral content;
High water-vapor pressure and temperature—high phosphorus;
High relative humidity—low magnesium, calcium, potassium, and sodium;
High humidity and high rainfall—uptake of minerals tends to lag;
Dry soils—high phosphorus and potassium; low calcium, magnesium, iron, and sodium;
Advancing age—low sodium; the concentration of phosphorus, calcium, potassium, magnesium, and iron decreased at a decreasing rate.

The overall effects of both soil and climate on the concentration of iron in the turnip leaf are shown in Table 16. In general, there appears to be little difference between the concentrations of iron in spring and fall, but a possible difference is seen between plots in both Georgia and North Carolina. Crops grown on the Cecil soil in North Carolina and the Vega Alta soil in Puerto Rico have a significantly higher concentration of iron than do crops from other locations.

### *Normal Variations in the Concentrations of Trace Elements in Plants*

The concentration of nutrient elements in plant tissue has been used for the diagnosis of nutrient deficiencies for more than 100 years (Jones, 1972). Threshold concentrations have been established and are maintained by soil fertilization to prevent symptoms of deficiency and to assure maximum yields. Of concern here, however, is the normal variation in concentration of the nutrient elements in plants essential in human nutrition.

It has been assumed, for example, that concentrations of certain nutrient elements in foods of plant origin grown

TABLE 16 Summary of Data for Iron Concentration in Turnip Leaves Sampled at Different Sites (Moisture-free Basis)[a]

| Station | Soil Series | Parent Material | Spring Mean ± SD[b] (ppm) | Fall Mean ± SD (ppm) |
|---|---|---|---|---|
| Georgia | Lloyd | Mixed acid and basic igneous rock | 380 ± 145 | 375 ± 80 |
| | Appling | Granite, gneiss | 210 ± 60 | 230 ± 47 |
| Texas | Lufkin | Coastal sediments | 220 ± 79 | 195 ± 56 |
| | Norwood | Calcareous alluvium | 285 ± 145 | 370 ± 185 |
| Puerto Rico | Vega Alta | Shale, limestone | 510 ± 173 | 505 ± 160 |
| North Carolina | Cecil | Gneiss, schist | 560 ± 138 | 435 ± 121 |
| | White Store | Triassic mudstone | 365 ± 119 | 345 ± 78 |

[a]Source: Speirs *et al.* (1955).
[b]Standard deviation.

on a soil containing a limited supply of that nutrient would be so low as to fail to supply a normal quantity for the human diet. If the element in question is required by the plant, the concentration of the element within the plant cannot fall below that level required for normal growth. The concentration may, in some instances, exceed the level required.

To illustrate this point, the idealized relationship between growth of a plant and the concentration in the plant tissue of a specific plant nutrient is illustrated in Figure 21. This idealized diagram assumes only one nutrient—the one under discussion—is limiting growth. It also assumes that the growth of the plant is normal, that is, there are no exterior symptoms of a physiological disorder even where yields are low.

Under these conditions, the addition of the limiting element to the soil medium may result both in an increase in uptake of the nutrient element and an increase in yield without a change in the concentration of the nutrient in the tissue of the plant (A to A′). This region may be classified as being deficient with respect to maximum yield, but it represents the minimum concentration of the nutrient in the plant that will support normal growth.

Again assuming no other limiting factor, a further addition of the nutrient to the soil medium could result in both an increase in yield and in the concentration in the plant tissue of the nutrient applied (A′ to B). This concentration range represents, then, the normal range of concentration of a nutrient element in a particular plant or in one of its parts where good agricultural practices prevail.

A larger addition of the nutrient to the soil medium may result in a higher concentration of the nutrient in the plant tissue without an increase in yield (B to C). One of the several factors that could be operating here is a limiting supply of some other nutrient required by the plant. A still larger application of the nutrient to the soil could result in a toxicity with retarded growth (C to D).

From this illustration, we may define the normal range of concentration of a nutrient element in a particular plant or its parts as being between that minimum concentration required to support a normal plant (A) and that minimum concentration that will not result in toxicity and retarded yield (C). However, under good agricultural practice where economical yields are sought, the upper limit of

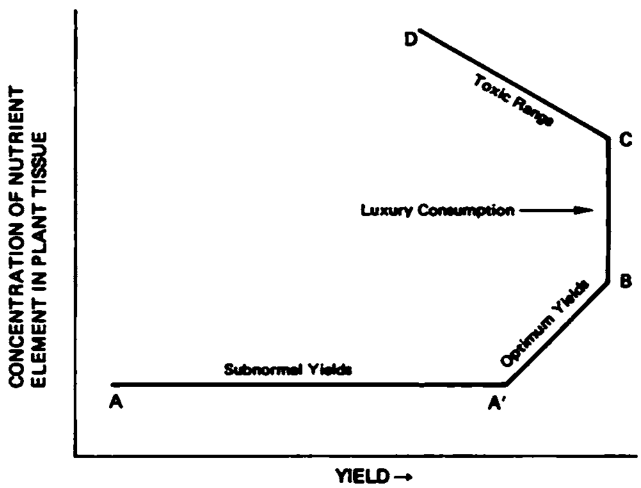


FIGURE 21 Diagrammatic representation of the effect of increments of fertilization to a soil on the concentration of a nutrient in the plant and the yield of the plant.

concentration will not exceed that required for maximum yields (B).

The normal range of concentration of nutrient elements in plants varies with the species of plant, the part of the plant, and the particular element under discussion. The concentration of copper in plants ranges within narrow limits, while that of zinc may be very wide depending on the supply in the soil. Elements such as selenium and iodine that are not required by the plant may vary from nearly zero concentration to high levels without disturbing the physiological functions of the plant.

Evidence of this relation is found in the following studies with trace elements. Schnappinger *et al.* (1972) determined the effect of doubling increments of zinc on the yield of corn (Table 17). The first increment of zinc resulted in an increase in yield of corn but no change in concentration of zinc in the plant tissue. The second and third increments resulted in both increases in yield and concentration of zinc. The fourth and fifth increments produced normal or maximum yields, although there is an indication of a probably nonsignificant toxic effect from the fifth increment as illustrated by line CD of Figure 21.

The data, shown in Table 18, were reported by Boawn and Rasmussen (1971) for several crops. Excessive uptake of zinc retarded yields of sweet corn and sorghum. Obviously, zinc is readily absorbed in quantities greater than the needs of the plants.

The effect of applications of arsenic to a soil on the concentration of arsenic in the tissue of potatoes and snap beans is shown in Table 19 (Jacobs *et al.*, 1970). Because arsenic is not an essential nutrient for plants, it had no positive effect on yields, but only a toxic effect. The data indicate that if a concentration of 0.5 ppm arsenic occurs in snap beans, or 0.3 ppm in the potato tuber, yields are retarded. The authors do not indicate that these levels of arsenic are toxic to man, but as such levels are not tolerated by the plant, it is not likely that higher levels will be found in these species because of the yield effects.

The concentration of any nutrient element will lie within a certain normal range corresponding to a normal growth for each plant species. Above and below that concentration range, yields will be below normal because of a deficiency or a toxicity, respectively, of the nutrient element. This concentration range will be relatively narrow. L. C. Boawn (USDA, Prosser, Washington, personal communication, September 1974) states that a zinc level of 15 ppm is the approximate threshold of adequate zinc in the vegetative portion of most plants. Jones (1972) considers a minimum of 25 ppm as sufficient for most plants. Data in this area are exceedingly difficult to find, and Boawn states, "The tissues taken for analysis are rarely the same as those consumed directly by man as food." However, it may be surmised without fear of contradiction that any plant, normal in growth and appearance, will provide in its tissue at least a normal concentration of the nutrient elements needed for normal growth and to prevent symptoms of nutrient deviations. More knowledge is required concerning effects in man, however, of both the

TABLE 17 Effect of Rate of Zinc Application as Broadcast Zinc Sulfate on Zinc Concentration and Yield of Corn Grown on Westmoreland Silty Clay Loam[a]

| Treatment Zinc (kg/ha) | Concentration of Zinc (ppm) | Yield (kg/ha) |
|---|---|---|
| 0.0 | 11.4 | 6540[b] |
| 3.4 | 11.8 | 8130[b] |
| 6.8 | 13.5 | 8308[b] |
| 13.6 | 17.4 | 8536[b] |
| 27.2 | 22.4 | 9799 |
| 54.4 | 24.5 | 9608 |

[a]Source: Schnappinger *et al.* (1972).
[b]Considered to be deficient.

TABLE 18 Growth Responses and Zinc Concentrations in Crops Grown with Excessive Rates of Zinc Fertilization[a]

| Crop | Zinc Added (ppm) 10 | 100 | 200 |
|---|---|---|---|
| Sweet corn | | | |
| Zinc in tops (ppm) | 41 | 255 | 367 |
| Yield decrease (%) | 0 | 8 | 12 |
| Sorghum | | | |
| Zinc in tops (ppm) | 34 | 380 | 506 |
| Yield decrease (%) | 0 | 10 | 30 |
| Wheat | | | |
| Zinc in tops (ppm) | 51 | 185 | 345 |
| Yield decrease (%) | 0 | 1 | 3 |
| Snap beans | | | |
| Zinc in tops (ppm) | 21 | 46 | 69 |
| Yield decrease (%) | 0 | 11 | 8 |
| Peas | | | |
| Zinc in tops (ppm) | 36 | 104 | 166 |
| Yield decrease (%) | 0 | 0 | 1 |
| Lettuce | | | |
| Zinc in tops (ppm) | 34 | 96 | 152 |
| Yield decrease (%) | 0 | 18 | 4 |

[a]Source: Boawn and Rasmussen (1971).

Table 19 Effect of Applied Arsenic on the Yield and Arsenic Concentration in Potatoes (Tubers) and Snap Beans (Pods and Seeds)[a]

| Arsenic Applied (kg/ha) | Tubers: Yield (kg/ha) | Tubers: Arsenic Concentration (ppm) Flesh | Tubers: Arsenic Concentration (ppm) Skin | Snap Beans: Yield (kg/ha) | Snap Beans: Arsenic Concentration (ppm) |
|---|---|---|---|---|---|
| 0 | 39,400 | ND[b] | 1.0 | 6100 | ND |
| 45 | 42,800 | 0.1 | 4.5 | 5420 | ND |
| 90 | 40,200 | 0.1 | 12.9 | 2780 | 0.5 |
| 180 | 31,000 | 0.3 | 27.3 | 1500 | 0.9 |
| 720 | 9,600 | 0.4 | 47.7 | None | — |

[a]Source: Jacobs *et al.* (1970).
[b]ND means no data.

normal concentration range of nutrient elements and the possible abnormal concentrations of other elements that do not interfere with the yield and marketable quality of the plant. In Table 20, there is presented a list of vegetables that are good sources of some mineral nutrients. This table was derived from many sources. A valuable contribution to nutrition of man would be the determination of the normal range of each of these elements in the foods listed.

### *Uptake of Heavy Metals by Plants*

Heavy-metal ions and other nonnutrient ions have received very little attention with respect to uptake and distribution in plants. Lisk (1972) has reviewed the chemistry of metals in soils and waters and has made some comments on their uptake by plants. He concludes that mercury does not appear to be concentrated to a greater extent in plants that usually contain less than 0.5 ppm in the fresh tissue. Plants tend to exclude lead, although this element has been found in tobacco. Significant concentrations of lead in the soil tend to be toxic to the plant. Cadmium in the soil also appears to be unavailable to plants. Arsenic appears to be readily taken up where it is present in soils (see Table 20). Levels of arsenic up to 30 ppm have been reported. Concentrations of chromium in plants seldom exceed 0.01 to 4.00 ppm in the dry tissue, and chromium may be retained largely in the roots of most plants.

TABLE 20 Important Vegetable Sources of Mineral Nutrients[a]

| Vegetable | Iron | Iodine | Copper | Zinc | Selenium | Calcium |
|---|---|---|---|---|---|---|
| Artichokes | | X | | | | |
| Asparagus | | X | | | | |
| Beans, lima | X | | | | | |
| Beans, snap | | | X | | | |
| Beet greens | X | | X | X | | X |
| Beet roots | | | X | | | |
| Broccoli | X | | | | X | X |
| Brussels sprouts | X | | | | | X |
| Cabbage | | | | | X | X |
| Carrots | | X | | X | | |
| Celery | | | | | X | |
| Chard | X | | X | | X | X |
| Collards | X | | | | | X |
| Cowpeas | X | | | | | |
| Cucumbers | | | | | X | |
| Dandelion greens | X | | | | | X |
| Kale | | | | | | X |
| Lettuce | X | X | X | X | | X |
| Mustard greens | X | | | | | X |
| Okra | | | | | X | |
| Onions | | | | | X | |
| Parsley | | | X | | | |
| Peas, green | X | | X | | X | |
| Pepper, green | | | | | X | |
| Potatoes | | | X | | | |
| Radish | | | X | X | X | |
| Soybeans | | X | | | | |
| Spinach | X | X | X | X | X | |
| Squash | X | | | | | |
| Sweet potatoes | X | | | | | |
| Turnip greens | X | X | | | | X |

[a]Source: K. C. Beeson.

### *Accumulator Plants*

An accumulator plant is one that takes up and stores unusual concentrations of a mineral element, generally an element not required for the nutrition of the plant. A well-known example is the accumulation of selenium by the *Astragalus* species (Anderson *et al.*, 1961). This matter was also discussed at the Asilomar Workshop (Beeson, 1974). Unfortunately, very few plants used for foods have been studied as possible accumulator plants. Notable exceptions are the tea plant, the Theaceae family, and the elderberry (*Sambucus*), which are accumulators of fluorine. Saunders (1957) has reported a number of other fluorine accumulators in South Africa, including peas, tomatoes, and lemons. Arnon (1938) reported that several varieties of coffee had been found to accumulate more than 40 ppm of rubidium. Cannon (1969) has summarized data on the concentration of zinc in vegetables from a high zinc peat in New York and reports a range of 24 to 1980 ppm of zinc in vegetables grown thereon.

Indications that lettuce, beet roots and tops, chard, and spinach might be classified as accumulators of zinc are present in the data of Warren *et al.* (1971). Lead and copper concentrations in the same vegetables were not abnormal. Hodgson *et al.* (1971) have also cited data indicating that spinach and lettuce take up larger quantities of zinc than do other vegetables.

### *Plants as a Criterion of Trace-Element Patterns in the Environment*

The use of food plants, or other plants, as a means of developing regional patterns of trace-element occurrence in the environment, offers certain advantages over direct analyses of rocks or soils. The plant is a principal source for man of the mineral elements, and because it discriminates in the kinds and quantities of these elements it takes up and supplies man, a study of plant composition can indicate the potentials of a particular geographical region as a source of a specific mineral element for man. This should be of importance to studies designed to relate the geochemical environment to health and disease, although the plant does not necessarily reflect the quantity nor proportion of the mineral elements prevailing in the soil and the rocks of the region. Several studies of the composition of crops or of other plants carried out over most of the United States have contributed to the development of techniques for this kind of an investigation.

The purposes and hence the designs of the studies differ, as do the conclusions reached.

*Occurrence of Mineral Deficiencies in Plants* Many plant species are precise indicators of soil aberrations with respect to available supplies of the mineral nutrients, especially the micronutrients and other trace elements, in the soil. Many criteria, including yield, visual symptoms, and chemical analyses of plant tissue, particularly those of the leaf, have contributed to systematic methods for recognizing or diagnosing a deficiency, a limited supply, or a toxic quantity of such minerals in the soil.

Geographical patterns of mineral deficiencies in plants based on published reports and personal experiences of many workers were first published by Beeson (1945). Data were plotted according to location within a county and in relation to soil associations.

The significance of such patterns of deficiency or toxicity to human nutritional problems is somewhat obscure. First, crops differ in their sensitivity to the supply of mineral elements—one crop may fail where others may grow normally. Second, as discussed in the section on Uptake of Nutrients by Plants, the concentration of the nutrient elements in the tissue of a plant does not necessarily represent the concentration of that element in the soil. Finally, where deficiencies of a nutrient element do exist in the soil, they are corrected with soil amendments to assure normal growth and yield of a crop. Hence, patterns of nutrient-element deficiencies in crops cannot be the sole criterion of a possible deficiency in food consumed by man.

*The National Corn Survey* In 1946, the Committee on Feed Composition of the National Research Council Agricultural Board was formed to compile complete and accurate tables of all feeding stuffs. At that time, the impact of hybrid corn varieties was not reflected in older tables of composition. Hence, surveys of the 1946 and 1947 crops were undertaken to establish more representative levels of nutrients in this important feed crop on a nationwide basis that would be representative of the crop as marketed and fed to animals (Schneider *et al.*, 1953).

Climate, plant species or variety, soil type, and management practices including fertilization were recognized as factors that might influence the nutrient composition of the crop. The nation was divided into ten regions on the basis of rainfall and temperature, in an attempt to ensure uniform growing conditions within each region.

The samples collected in a region or state were proportional to the total corn production of that region. Within a state, the counties were stratified according to their production; the number of strata was equal to the number of samples to be taken in the state, and the total production in all strata was equal. One county was selected at random from each stratum. There is no apparent year-to-year or regional difference in concentration of the micronutrients (copper, iron, cobalt, and manganese) indicating any important climatic or soil effect. The seed is not usually a good criterion, in this respect, of the effect of soil and climatic variables. The organization of the sampling procedure is, however, one that can serve as a model for other surveys.

*Nationwide Cobalt Survey* Kubota (1968) divided the United States into three main areas based on cobalt levels in legumes. Alfalfa, other legumes, or comparative vegetation were sampled from sites carefully selected to represent soils with properties likely to affect the plant cobalt concentrations. In the area classified as adequate with respect to cobalt, 90 percent or more of the legumes had 0.07 ppm or more of cobalt and a general level of 0.1 to 0.2 ppm. Only 20 percent of the samples from the low cobalt area contained 0.07 ppm or more of cobalt. In the intermediate range (0.09 ppm of cobalt, average), about 23 percent of the samples contained 0.07 ppm of cobalt or less.

*Selenium Surveys in Relation to Toxicities* Some of the most important early surveys of mineral aberrations in soils and plants are those of H. G. Byers, H. W. Lakin, and others, whose work to determine the extent of toxic quantities of selenium in forages and other plants, including wheat, has been reviewed by Anderson *et al.* (1961). Studies began in those areas where cattle were suffering from "alkali disease," but it was gradually expanded to investigate any areas where the existence of selenium-bearing formations was suspected. Indicator plants—indigenous plants that were selenium accumulators—were effectively used in this work.

*Survey of Selenium Deficiency in Forages* A study of selenium occurrence in the United States using alfalfa as the test plant has been made by Kubota *et al.* (1967). Alfalfa had proven to be a reliable indicator of available selenium in soils, and the variety and stage of maturity did not seriously limit interpretations. Comparative analyses of other forages growing in the same fields as alfalfa made it possible to use those forages where no alfalfa was present.

The data were first plotted on large-scale maps of the United States according to broad soil groups, physiographic regions, and soil parent material. On the basis of these tabulations, the most suitable delineations for a U.S. map appeared to be (1) areas where approximately 80 percent of the crops contained less than 0.05 ppm of selenium, (2) areas where the selenium content of the crops was variable with both low and adequate selenium levels fairly common, (3) areas where approximately 80 percent of the crops contained more than 0.10 ppm of selenium, and (4) local areas where crops contained more than 50 ppm of selenium (Figure 22).

Allaway (1972) has discussed the possible implications of these patterns concerning human health. Although there were interesting correlations of selenium in samples of human blood and the generalized selenium characteristics of a region, there were sufficient inconsistencies to raise some doubt concerning significant relations between them.

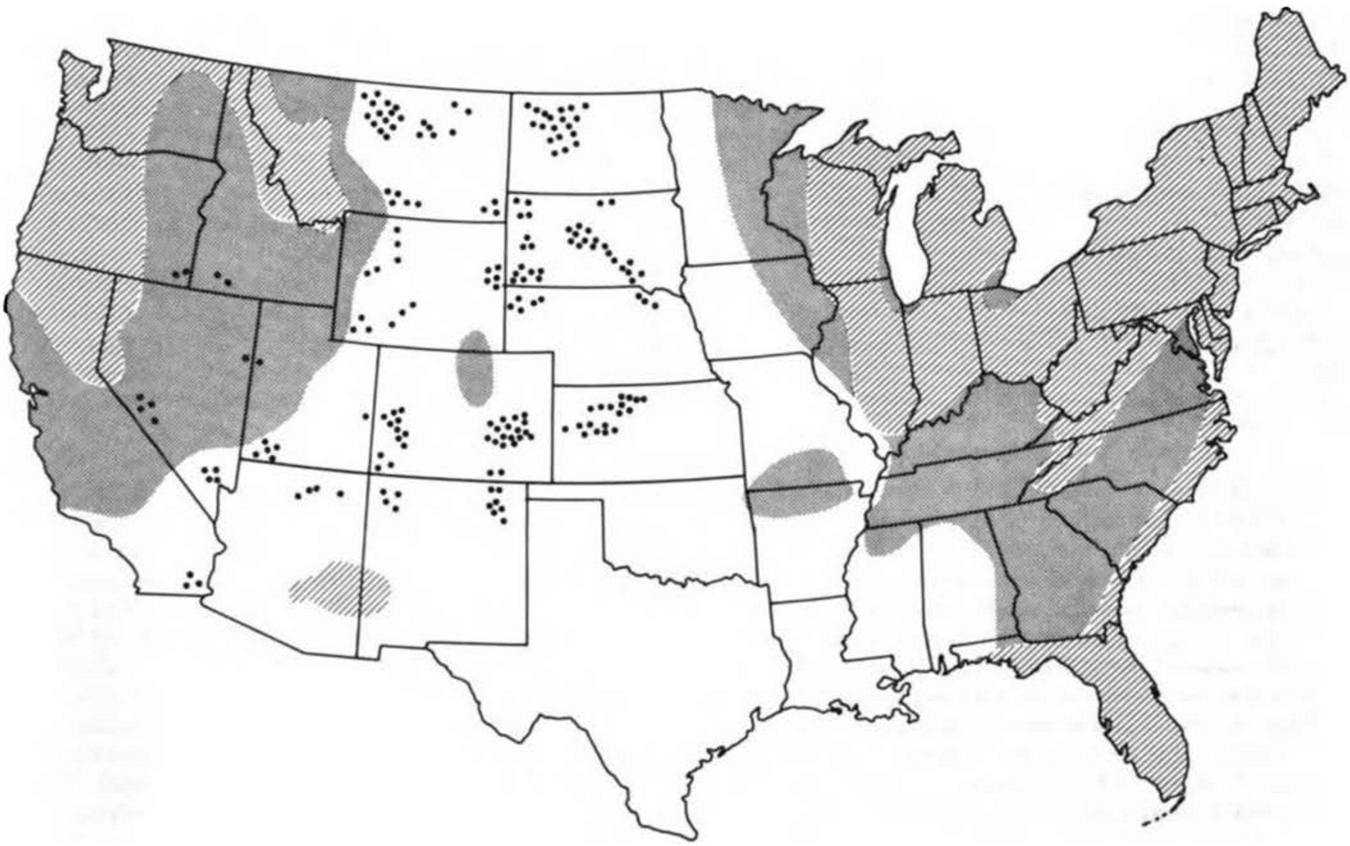


FIGURE 22 Map showing concentration of selenium in plants in the United States (Kubota and Allaway, 1972). Reproduced from *Micronutrients in Agriculture*, 1972, page 542, by permission of the Soil Science Society of America.

*Surveys of Diets* Recognizing that food as actually consumed, rather than the individual items comprising the diet, was a better criterion of mineral element intake by man, Murthy and co-workers (1971) analyzed institutional diets from 28 locations in the United States. Samples of the diets of children were supplied monthly by each institution. Each sample represented the edible portion of the diet for a full week (21 meals plus soft drinks, candy bars, or between-meal snacks) and drinking water. Analyses included antimony, cadmium, chromium, cobalt, manganese, and zinc.

A comparison of selected locations (where all differences except for zinc are significant at the 0.01 probability level) is shown in Table 21. To what degree the diets are comparable and represent in some manner the local geochemical environment is not clear. Because the sampling was done throughout the year, the diets in some locations must have been largely imported from the important vegetable- and fruit-growing areas. Nevertheless, in many areas there are differences of 50 percent or more in the intake of these elements.

The study does demonstrate how an assessment of the mineral-element intake can be made in areas where there are specific health problems.

### *Some Criteria for Relating the Geochemical Environment to Disease*

The following discussion is taken from a paper presented at the New York Academy of Sciences meeting on the Geochemical Environment in Relation to Health and Disease by Allaway (1972):

> We believe the following criteria can be useful in selecting and planning studies relating trace element concentrations in plants to human nutritional diseases in environments where industrial pollution is not a factor in plant composition:

TABLE 21 Mean Trace-Element Concentration in Diets (mg/day). All Differences Are Significant at the 0.01 Probability Level[a]

| Contrast by States | Antimony | Cadmium | Chromium | Cobalt | Manganese |
|---|---|---|---|---|---|
| Pennsylvania versus | 0.812 | 0.113 | 0.739 | 1.177 | 1.732 |
| Vermont | 0.528 | 0.079 | 0.529 | 0.758 | 1.240 |
| Arkansas and Louisiana versus | 0.726 | 0.087 | 0.559 | 0.982 | 1.339 |
| Mississippi | 0.977 | 0.126 | 0.893 | 1.253 | 3.558 |
| Nebraska, South Dakota, and Idaho versus | 0.761 | 0.105 | 0.720 | 1.116 | 1.566 |
| Colorado, Utah, and Nevada | 0.480 | 0.065 | 0.502 | 0.754 | 1.128 |
| South Dakota versus | 0.507 | 0.068 | 0.455 | 0.672 | 1.125 |
| Idaho | 0.892 | 0.116 | 0.824 | 1.329 | 1.899 |

[a]Source: Murthy *et al.* (1971).

1. ***The particular element or elements studied should have a more pronounced effect in animals, including man, than they do in plants*** [emphasis added]. In the case of an element required by man or animals, plants should be able to achieve near-optimum growth, even though the concentration of the element in plant tissues is too low to meet the dietary requirements of man and animals. Iodine and selenium can be cited as examples of elements meeting this requirement. Potassium can be used as an example of an element that clearly does not meet this requirement. Or, if the element is potentially toxic, plants should grow normally even though the concentration of the element in plant tissues is high enough to be damaging to man or animals. Selenium and molybdenum can be used as elements that meet this requirement . . . .

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3. ***The chemical combinations in which the element under investigation is found in plant tissue must be biologically effective in man*** [emphasis added]. Cobalt is an excellent example of this requirement. People require cobalt as part of the molecule of vitamin $B_{12}$. Since higher plants do not synthesize vitamin $B_{12}$, a search for a direct association between cobalt in plants and human health is thus doomed to fail . . . .

4. ***The people studied in attempts to associate human health to trace element concentrations in food plants should obviously obtain most of their food from a specific geochemical environment*** [emphasis added] . . . .

## BIOAVAILABILITY OF MINERAL ELEMENTS FROM PLANT SOURCES

(Kenneth C. Beeson)

Plants are the primary source of the mineral elements for the herbiverous animal and are a principal source of these nutrients for man. Plants that go directly into human consumption will reflect the impact of the geochemical environment on man much more than if it were to go to man indirectly via the meat animal. The latter is certainly an efficient buffer against deficiencies and excesses of many trace elements in the plant world. Because animal foods buffer the effects of possible toxic or deficient concentrations of trace elements in plants, diets rich in foods of vegetable origin and very limited in foods of animal origin will be likely to affect the trace-element nutrition of those consuming such diets. In general, it appears that trace elements are more available in foods of animal origin than they are from vegetables. This is particularly true of iron and zinc, for example (H. H. Sandstead, Human Nutrition Laboratory, ARS, USDA, Grand Forks, N.D., personal communication, 1977). If we investigate the means by which the environment can influence health and disease processes, foods of vegetable origin would have a stronger influence than those of animal origin. For this reason it is necessary to understand better than we do now the factors that determine availability of trace elements in plant sources to man. Mertz (1974), in a discussion of dietary allowances, states "the input of dietary planning and counseling would be greatly enhanced by a more complete knowledge of the biological availability of trace elements in individual foods."

Although plants are only a moderate source of iron, zinc, and chromium, they are an important source of magnesium, manganese, iodine, and silicon. In the latter case it is doubtful if animal sources would be sufficient to meet the requirements of man. It is apparent, moreover, that the absorption of the trace elements from a food—plant or animal—depends on their reactions and interactions with other constituents in that food and with other foods present at the intestinal or intraluminal level. The net effect of all these individual effects and interactions on a specific element is not clear. A summary of current knowledge concerning these interactions is included in Chapter VII on cardiovascular diseases.

Factors affecting the bioavailability of iron and other minerals are incompletely defined, and the following discussion provides illustrations of some of the factors that appear to be involved.

Those substances normally present in foods that limit or interfere with iron absorption were outlined by Van Campen (1970a). He pointed out that the availability to man of iron from plant sources varies from 1 to 10 percent of that present. Both antagonistic and synergistic effects of the components of food on iron are common. Thus, iron appears to be less available when the diet is low in protein. Short-chain carbohydrates appear to have little effect. In addition to phytates, a number of naturally occurring anions, including phosphate, bicarbonate, and oxalate, interfere with the absorption of iron. Among the mineral cations, calcium, copper, zinc, cadmium, and manganese depress iron uptake when fed at very high levels. Apparently, the levels indicated are well above those normally present in plant tissues.

Ranhotra *et al.* (1974) suggest that part of the uncertainty concerning the effect of phytates on iron is due to the mutual interrelationships between dietary iron and calcium, iron, and phosphates added to the diet. Working with rats, these investigators increased the level of phytate but maintained protein, calcium, iron, phosphate, and vitamin D levels intact, with no apparent change in the availability of iron naturally occurring in wheat. The availability of phytate phosphorus was also not affected appreciably.

About 2 percent of the iron in spinach is available to man according to Martinez-Torres and Layrisse (1973). Welch and Van Campen (1975) have reported that iron in immature soybeans is much less available than that in mature beans, although the mature seeds contained approximately three times as much phytic acid. Obviously, other nonnutritive substances may be acting here.

Other studies under way include the effects of low and high levels of endogenous phytic acid in pea seeds on the availability of zinc to rats. When rats were fed seeds at the same stage of development, the efficiency of zinc absorption by rats was not influenced significantly by the level of zinc in the seeds (Welch *et al.*, 1974). Although the absorption by the rat of zinc in mature seeds was significantly lower than that from immature seeds, both seed types appear to be good dietary sources of zinc. Most of the zinc in the seed was in the form of a soluble small anionic complex (<1000 mol wt) and did not appear to be present as a zinc–phytate complex. It was concluded that phytic acid in mature pea seeds was not solely responsible for the decreased availability to rats of zinc in seeds to zinc-depleted rats. Moreover, it was suggested that the nutritional value of legume seeds with respect to zinc content can be increased by applying zinc fertilizer possibly in excess of requirements for optimum plant yields.

The interaction of zinc, calcium, and phytate that results in a decrease in zinc availability was investigated by Byrd and Matrone (1965). They concluded that an increase in the amount of calcium in high-phytate diets, which aggravates a zinc deficiency, is due to a coprecipitation of zinc and calcium phytates. Zinc in the presence of calcium and phytic acid would therefore not be available for absorption, and zinc deficiency would result.

The absorption of copper from the gastrointestinal tract has been reviewed by Van Campen (1970b). Copper absorption is influenced by the level of copper in the diet and by high levels of certain other constituents of the diet including molybdenum, sulfur, calcium, iron, zinc, and cadmium. Neither mercury nor silver produced a significant reduction in copper absorption at the levels tested.

Only traces of chromium from plant sources appear to be available to the rat according to the findings of Huffman and Allaway (1973). Furthermore, the plant may restrict the movement of chromium from the soil to human and animal diets. Most of the chromium taken up from the soil may remain in the plant roots, and very little of that taken up is transmitted to the seed. Less than 0.5 percent of the chromium in the leaf was available to the rat. The balance was excreted with the feces within 48 hours.

A summary of the factors that affect bioavailability to man of chromium, manganese, iron, cobalt, copper, and zinc from plants has been compiled by O'Dell (1972). Extrinsic factors that affect the biological availability of trace elements are the following:

- Competitive antagonism among elements with similar properties.
- Physical characteristics (solubility and ionization) of inorganic compounds consumed or formed in the gut.
- Adsorption on surfaces of insoluble compounds in the gastrointestinal tract.
- Chelate and complex formation in the diet or gut: (a) absorbable material; (b) nonabsorbable material.
- Naturally occurring metallo-organic compounds of an essential or semi-essential nature.
- Oxidizing and reducing compounds in the diet.
- Compounds that prevent tissue uptake and utilization of elements.
- Microbial flora in the gut.

Several other reviews of the literature are available, including those of Gontzea and Sutzescu (1968), Ammerman and Miller (1972), Hoekstra *et al.* (1974), Quarterman (1973), and Underwood (1971). It is clear that there is much to be learned concerning not only the factors that affect bioavailability but also how plant composition can be modified to improve bioavailability. Little is known about several elements that occur in plants, including vanadium, nickel, tin, and others more recently identified as possible nutrients.

A word of caution has been sounded by Mertz (1972) in his discussion of human requirements for trace elements. He thinks that the present trend toward the use of isolated plant proteins at the expense of meat will have an impact at least as great as the trend in the past toward the substitution of refined carbohydrates for the less refined, natural sources. The consequences can well be a lowering of these important nutrients in the diet, unless such refined foods are enriched with available sources of the essential micronutrients.

The author wishes to acknowledge the extensive help and cooperation of Harold H. Sandstead, Walter Mertz, and Ross M. Welch.

## MINERAL CONTENT OF FOOD AS PRODUCED COMPARED WITH THAT OF FOOD AS CONSUMED

(Allan L. Forbes)

Numerous tables of food composition give the nutrients of the food as produced. However, not many foods are consumed as produced or grown. The effect of processing can be important, especially with respect to the mineral content. Minerals are often lost during processing. For example, removal of the bran and middlings from wheat results in a low mineral content of the resulting flour. On the other hand, minerals may be added during processing. An example of incidental addition may result from metals contributed by the grinding and other processing equipment. A more deliberate addition is seen when nutrients are added to the processed food, either to restore those lost during processing or to increase dietary intake of nutrients that are in short supply in our diet. Two examples selected for illustrative purposes are iron and iodine.

### *Iron Enrichment*

Iron enrichment, primarily of cereal-based foods, has been widely practiced in the United States, Canada, and elsewhere since the early days of World War II to prevent iron deficiency. Today, approximately three quarters of the cereal-based foods consumed in the United States are enriched. For example, enriched white bread provides between 8.0 and 12.5 mg of iron per pound. Cereal-based foods, in turn, provide about one quarter of the total calories consumed. This level of consumption has remained relatively constant for many decades, although the specific cereal-based food items may have changed, e.g., ready-to-eat breakfast cereals and pizza may have replaced porridge and bread. Although iron intakes from foods *per se* have also remained relatively constant, the total iron intakes may have decreased substantially because of the gradual abandonment of iron cooking vessels and plumbing and the extraordinary cleanliness of our marketplace food as compared with its condition in the past. Despite enrichment, very large proportions of the population still do not receive their daily recommended iron intakes. For example, approximately 45 percent of adolescent boys and girls in the general populations of Canada do not attain recommended levels. Furthermore, about 15 percent and 40 percent, respectively, have grossly inadequate intakes (Canada, 1972, 1973, 1975a, 1975b). If U.S. recommended allowances are used as the standard for comparison, the results would be even worse. The prevalence of actual anemia is much lower for the same groups, but other indicators of iron deficiency such as mean corpuscular hemoglobin concentrations and transferrin saturations—with or without anemia—show substantial numbers with abnormally low values. Obviously, mapping of iron-deficiency status would be useful, particularly for teaching purposes, but, to be truthful, for this particular problem, knowledge about the problem is reasonably good. The dilemma is the inadequacy of corrective programs.

The status of iron nutriture in the United States is similar to that observed in Canada (U.S. Department of Health, Education, and Welfare, 1974, 1977). As a result, the Food and Drug Administration is currently giving serious consideration to increasing the level of iron in enriched flour and bread by a factor of approximately 2½, e.g., enriched bread would provide 25 mg of iron per pound. This would represent the first significant change in enrichment practices for flour and bread since 1942. Reaching even the present point of consideration of this change in enrichment regulations has not been easy, primarily because of a very few, but very vocal, individuals who have based most of their arguments on the specter of precipitating iron-storage disorders in heavy consumers of cereal-based products. (Effective November 27, 1978, FDA withdrew its regulations to increase iron levels, based on the Commissioner's conclusion that there is insufficient evidence to establish safety and efficacy.)

Several other aspects of iron enrichment warrant mention. The first is toxicity. Like most trace minerals, iron has a relatively narrow margin of safety. An accidental intake of 500 mg, e.g., by ingestion of only 8 or 9 tablets of the usual variety used to treat iron-deficiency anemia, can kill a toddler of 2 or 3 years of age. There is, on the other hand, no evidence whatever to indicate that the maximum intakes that could conceivably be attained in the American diet, including judicious enrichment, would be anywhere near those intakes associated with iron-storage disorders. Even the clinical significance of most iron-storage disorders, for example the hemosiderosis observed among South African Bantu with daily iron intakes in excess of 100 mg per day, is doubtful. Our principal iron-storage disease—hemochromatosis—appears to be a genetic disorder, the pathogenesis of which is independent of the amount of iron in the diet and the treatment of which does not involve dietary iron restriction.

A second aspect of iron enrichment is the efficacy of added iron. When iron is solubilized in the digestive tract, it is believed to enter two pools: heme iron, from meat, for example, and nonheme iron. The heme iron is believed to be absorbed directly into the blood stream. Usually a much smaller percentage of the nonheme iron is absorbed. The recent use of a double-isotope technique by investigators such as Layrisse *et al.* (1973), in Caracas, Venezuela, and Cook *et al.* (1973) in Seattle has clearly demonstrated that, in man, added iron enters the nonheme iron pool, provided that the iron is soluble, i.e., the iron derived from plant foods, which in turn is uniformly absorbed to a specific degree, depending on the total composition of the meal being consumed. Generally, about 5 percent of the iron in the nonheme iron pool is absorbed, in contrast to about 20 percent of the heme iron pool. In addition, the presence of heme iron has a synergistic effect on absorption of the nonheme iron. The double-isotope technique of labeling the food as grown with one isotope and the added mineral nutrient with a second isotope has certainly clarified the issues surrounding the question of efficacy of enrichment iron—and the results have vindicated enrichment. Presumably, similar miscible pools of other mineral nutrients exist and could be demonstrated by the double-labeling technique. Of course, single-label techniques are in themselves useful for determining absorption of mineral nutrients endogenous to the plant food.

A third point for general information consists of a few comments on iron-enrichment sources. Ferrous sulfate is the standard source and is the principal one used in enriched American breads and many ready-to-eat cereals. Simple metallic iron, or "iron reductum," usually 300-mesh size, is the principal source in enriched flour. In Canada, most bread enrichment is achieved by enrichment of the flour with metallic iron. Most of finely powdered metallic iron used has biological availability of about half that of ferrous sulfate, but this can be improved by using finer particle sizes. Presumably the increased surface area of the particles results in increased solubility in the acid environment of the stomach. Sodium iron pyrophosphate and orthophosphates generally have much lower bioavailabilities, but fortunately their use is declining.

A brief look into the future produces a final point of information concerning iron. Presumably enrichment iron will steadily increase as a contributor to total iron intakes, particularly as economic forces decrease the contribution of heme iron from meats.

The Food and Drug Administration has proposed (not yet effective) a series of guidelines and standards for various classes of foodstuffs, which would provide a reasonable degree of uniformity of enrichment with iron and other nutrients. A final nutritional-quality guideline regulation already exists for frozen convenience dinners. The new proposals involving iron-fortification concern: (1) enriched farina, frequently used as a cereal; (2) plant-protein products, used as meat extenders and analogs; (3) fortified hot breakfast cereals; (4) fortified ready-to-eat breakfast cereals; (5) formulated meal replacements; and (6) main-dish products, such as chicken potpies, macaroni and cheese, and pizzas.

### *Iodine Enrichment*

Since David Marine demonstrated the efficacy of iodine in prevention of endemic goiter (Marine and Kimball, 1920) and iodized salt came into widespread use in the 1920's, iodine was simply forgotten until recently. In the ten-state Nutrition Survey (U.S. Department of Health, Education, and Welfare, 1972) and in several epidemiologic studies immediately thereafter, conducted under the stimulus of Trowbridge of the Center for Disease Control (CDC) (Trowbridge *et al.*, 1973), two findings came as a bit of a shock: (1) there is much goiter in specific regions, more or less coincident with the former endemic-goiter belts; and (2) much more iodine is found in the urine than one would have expected—of the order of 200–500 $\mu$g/g of creatinine—and with some degree of positive correlation with the prevalence of goiter. The nutrition survey in Canada showed much the same thing, i.e., (1) high prevalences of low-grade goiter in Manitoba, Saskatchewan, and Alberta, moderate prevalences in British Columbia and Newfoundland; and (2) higher than expected iodine excretions of the order of 200–300 $\mu$g/g of creatinine but without any obvious correlation with the goiter prevalence. Hence, there are two problems, both of which are worrisome: (1) frequent low-grade goiter of unknown etiology, apparently not due to iodine deficiency and (2) more iodine in the diet than we thought was there. Generally, one would not expect to see iodine-deficiency goiter unless the iodine excretion were less than 50 $\mu$g/g of creatinine. Individuals with such low excretions were scarcely seen at all in either the U.S. or the Canadian surveys.

Some light is beginning to be shed on the possible sources of the unexpected iodine in our diet, through the efforts of groups such as that of Mickelsen (1974) at Michigan State University and the Life Sciences Research Office of Federation for American Scientific and Experimental Biology (FASEB), who have recently completed reviews of what is known to date for the Food and Drug Administration. A key source appears to be iodophors used as cleansing agents throughout the milk industry. Concentrations as high as 2000 $\mu$g of $I_2$/liter of milk have been measured in Michigan and Maryland. A second source of iodine is created by the use of potassium iodate as a dough conditioner in the continuous process for making bread. A third source is Red #3, an iodine-containing dye commonly used in breakfast cereals, maraschino cherries, and coated tablets of various sorts. A fourth source is silver iodide, used in seeding rain clouds, particularly in the Southwest, for which many tons (megagrams) of iodine are sprayed in the atmosphere. A fifth source is increased consumption of kelp. A sixth source is the use of iodized brine in the preparation of frozen vegetables. In addition, one has the continued use of iodized salt in the household. It is not suggested that this extraneous iodine is harmful, but "extra" sources of nutrients, particularly minerals, can sneak into the food supply without our being aware that it is happening, and we should watch for these kinds of events with increasing care, for fear they may have some relation to disease.

In summary, many things can happen to a food from the time it is produced on the farm to the time it is actually consumed by man, and these events very much involve trace minerals.

## WHAT FOODS ARE EATEN, HOW OFTEN, BY WHOM?

(Frank W. Lowenstein)

The following is based on food frequency data from the first Health and Nutrition Examination Survey (HANES I) in the Division of Health Examination Statistics, National Center for Health Statistics, Hyattsville, Maryland (U.S. Department of Health, Education, and Welfare, 1977; Dresser and Lowenstein, 1977).

*Whole Milk and 2 Percent Butterfat Milk* As might be expected, the consumption of milk decreases with age; while 85 percent of young children drink milk one or more times a day, this percentage decreases to less than 50 percent in adults. Differences exist in consumption according to sex; adolescent girls consume less than boys in the same age groups. Adult women also drink milk less often than men, particularly women of child-bearing age; while 56 percent of white women, aged 18–44, drink milk less than once a day, this percentage is only 43 percent for white men of the same age; for black women and men in the same age group the corresponding percentages are 72 percent and 63 percent. Between 30 and 44 percent of all women rarely or never drink milk; this percentage is usually greater in black women.

*Meat and Poultry* There is a slight increase of consumption with age from young children to adolescents. The great majority in all age groups eat meat at least once a day or more. This majority, however, decreases in the older age groups. Differences according to sex are negligible in adolescents; in adults, men eat meat more often than women.

*Fish or Shellfish* Consumption of fish or shellfish is relatively low in all age groups. The percentage of people who rarely or never eat fish ranges from about 33 percent in black women aged 45–64 to 53 percent in white women 65+. A majority have fish between one and six times a week. Adult women aged 18–64 seem to eat fish somewhat more frequently than men. Blacks of all ages eat fish more frequently than whites with one exception—men aged 18–44 years.

*Eggs* Between 15 and 20 percent of teenage boys and girls rarely or never eat eggs. The majority in all age groups eat eggs between one and six times a week. Older men tend to eat eggs somewhat more frequently than women (almost 30 percent of men aged 60+ eat eggs once a day).

*Cheese* A fairly high percentage in all age groups (between 21 and 30.4 percent) rarely or never eat cheese. The majority in all ages use cheese one to six times a week. Older women consume cheese more often than older men. Blacks eat less cheese than whites.

*Dry Beans* Consumption of dry beans decreases markedly with age. In the 60+ age group, more than half of all women rarely or never eat beans. In the younger age groups the majority eat dry beans one to six times a week. Between 10 and 20 percent of children aged 1–17 eat beans once a day. Women and teenage girls consume dry beans less often than men and teenage boys.

*Fruits and Vegetables* The great majority in all age groups consume fruits and vegetables once a day or more. The percentage of people in all age groups who rarely or never eat fruits and vegetables is very small (highest in men aged 60+). Women and teenage girls tend to eat fruits and vegetables more often than men and teenage boys.

*Vitamin A-Rich Fruits and Vegetables* Yellow melons (cantaloupes) and carrots are very good sources of provitamin A among the fruits and vegetables, respectively. Between 21 and 42 percent rarely or never consume vitamin A-rich fruits and vegetables over all ages. A majority of people of all ages eat such foods between one and six times a week (55–72 percent). Older women tend to consume vitamin A-rich fruits and vegetables somewhat more often than do older men. Blacks regardless of age, sex, and income eat these foods more frequently than do whites. Age differences are negligible.

*Vitamin C-Rich Fruits and Vegetables* Citrus fruits and potatoes are good sources of vitamin C commonly used. The percentage of people who rarely or never eat vitamin C-rich fruits and vegetables is smaller than the percentage of people who seldom or never eat vitamin A-rich fruits and vegetables. Between 20 and 40 percent of people of all ages eat vitamin C-rich fruits and vegetables once a day; less than 10 percent eat them more than once daily. Adult women of all ages eat these foods more frequently than adult men. There is a tendency in both older men and women to consume vitamin C-rich fruits and vegetables more often than at younger ages.

*Bread* Bread is eaten more than once a day by the majority of people in all age groups (50–75 percent) except in women aged 18–64. The percentage of people who rarely or never eat bread is very low at all ages, with some increase in the older age groups. Females consume bread less frequently than do males.

*Butter and Margarine (Including Oil)* The percentage of persons who rarely or never use butter, margarine, or oil is relatively small in children but rises to more than 50 percent in young adults; it decreases again in the 60+ age group. The percentage of persons using butter and margarine more than once a day is very small in all age groups, it is higher in children than in adults. Teenage girls consume fats and oils less often than boys.

*Cereals* The percentage of persons who rarely or never eat cereals increases sharply with age, reaching more than 50 percent in most adults. The majority of children aged 1–17 use cereals between one and six times per week, but only between 30 and 42 percent of adults use them that often. Women over age 65 tend to eat cereals somewhat more frequently than do men in that age bracket.

*Snack Foods* Snack foods are consumed most frequently by children and youths, aged 1–17 years with only 12 percent reporting they seldom or never eat these foods. Twenty percent consume snack foods on a once daily basis, while 65 percent reported consuming foods from this group 1–6 times a week. Snack-food consumption declines greatly with age. Even though 6 percent of adults aged 18–74 years reported consuming snack foods once daily (or 7 times weekly), 34 percent reported 1–6 times a week consumption and 60 percent stated they seldom or never eat snack foods. There are few differences in snack consumption patterns between the sexes for either whites or blacks, but with few exceptions more black males and females consume these foods once a day than do white males and females.

*Desserts* The majority of persons in all age groups eat desserts once or more times a day. The percentage of those who rarely or never use desserts increases with age from childhood to old age. Sex differences are negligible.

*Candy* Candy consumption like desserts is greater among the children and youths aged 1–17 than among the adult population and declines with age. Eight percent of persons 1–17 of age reported consuming candy 2–4 times per day, while 27 percent reported consuming candy at least once daily. Fifty-one percent consume candy 1–6 times per week, while only 14 percent stated they "seldom or never" eat candy. Fifty-five percent of the adults aged 18–74 reported they "seldom or never" eat candy, while 11 percent consume candy on a once daily basis. But 32 percent of the people in these age groups reported consuming candy 1–6 times per week. On a once daily basis, more black females in all age groups consume candy than do white females. Black males also consume more candy than white males, with the exception of age groups 45–64 and 65+.

*Soda Pop* Around half of all children aged 1–17 drink pop once or more times a day. Young adults have an intake of similar magnitude. There is a marked decrease, however, in the percentage of older adults using pop once or more times a day, corresponding to a marked increase in the percentage of those who rarely or never use it. Women in all age groups and teenage girls drink soda pop less often than do men and teenage boys.

*Coffee or Tea* There is an abrupt increase in the percentage of persons using coffee or tea more than once a day after age 18, reaching a majority after age 45 in white men and women but not in black men and women. Sex differences are very small.

### *Summary*

To sum up, meat and poultry, fruits and vegetables, and bread are the foods most frequently used by 20,749 persons aged 1–74 in 65 locations across 48 contiguous states. Fish and shellfish, cheese, dry beans, and fruits and vegetables rich in pro-vitamin A are among the foods used the least. The use of foods of relatively low nutritional value, such as snacks, candy, and soda pop, is generally higher in children than in adults, particularly in the older age groups.

Nothing is known of the trace-element content in these diets. Analyses based on USDA Handbook 8 (Watt and Merrill, 1963) and additional sources provided by the food industry have been published for calories, protein, calcium, iron, vitamins A and C, thiamine, riboflavin, and niacin in the foods consumed by the examined persons in the 24 hours preceding the day of examination.

## EFFECTS OF SEWAGE-RECYCLING ACTIVITIES AND LAND APPLICATION OF COAL FLY ASH ON THE TRACE-ELEMENT CONCENTRATION IN FOODS OF PLANT ORIGIN

(Donald J. Horvath)

Interest in the use of various forms of sewage as sources of nitrogen and phosphorus, as well as irrigation water, is increasing as these plant nutrients become more costly.

It has been estimated that U.S. sludge contains the equivalent of about 3 percent of the nitrogen fertilizer and 6 percent of the phosphorus fertilizer used in the United States in 1973 (Larson in Dowdy *et al.*, 1976). This is a modest amount, but world phosphorus supplies are sufficiently scarce to make it attractive.

In areas of low population density, acreage necessary for rational sludge disposal is trivial, whereas it has been estimated that 55 percent of New Jersey's cropland will be needed by 1985 for sludge disposal (Council for Agricultural Science and Technology, 1976). Soil is a logical depository since it not only permits recycling of nutrients but may safely complex some harmful elements that would otherwise enter the air, if the sludge were to be incinerated, or the watershed, if the sludge were not recovered from the wastewater stream.

These same harmful elements, some of which are beneficial at low levels, provide a major obstacle to recycling sludge and will continue to do so until all industrial discharges are adequately pretreated before they are permitted to enter community wastewater streams.

Repeated, or heavy, application of sludge or effluent may cause sharp increases in soil levels of lead, copper, zinc, chromium, and cadmium. The lead does not readily move into the aerial portion of actively growing plants (Haye *et al.*, 1975), but phytotoxic levels of copper, zinc, chromium, and nickel may develop, and these may also be found in plants at levels sufficient to be of concern if they are to be eaten by animals including man. These aspects have been reviewed by Patterson (1971), Chaney (1973), Dowdy *et al.* (1976), and a Council for Agricultural Science and Technology (CAST) Committee (Council for Agricultural Science and Technology, 1976).

Briefly, these reviews suggest that cadmium is of greatest concern to animals since it moves into plants readily, particularly in acid soil, and it accumulates in animals, particularly in the kidney, and is capable of inducing hypertension in experimental animals and perhaps also in man. Copper, nickel, and zinc are of concern largely because of plant toxicity, particularly in more

TABLE 22 Effect of Digested Sewage Sludge (5 percent)[a] on Zinc Content of Several Crops at Two Levels of pH[b]

| Crop | Leaf Zn Content (ppm dry weight) | |
|---|---|---|
| | Low pH | High pH |
| Corn | 655 | 295 |
| Soybean | 444 | 222 |
| Tomato | 628 | 335 |
| Mustard | 1500 | 660 |
| Sugar beet | 1369 | 1193 |
| Chard | 1270 | 1330 |
| Rye | 228 | 296 |
| Wheat | 194 | 272 |
| Fescue | 260 | 301 |

[a]Five percent Baltimore digested sewage sludge added 186 ppm of zinc and 66 ppm of copper to Evesboro loamy sand soil.
[b]Source: Chaney (1973).

acid soils. Nickel had been suggested in a British sludge application guideline as being eight times as toxic as zinc, and this ratio appears to have been incorporated into the U.S. Environmental Protection Agency (EPA) tentative guidelines for sludge use, whereas Mitchell *et al.* (1978a) found nickel to be only about twice as toxic as zinc. Alexander *et al.* (1978) have found approximately 30 ppm of nickel in sludge-fertilized soybeans, but voles (*Microtus pennsylvanicus*) fed such soybeans as 60 percent of their diet for 7 weeks had little nickel accumulation in their tissues and no evidence of toxic effects.

Mercury is only occasionally present in sludges at levels above 100 ppm, but a report from Canada (Van Loon, 1974) indicates that on alkaline soils it may move into the edible portion of beans and tomatoes. To date, confirming studies have not been located. (Mercury determinations require careful reflux digestion of fresh, not dried, samples. Cold digestion may also be safe. In the absence of such precautions, low values may be false.)

With respect to geochemistry, the differences in availability with soil pH reflect soil parent material differences as modified by climatic conditions. For example, zinc in sludge is generally less available than zinc in some zinc salts in humid acid-soil areas but more available than zinc salts in low-rainfall alkaline-soil areas. The effect of pH on uptake of zinc from sludge by different plants is shown in Table 22.

Fly ash is another, and more abundant, material that may be applied to soils. Annual U.S. tonnage approaches 40,000,000 (Bern, 1976). Further, should fluidized bed coal combustion be adopted, a gypsum-ash sludge would be produced at the rate of approximately one ton for every three tons of coal burned. Fly ash may be a significant source of boron, molybdenum, and selenium in the food chain. Fly-ash boron levels are phytotoxic (Martens *et al.*, 1970), but in areas of ample rainfall, boron soon leaches out. Aluminum and manganese also may be phytotoxic if soil pH declines. Molybdenum could accumulate to levels able to disturb copper metabolism in ruminants (Doran and Martens, 1972), particularly since many ashes are alkaline and higher pH's favor molybdenum uptake. Selenium moves readily in the food chain, and Gutenman *et al.* (1976) found that sweet clover on a fly-ash dump had sufficient selenium to elevate tissue selenium levels in guinea pigs fed the sweet clover. Ranges for elemental composition of ashes were summarized by Bern (1976).

In summary, these materials may be used advantageously in some areas but because of their variability (Table 23) application must be based on actual analyses, not average values. Figure 23 (Dowdy *et al.*, 1976) summarizes a scheme for rational application of sludge. Representative values for soils of various cation exchange capacities are displayed in Table 24.

## RECOMMENDATIONS

### *Research Needed on Relation of Mineral Elements in Foods to Disease*

There are valid leads to suggest a role of mineral elements, particularly those occurring in trace amounts in

TABLE 23 Total Elemental Composition of Sewage Sludge[a,b]

| Component | Concentration[c] | | |
|---|---|---|---|
| | Minimum | Maximum | Median |
| | | % | |
| Organic C | 6.5 | 48.0 | 30.4 |
| Inorganic C | 0.3 | 543.0 | 1.4 |
| Total N | 0.1 | 17.6 | 3.3 |
| $NH_4$-N | 0.1 | 6.7 | 1.0 |
| $NO_3$-N | 0.1 | 0.5 | 0.1 |
| Total P | 0.1 | 14.3 | 2.3 |
| Inorganic P | 0.1 | 2.4 | 1.6 |
| Total S | 0.6 | 1.5 | 1.1 |
| Ca | 0.10 | 25.0 | 3.9 |
| Fe | 0.10 | 15.3 | 1.1 |
| Al | 0.10 | 13.5 | 0.4 |
| Na | 0.01 | 3.1 | 0.2 |
| K | 0.02 | 2.6 | 0.3 |
| Mg | 0.03 | 2.0 | 0.4 |
| | | ppm | |
| Zn | 101 | 27,800 | 1,740 |
| Cu | 84 | 10,400 | 850 |
| Ni | 2 | 3,515 | 82 |
| Cr | 10 | 99,000 | 890 |
| Mn | 18 | 7,100 | 260 |
| Cd | 3 | 3,410 | 16 |
| Pb | 13 | 19,730 | 500 |
| Hg | 1 | 10,600 | 5 |
| Co | 1 | 18 | 4 |
| Mo | 5 | 39 | 30 |
| Ba | 21 | 8,980 | 162 |
| As | 6 | 230 | 10 |
| B | 4 | 757 | 33 |

[a]Source: Dowdy *et al.*, 1976.
[b]Data compiled from over 200 samples from 8 states.
[c]Values expressed on a dry weight basis.

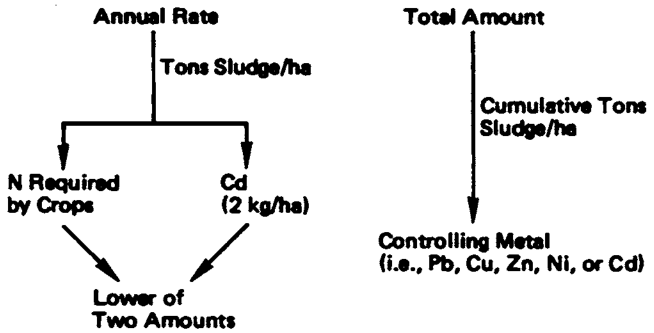


FIGURE 23 Factors determining the total and annual application rates of sewage sludge (after Dowdy *et al.*, 1976).

water and food, in the etiology of human disease. Hence, it is necessary to understand how much of the variability in human illness is attributed to the variability in intake of these elements.

The geochemical environment, embracing rocks, water, soils, and plants, plays a leading part in contributing to this variability in intake and, consequently, in the occurrence of disease. It is important in considering mineral elements as they relate to specific disease to keep in mind that large proportions of the total mineral element intake are derived from deliberate food-enrichment practices, e.g., iron, and inadvertent entry of mineral elements into the food supply because of technical practices, e.g., iodine.

The commercial production and distribution of fruits and vegetables is so concentrated in a relatively few regions, and the difficulties of relating rock, soil, and plant composition to diseases of man are so profound, that it is recommended that research be directed toward the development of methods for the study of trace-element concentration and degrees of variability in prepared individual foods, meals, and total diets, including foods of animal origin, that are actually eaten by various segments of the population.

Such investigations would necessarily stress the possibility that certain accumulator plants (those that tend to concentrate in their tissue unusual quantities of a chemical element from the soil) will enter the human diet. Special attention should be given to those elements that are considered to be toxic when present in appreciable quantity in the edible portions of such plants.

TABLE 24 Maximum Recommended Sludge Metal Applications for Privately Owned Farmland[a,b]

| Metal | Less than 5 | 5–15 | Greater than 15 |
|---|---|---|---|
| Pb | 500 | 1,000 | 2,000 |
| Zn | 250 500 | 500 | 1,000 |
| Cu | 125 | 250 | 500 |
| Ni | 50 | 100 | 200 |
| Cd | 5 | 10 | 20 |

[a]Source: Dowdy *et al.* (1976).
[b]Maximum metal addition (kg/ha) with a soil cation exchange capacity (meq/100 g).

The methods of study developed and the knowledge acquired concerning the composition of individual foods, meals, and total diets can be directed, in collaboration with workers in other disciplines, to trace-element intake by man in specific target areas. Unusually high-disease-incidence areas can be compared with areas of low incidence to develop possible relationships of one or more mineral elements to a specific disease.

### *Research Needed on Bioavailability of Trace Elements in Foods to Man*

The role and importance of the metal complexes in plants and the factors in plants that influence the utilization of those metals by man should be the subjects of an accelerated investigation emphasizing new approaches to bioavailability such as the single- and double-isotope techniques of labeling foods and added nutrients. Both the antagonisms and synergisms that may exist among the mineral elements as they affect biological availability should be investigated, along with greater emphasis on the effects of fertilizers.

The possibility of developing a breeding program with plants with the objective of eliminating or reducing the concentration of phytic acids, oxalic acids, or other inhibitors to utilization should also be considered.

### *Research Needed on Recycling of Sewage Sludge and Effluents and Land Application of Coal Fly Ash*

There is a growing tendency to reduce the dumping of waste materials into rivers and other bodies of water and to use soils for this purpose. While there are advantages—the conservation of nitrogen and phosphorus and the need for irrigation waters in some regions—disadvantages such as the accumulation in soils of high concentrations of the heavy metals, often as organic complexes, and their subsequent uptake by food crops and the acreage of land ultimately required must be carefully considered (Mitchell *et al.*, 1978b). Accordingly, we make the following recommendations:

- For long-range action, remove heavy metals from industrial wastes prior to entry into municipal treatment plants.
- For short-term action, require periodic analyses as the basis for restraints to application to soils of sewage effluents containing zinc, copper, nickel, mercury, and cadmium and fly ashes containing molybdenum and boron.
- Sludges should not be incinerated, as considerable proportions of cadmium, lead, and mercury, for example, are thereby volatilized. Binding of such materials to clay and organic particles of soils may be preferable to inhaling them.
- More data should be obtained on the movement by recycling into the food chain of nickel, mercury, cadmium, and other elements.
- Measure the flow of elements in ecosystems by alternative disposal procedures.

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# PART TWO

# *Trace Elements and Certain Diseases Related to the Geochemical Environment*

# VI

# *Cancer*

HOWARD C. HOPPS, *Chairman*

*John F. Annegers, Pelayo Correa, Carlos Cuello, James E. Enstrom, William Haenszel, Leonard T. Kurland, Malcolm C. Pike, Raymond Shamberger*

## THE GEOCHEMICAL ENVIRONMENT AND CANCER

(Howard C. Hopps)

### *Cancer Related to Environment*

The press has recently discovered something that many cancer epidemiologists and those interested in environmental factors and disease have known for a long time—some 80 percent of human cancer is attributable to environmental factors. This does not mean that environmental factors in question are the *total* cause, but they are a *major* causal factor. In this connection, it is important to recognize that virtually all disease is *multicausal*, and cancer is no exception. In the words of Foulds (1965):

> Overt neoplasia depends on multiple factors which act simultaneously or consecutively and which vary at different stages of the neoplastic disease. At each stage there is a complex interplay of genetic and nongenetic factors. The action of the recognized carcinogenic, inductive or *initiating* agents is conditioned by varied *permissive* factors, and the quality of the resulting neoplasia may be determined in part by *directive* factors. Varied genetic and physiologic factors are involved in delivering an initiating carcinogen to the target tissue in effective form and amount, and others control the responsiveness of the target tissue. [See also Weisburger, 1975.]

The great majority of environmentally induced human cancer is not produced by chemically or physically defined carcinogens, because many of the specific environmental factors occur as complex mixtures, which, incidentally, have been inadequately studied and are thus inadequately understood. What proportion of these factors represents chemical agents produced deliberately or inadvertently by man is not known. There is reason to believe, however, that the geochemical environment contributes a significant portion of the total. As epidemiologic studies yield further clues to the identity of these naturally occurring carcinogens, they can be tested in the laboratory. But this is not so simple as it seems. There are problems in selecting the right species of animals, determining the appropriate dose schedule, supplying critical cofactors, and so forth. Even so, there are such obvious advantages to studying mechanisms of carcinogenesis under carefully controlled laboratory conditions, using highly inbred strains of mice or clones of mammalian cells, that many laboratory-oriented oncologists believe this to be the only practical way. It is a serious mistake, however, to think that the study of cancer in man is so difficult and uncertain that costs outweigh benefits. A great deal has been learned from studying the occurrence of cancer in human beings under natural conditions. For example, of the 22 specific stimuli or categories of stimuli known to be carcinogenic for man, only 5 were first identified in experimental animals (Higginson, 1976). Moreover, studies of cancer in man have provided the basis for very substantial findings in the experimental laboratory; recovery of the Epstein-Barr virus from the lymph node of a child with Burkitt's tumor, in Uganda, is one of many examples. Perhaps most important, as has been implied, is the fact that epidemiologic studies of human beings is *by far* the most likely way to discover environmental causes of human cancer.

It is well established that certain trace elements (or simple compounds that contain them) are carcinogenic for human beings and other animals. In recent authoritative publications, Sunderman (1977), Furst (1977), Williams (1976), and Beliles (1975) list arsenic, beryllium, cadmium, cobalt, copper, chromium, iron, lead, nickel, selenium, titanium, and zinc among the trace elements that have been reported to produce cancer in experimental animals or humans. This list does not include radioactive elements nor those metals that produce "nonspecific solid-state carcinogens," e.g., silver foil and mercury droplets. There is still question about copper and selenium. Unfortunately, most of the evidence for such carcinogenicity comes either from controlled laboratory studies in which experimental animals are given these materials in an unnatural way—added directly to their food or water or by injection—*or* from epidemiologic studies on selected groups of human beings who have been exposed to unusually high levels of the carcinogen in question as a result of occupational exposure or heavy focal contamination or pollution.

*Nutrition Related to Environment* In a recent symposium on Nutrition and Cancer, Wynder (1976) pointed out that occupational factors make up only a small proportion of the environmental factors that are causally related to cancer and discussed the "... increasing epidemiologic evidence that nutrition plays a dominant role in the pathogenesis of several types of human cancer." Much of the interest in nutritional factors has to do with overt nutritional deficiencies or imbalances. More subtle factors, involving the interplay of trace elements derived from natural sources, have received relatively little attention. Because of this, relatively few hard data are available that relate carcinogenesis to the geochemical environment. This certainly does not mean that there is no causal connection, rather, it means that we do not know what the connections are, aside from a few dramatic examples, e.g., skin cancer associated with the high arsenic content of water in portions of Taiwan and lung cancer associated with pitchblende deposits at Schneeberg and Joachimsthal, Czechoslovakia. Naturally occurring trace-element deficiency may also play an etiologic role; regions in which the geochemical environment is very low in iodine are associated not only with endemic goiter but also with increased incidence of carcinoma of the thyroid. Almost surely, many other important geochemical associations remain to be identified. We are unable to produce evidence that would support or refute this contention because of deficiencies that exist in our data base and/or in the techniques we are using to manipulate the data. Miller (1976), speaking pertinently of clues to the origins of cancer that come from studying peculiarities in its distribution, remarked: "Some important findings lie very close to the surface, but go undiscovered because that kind of research-probing has not been fashionable."

*Environmental Effects on Cancer* In addition to providing carcinogens and/or cocarcinogens, the geochemical environment may affect the occurrence of cancer by contributing the following:

Factors that operate *during the stage of initiation* by:

- Modifying host metabolism to affect conversion of precarcinogens to carcinogens or, conversely, degrading active carcinogens. This is not an all or none phenomenon; quantitative aspects, including rate, are important. For example, $CCl_4$ intoxication in experimental animals has been shown to double the incidence of cancer from benzo(a)pyrene, because of interference with metabolism of the carcinogen by the liver (Kotin, 1970);
- Enhancing (or suppressing) activity of viruses or virus-related genes;
- Altering the cell's ability to repair DNA or RNA damage;
- Affecting cellular sites to increase (or decrease) their reactivity to carcinogens—acting as a preparatory factor.

Factors that operate *after initiation* by:

- Effecting exposure or modifying reactivity to promoting factors that act in a direct, positive way upon incipient cancers·
- Influencing such factors as wound healing and regeneration in such a way that *precancerous lesions*, e.g., posthepatic cirrhosis, atrophic gastritis, and exuberant burn scars, are less (or more) likely to occur;
- Involving defensive mechanisms of the host that act in an indirect way to destroy cancer cells or to suppress overt expression of incipient cancers;
- Affecting production of factors (e.g., estrogens and androgens) upon which so-called conditional tumors depend.

Less direct effects of the geochemical environment can result from the following (which is not a comprehensive list):

- Altering the intestinal microflora;
- Interfering with the intermediate metabolism of specific microorganisms that produce carcinogens. For example, zinc deficiency can virtually abolish production of aflatoxin by *Aspergillus flavus*.

Saffiotti (1973) has shown schematically some of the events involved in carcinogenesis, identifying specific points at which the multistage process can be blocked (Figure 24).

*Trace Elements and Chemical Complexes* In considering trace elements, one must be careful not to attribute biological effects to the element itself when such effects are dependent upon a *chemical complex* that includes the element. *Quantitative variations* in effects of simple in-

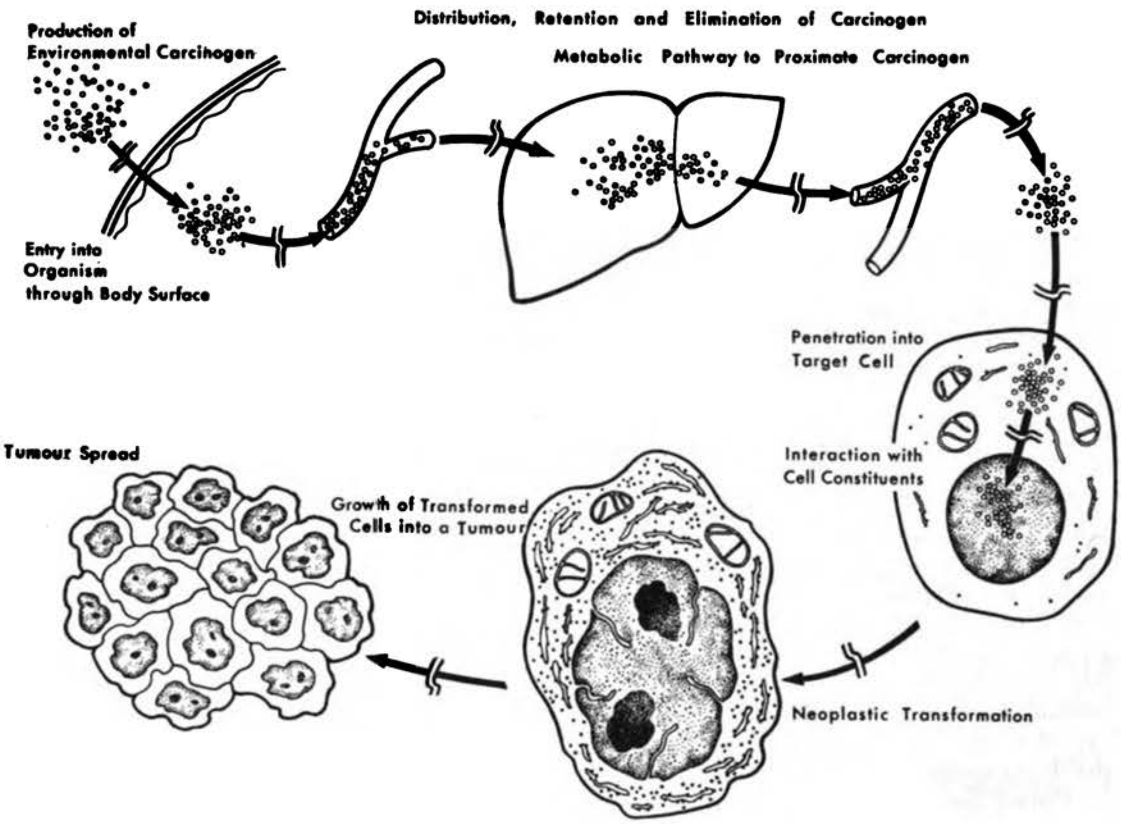


FIGURE 24 Pathways for carcinogenesis. Small circles represent the molecules of an environmental carcinogen in their route from the external environment through the body to the target cells. Breaks in the arrows are points where the chain of events may be interrupted, preventing cancer formation (Saffiotti, 1972, 1973).
Reproduced with permission from *Proceedings of the Ninth Canadian Cancer Research Conference*, 1971, Umberto Saffiotti and University of Toronto Press.

organic compounds containing the same trace element may simply reflect its availability. For example, effects of sodium selenate, selenite, and selenide are qualitatively similar and relate primarily to selenium; quantitative differences reflect differences in solubility. The same is true for many other trace elements, e.g., ferrous salts tend to be more readily absorbed than ferric salts. Important *qualitative differences* frequently occur, however; of the many iron compounds tested, only iron–carbohydrate complexes have been shown to produce cancer in experimental animals. The problem is further complicated because of differences related to the *physical form* in which the complex enters the body; particle size is particularly important in inhalation. Other biologic effects related to physical form, e.g., carcinogenesis at solid-state surfaces, are much less well understood. [Implantation of metallic *foils* of silver, gold, and platinum produces tumors, usually fibrosarcomas, in rats and mice (Foulds, 1975).]

*Complicating Factors* Host factors are at least as complex as environmental ones in determining connections between geochemistry and cancer in humans. Some of the factors that present major difficulties include a long, 20-or-more-year incubation period for cancer; the tendency for people (particularly in the United States) to migrate often; and food processing and market practices (particularly in the United States) that profoundly influence the geographic origin and thus the geochemical influence of foods consumed.

Even common cancers have a relatively low incidence. For example, in the United States, one can expect only one (new) case per year from a cross-sectional group of *2300 persons* (H. I. Sauer, University of Missouri, Columbia, personal communication, 1977). Thus, large numbers of individuals must be studied during a relatively long time in order for rates of occurrence under different environmental conditions to have statistical significance. Some of the proposed studies, involving populations of several thousand, in a region carefully selected because the geochemical environment was known in detail, would probably not yield valid conclusions.

*Influences on Carcinogens* Still more problems are encountered in efforts to identify specific factors that contribute to cancer formation because carcinogenic agents are influenced in their effects, sometimes profoundly, by the following:

- Genetic predisposition or resistance of the host to the agent;
- A multiplicity of agents, acting in concert or sequentially (effects may be synergistic, additive, or counteractive);
- The route of administration (ingestion, inhalation, skin contact, injection);
- The dosage (amount and manner given) as a single dose or as repeated doses (the time intervals may have great influence) or by continuous application or exposure;
- The time of life when administered—normally, susceptibility decreases in the following order: embryo, fetus, infant, child, and adult.

*Effects of the Geochemical Environment* Because of the intimate relationships among rocks, soils, waters, flora, and fauna, possible effects of geochemical environment on the occurrence and behavior of cancer are very complex indeed. We ordinarily think of soil, for example, as contributing trace elements to man via surface water and through plants eaten directly or, in a secondary fashion, from man's consumption of meat, milk, eggs, and other products derived from animals that are nourished by plants. A more direct mechanism of contribution in many regions of the United States, particularly among farmers, is *ingestion of windborne particles of soil.* Much depends on the particle size as to what happens to inhaled particles. Those larger than approximately 20 μm in diameter are likely to be filtered out in the nasal passages and discharged. Those smaller than 1–2 μm are likely to be ingested by phagocytic cells deep within the lungs and held within alveoli for varying periods of time. Many of these phagocytic cells will enter the lymphatic system, carrying their ingested dust to lymph nodes or to other reticuloendothelial tissues, e.g., the spleen, liver, or bone marrow, where intracellular enzymes dissolve many chemical components of the particle that ultimately, upon death of the phagocytic cell, are released into the body. A considerable portion of the particles between these two size ranges, i.e., 2–20 μm, impinge upon and are trapped in the mucous layer that covers the tracheobronchial mucosa. As a result of ciliary action of the cells of the respiratory mucosa, they are swept up to the hypopharynx, swallowed and subjected to the digestive processes, and absorbed, at least in part. There are few hard data on the amounts of finely particulate soil inhaled, but it is possible to get some idea of intake by putting bits and pieces together. Reference Man (a hypothetical average man 70 kg in weight and 172 cm in height), working at light activity, takes into his lungs approximately 9600 liters of air per 8 hours. During dust storms in the Great Plains in the 1950's, the median dust concentration was 4.85 $mg/m^3$ (Hagen and Woodruff, 1973), and dust particles, in the size range 10–20 μm carried at a level of 5 feet over two soil class groups during 1955 Kansas and Colorado dust storms comprised 3.7 and 7.6 percent, respectively, of the total dust (Chepil, 1957). Under these conditions, Reference Man might well have taken *into his digestive system* 3 mg of finely particulate soil during an 8-hour period, which would have provided amounts of certain *trace elements* equal to or in excess of those he obtained from drinking water. If one extrapolates further, considering the amount of finely particulate soil that becomes airborne during farming activities such as plowing, harrowing, cultivating, and combining (particularly in the Midwest), it is obvious that windblown soil can be an important direct source of materials derived from the geochemical environment. Relatively little research has been done to determine the amounts of trace elements that are absorbed by men from ingested soil. Certainly absorption would be strongly affected by the chemical form of the element, associated compounds, and physiologic characteristics of the individual, e.g., gastric pH. In an experimental study by Healy *et al.* (1970) approximately 34 percent of selenium, 14 percent of zinc, 1 percent of cobalt, and 0.4 percent of manganese were absorbed from "... a yellow-brown earth, Korokoro silt loam ..." fed to sheep in New Zealand.

*Effects of Environmental Derivatives* Nitrates and nitrites that are derived from the geochemical environment (as well as from food additives and pollution) contribute to the formation of *N*-nitroso compounds, which *may* represent one of the most important categories of carcinogens. Of the more than 100 *N*-nitroso compounds that have been examined, approximately 75 have been shown to be carcinogenic, and every animal species tested has been found susceptible to at least one of these compounds (Lijinsky *et al.*, 1975). Although some of the compounds will induce tumors when given as a single large dose, small doses administered frequently over a long time are more effective. Moreover, of the many secondary amines of low or moderate basicity, most of those that react well with nitrites *in vitro* are carcinogenic in experimental animals when fed concurrently with nitrite (Sander *et al.*, 1975). With respect to human beings, Lijinsky *et al.* (1975) point out that: "The most significant source of nitroso compounds is their formation in the stomach, a highly favorable milieu for nitrosation of [ingested] secondary and tertiary amino compounds," and that "... residence time in the stomach or other medium is measured in hours and the yield of nitroso compound could be significant in this time even from a slowly reacting amine." It has also been shown that the microflora of the vagina, of the achlorhydric stomach (perhaps), and of the infected urinary bladder may synthesize *N*-nitroso compounds (International Agency for Research in Cancer, 1974). There is now abundant evidence that *N*-nitroso compounds (and their precursors) occur not only in certain foods but also in air, water, and soil (Shapley, 1976). Virtually all of the hard information about carcinogenicity of *N*-nitrosamine compounds currently available relates to experimental animals. There is some epidemiologic evidence that *N*-nitrosamines may be causally related to carcinoma of the stomach and of the colon, however.

*Microfloral Modifications of the Environment*

The importance of the ***intestinal microflora*** in producing or inactivating carcinogens is well known. Bras (1973) described the situation very well: "The commensal bacteria of the gastro-intestinal tract . . . constitute a large metabolically active mass that responds to and modifies the environment." He further states: "The gut bacterial flora can certainly produce carcinogens and may, through their enzymes, also activate such agents as cycasin. They may increase, decrease, or even reverse the action of the agent. Thus, the gut flora has a role to play in the etiology of human cancer, and this role is almost totally unexplored." The effects of dietary lipid and "fiber" on the occurrence of cancer (particularly carcinoma of the colon and rectum) may be mediated by changes in the intestinal microflora (Reddy *et al.*, 1975; Hill and Williams, 1973; Moore and Holdeman, 1975).

*Microbial Toxins* Another possibly important aspect of the geochemical environment in cancer causation concerns the effects of trace elements in the soil and in plants ***on intermediary metabolisms of microorganisms***. An increasing number of preformed toxins from bacteria and fungi have emerged as potent agents of human disease, including cancer. One of these, aflatoxin, a product of certain strains of ***Aspergillus flavus***, is a powerful carcinogen in various mammals, birds, and fish. Epidemiologic data suggest that it is causally related to human cancer of the liver and, perhaps, other organs. Deficiency of zinc in the growth medium can virtually eliminate aflatoxin production from toxigenic strains of *A. flavus* at a level that does not significantly decrease their rate of cellular reproduction. Excess cadmium or copper (not sufficient to inhibit growth) also limits aflatoxin production (Weinberg, 1977). Other trace elements may act indirectly. Burrell *et al.* (1966) observed that molybdenum deficiency of the soil "rendered maize cobs prone to fungal attack."

*Cancer as a Group of Diseases*

Turning to quite another issue, cancer is a *generic term*, and different cancers vary so enormously with respect to their general behavior, the causal factors involved, characteristics of the population at risk, and other factors that one should think of cancer as a *group* of diseases. Although they have certain things in common, they are quite diverse, somewhat analogous to bacterial diseases. Many epidemiologists, in characterizing cancers, have been satisfied with a specificity that considers only whether the cancer is a sarcoma or carcinoma and the organ in which the cancer arises. Such a broad classification as carcinoma of the lung, stomach, thyroid gland, esophagus, or liver is simply not adequate for the kind of studies that are required, because each of these categories includes several epidemiological entities with clearly different risk factors.

- Squamous cell carcinoma of the *lung* is causally related to cigarette smoking; undifferentiated cell carcinoma and adenocarcinoma of the lung are not.
- Correa *et al.* (1969) have shown, in Colombia at any rate, that the kind of carcinoma of the *thyroid* occurring in areas of endemic goiter presents a significantly different picture histologically than the kind that occurs in nongoiterous regions. The types related to goiter are follicular or anaplastic; the papillary type is not significantly associated with goiter.
- Carcinoma of the ***esophagus***, which has one of the most striking geographic patterns of all malignant neoplasms—a 200-fold difference depending on geographic occurrence—can involve at least three different types of cells when it occurs in the distal portion. The cancer may be squamous cell or adenocarcinoma; if adenocarcinoma, it can arise from esophageal mucous glands or from foci of aberrant gastric epithelium that are often found within the first several centimeters of the distal esophagus. It seems likely that each of these histologic types is causally related to a different (probably overlapping) complex of environmental factors.
- The high prevalence of cancer of the *liver* in much of Africa is accounted for by hepatocellular carcinoma; cholangiocarcinoma is not increased.
- It has been shown that among the several types of carcinoma of the ***stomach***, two, characterized by histologic appearance, are quite different in patterns of geographic distribution and, persumably, the environmental factors that contribute to their occurrence. The intestinal type is primarily responsible for the excess number of cases found in high-risk geographic regions; the diffuse type has essentially the same prevalence in low- as in high-risk areas. (See section by Correa *et al.*, below.)

*Gastric Cancer* Stemmermann (1975), in reviewing the epidemiologic pathology of gastric carcinoma, supports the view of Correa and his associates that the intestinal form of gastric cancer is the one most common in high-mortality areas and further states: ". . . it is the prevailing view that the role of precursor may be played by intestinal metaplasia of the pyloric antrum," and that ". . . it is the distal or antral form of gastritis which predominates in populations at high risk for gastric cancer" (Figure 25). A recent report by Cady and Choe (in press) lends additional support to this view. They studied data from more than a thousand patients operated on for gastric cancer at Boston's New England Deaconness Hospital over a 30-year period (1939–1969) and found that during this period,

> Gastric cancer seems to consist of three separate anatomic varieties with distinctive incidence patterns in time. Distal gastric cancer has decreased dramatically by at least 75 percent from 12 to 3.5 cases per 100,000 population per year. Cancer of the body of the stomach has decreased by 50 percent from 3 to 1.5 cases per 100,000 population per year, but proximal gastric cancer has remained sta-

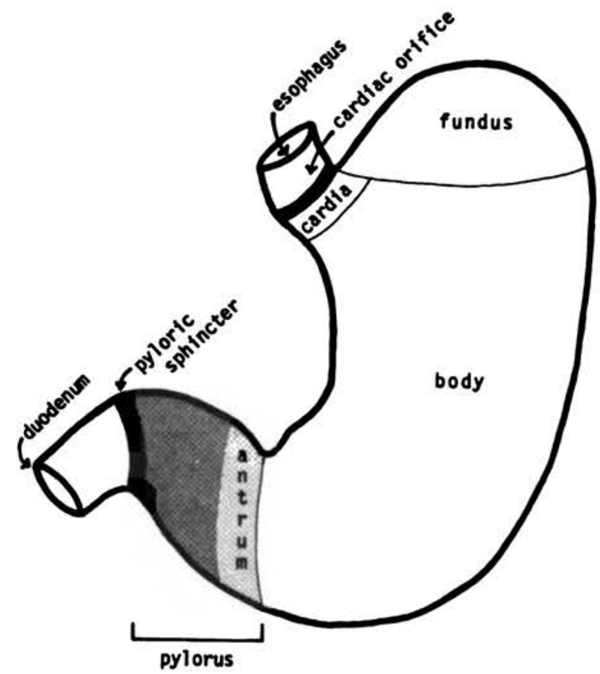


FIGURE 25 The portion of the stomach referred to in the text as distal is predominately pyloric; proximal refers principally to fundus and cardia. As indicated, antrum is a portion of the pylorus.

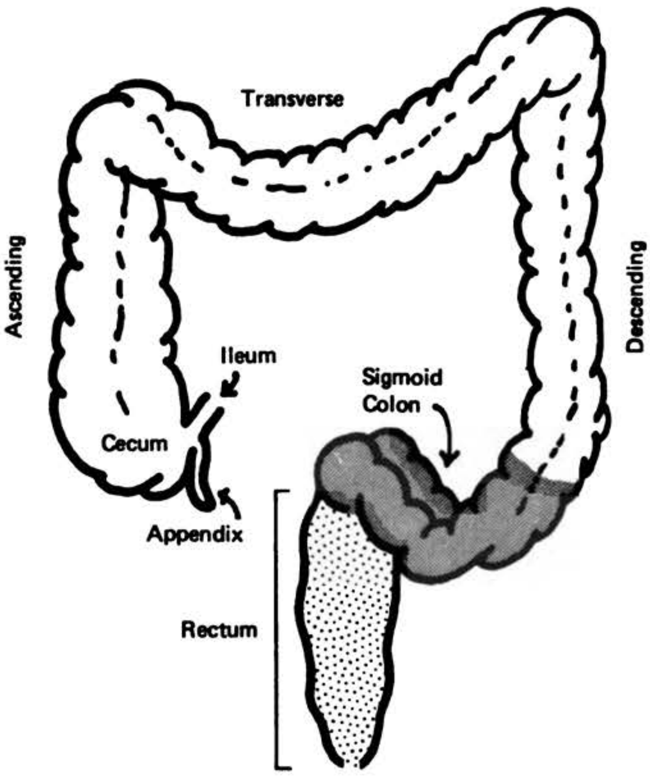


FIGURE 26 These anatomic subcategories of the large intestine are discussed in the text.

ble in incidence at about 3 cases per 100,000 population per year.

*Colorectal Cancer* Turning to cancer of the colon and rectum, approximately two thirds of cancers of the large bowel arise from epithelial cells of the mucosal lining of the rectosigmoid portion (Figure 26). Sharp separation between cancer of the sigmoid colon and rectum is difficult because the precise boundary between the two portions is not well defined; moreover, the length of the rectum varies from individual to individual. Various measurements are given in anatomy texts: from 12 to 15 cm, ordinarily, but it is admitted that the rectum may be much longer. Blot *et al*. (1976), in their important paper on the Geographic Patterns of Large Bowel Cancer in the United States, report that

> Part of the geographic variation in colon [and rectal] cancer mortality was . . . attributable to urbanization and socioeconomic class, which were at highest levels in the Northeast. However, even when these factors were taken into account, substantial regional differences in mortality persisted.

Their data revealed an essentially similar geographic pattern of colon and rectal cancer, which suggests that the same environmental factors are probably responsible. This similarity in pattern may simply reflect errors in diagnosis, however, because of the difficulty in determining the boundary line between colon and rectum, also the fact that, in mortality statistics, cancers of the rectum are not ordinarily further localized anatomically. The lower sigmoid colon and *upper rectum* are histologically similar and have a comparable microflora and a similar function—serving primarily as the repository of solid or semisolid feces—which suggests that causal environmental factors may be similar. Recent studies by Correa (1975) and Berg (quoted by Correa), however, show that when the portion of the rectum in which cancer arises is defined by actual measurement of its distance from the anus, a definite geographic pattern of occurrence can be related to whether the cancer arises in the proximal or distal third of the rectum. An "excess of tumors of the upper rectum and sigmoid were found in New Orleans contrasted with an excess of tumors in the lower rectum in Cali [Colombia]."

In addition to the sigmoid colon and upper rectum, and the lower rectum, two other parts of the large intestine, which are not ordinarily identified anatomically in mortality data, are also exposed to quite different internal environments. These portions, (a) the cecum and ascending colon and (b) the transverse colon and upper descending portion, could reasonably be expected to have different environmental causes. Fortunately, with respect to the limitations in diagnostic data generally available, categories (a) and (b) represent only approximately 20 percent of the cancers arising in the large intestine.

From these examples, it is evident that the discovery of causal relationships between the geochemical environment and cancer requires the matching of very specific geochemical factors with very specific types of cancer, types that often represent histologic and/or gross anatomic subcategories.

*Deficiencies of Data and Information*

*If* we had the necessary data about occurrence of different kinds of cancers in the context of the time and environment in which they began, we could search much more effectively for the factors involved by carcinogenesis. Alternatively, *if* we had comprehensive information about the factors and parameters responsible for carcinogenesis, we could concentrate our efforts toward identifying the environmental areas (and situations) in which these factors were operating at significant levels. Because we lack sufficient data about cancer occurrence as well as the necessary information about carcinogenesis, we must depend mainly on epidemiologic data to learn where and under what circumstances *specific* types of cancer are occurring in greater than expected numbers and then decide whether certain associated circumstances contribute cause. In the process, we must be continually aware of Burkitt's (1975) admonition "... epidemiological relationships do not prove anything. However, they do provide an opportunity for formulating hypotheses that subsequently can be tested, and disproved, modified, or confirmed."

*Maps and the Presentation of Data* The factors involved in associating geochemical environment with the occurrence and behavior of cancer are so numerous and complex that a large data base and automatic data processing are essential. Maps can be of enormous value in showing and assessing spatial/temporal coincidence because they increase perception, understanding, and communication. Contour (isopleth) maps are particularly useful because they show rates of change and are much less likely to be influenced by political boundaries that, of course, have little effect on the occurrence of disease. Moreover, maps can show the distribution of *data complexes* that relate directly and comprehensively to the problem at hand. A data complex, which, in effect, represents the product of an equation, can represent a number of factors and parameters that are suspected to contribute cause to a specific cancer. For example, a single data complex might incorporate several of the following:

- Age and sex;
- Diagnostic data, including assessment of its validity;
- Histologic subsets of particular cancers categorized by organ site (e.g., *intestinal* type carcinoma of stomach) or tissue;
- Geographic location correlated with *time of initiation* of the cancer;
- Race, tribe, ethnic group, and socioeconomic status;
- Dietary history;
- Specific occupational exposure (at various levels);
- Specific aspects of past medical history including therapy (e.g., x-ray) and social history;
- External aspects of the environment, including weather and climate, geochemistry (rocks, water, and soil), and man-made pollution.

With particular cancers in which important causal environmental factors are known, one could design a data complex that excluded those factors, concentrating on the *unexplained residual* variation.

From the foregoing, it is evident that appropriately constructed maps may be used as highly effective research tools (Hopps, 1972, 1977; Hopps *et al.*, 1969). The feasibility of such an approach to the cancer problem is greatly enhanced by present-day abilities to produce maps by computer quickly and accurately, in many projections and scales, and in hard copy or on cathode-ray tubes (Hopps, 1975). The recent National Cancer Institute *Atlas of Cancer Mortality for U.S. Counties, 1950–1969* (Mason *et al.*, 1975, see Appendix A), which presents maps that show the spatial distribution of some 33 kinds of cancer, is an important step in the right direction, but much more needs to be done if we are to discover important new situations in which the geochemical environment is causally related to cancer.

*General Comments*

To conclude these remarks, a comment by A. B. Miller and an admonition by C. S. Muir seem imminently appropriate.

> A substantial endeavor is required to obtain the necessary data to assure that individuals at high risk can be identified with precision. In some respects the barrier between etiology and control is artificial; control endeavors, even when based on incomplete etiologic information, may well help to clarify etiologic relationships either by their effect or lack of effect (when primary prevention is attempted) or through the opportunities such programs provide to obtain etiologic data. Nevertheless, while recognizing that sometimes action based on relative ignorance may be unavoidable, etiologists in general would argue for the sequence: research on etiology followed by appropriate control based on the knowledge gained. Much etiologic research therefore is vital before our control colleagues can be completely unleashed (Miller, 1975).
>
> As in any other branch of science, the demonstration of a risk differential is no guarantee that a hypothesis, i.e., an explanatory conjecture, will follow. As Medawar comments "The generative or elementary act of discovery is 'having an idea' or proposing a hypothesis. Although one can ... abet the process, the process itself is outside logic and cannot be made the subject of logical rules." No

general statement can arise from the conjunction of raw data. The mind must make some imaginative contribution of its own (Muir, 1973).

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## GASTROINTESTINAL CANCER AND THE GEOCHEMICAL ENVIRONMENT

(Malcolm C. Pike)

### *General Comments*

Epidemiological studies of cancers of the stomach, colon, and rectum have demonstrated that all three diseases are largely environmental. That is, their rates of occurrence can be drastically altered by manipulation of peoples' modes of living. Cancer rates at these body sites in migrant populations generally approach the rates of their adoptive country with time. On a world distribution, stomach cancer rates vary 30-fold and colorectal cancer rates 10-fold (Doll, 1967)—these are such large differences that it is clearly of public-health interest to find out what it is that is producing them.

A number of dietary factors have been suggested to explain the observed large differences in these cancer rates (see sections by Correa *et al.* and Enstrom below), and Berg and Howell (1974) and Shamberger (see below) have drawn attention to correlations between these rates and certain trace elements.

To establish a factor as causally related to any of these cancers, a number of relationships need to be identified. Clearly there should be some correlation between the factor and the tumor on a geographical or ethnic basis. Similarly, any large change in the level of the factor should be reflected in the disease rate (perhaps only after 20 or more years). Also, if a high (or low) cancer-rate area can be found within a low (or high) rate area, this should be reflected in different levels of the factor. These broad community relationships are, however, only a first step, since confounding variables are usually present. For example, finding a correlation between some trace element and stomach cancer rates by state in the United States will be severely confounded by ethnic factors, as immigrants from high stomach-cancer rates in Europe have tended to settle in certain north-central states, and they will have to some extent brought their high rates with them. Adjustments can sometimes be made for such variables, but this is seldom completely satisfactory.

After noting gross correlations, it is then necessary to test the suggested causal agent by relating the occurrence of the disease to the personal exposure of patients and controls, either by case-control or cohort studies (MacMahon and Pugh, 1970).

Relationships between diet and cancers at many sites have been found on a geographical basis (Armstrong and Doll, 1975), but evidence at the individual level is unconvincing (Burkitt, 1975; Wynder and Reddy, 1975; Modan *et al.*, 1975), and our understanding of certain dietary constituents still appears to be very crude. In particular, regarding the suggested relationship between low dietary fiber intake and high colorectal cancer rates, it appears that we are only just beginning to understand that *fiber* is a collective name for a wide variety of substances having very different effects on bowel contents (Anonymous, 1975), and the data to make proper geographical correlations are lacking.

The suggestion of Breslow and Enstrom (1974) that beer consumption may have an etiological role in rectal cancer, in particular, needs further careful study at the individual level. Further correlative studies can hardly add much to the impressive evidence they have already put forward, and, as beer drinking habits clearly are to some extent ethnically determined, what they are observing may be nothing more than a measure of such with the true cause being elsewhere.

Suggested dietary factors related to stomach-cancer etiology are likewise far from convincing (see Correa *et al.* below). Moreover, the high rates in countries with such different diets, Iceland and Japan, for example, make it more than likely that no single major cause of stomach cancer exists and that its epidemiology will have to be worked out separately in different places. Finding that a single agent—cigarette smoking—was far and away the main cause of lung cancer is likely to be the exception rather than the rule in cancer epidemiology.

### *Trace Elements*

Berg and Burbank (1972) calculated correlation coefficients between U.S. mortality rates by state and the water content of certain trace elements suspected to be carcinogenic. They did this by considering the 10 of the 16 stream drainage basins that included whole states, given by Kopp and Kroner (1972) in their report on metal content of rivers and lakes of the United States. The metals they studied were arsenic, beryllium, cadmium, chromium, cobalt, iron, lead, and nickel. Using age-adjusted mortality rates (1950–1967) separately for the four subdivisions of male/female and white/black, they found a number of significant positive relationships to gastrointestinal cancer rates (Table 25).

The correlation of cadmium and large-bowel cancer is much larger than the others and is of the same order of magnitude as the relationship to beer discussed by Enstrom (see below).

As pointed out by Berg and Burbank (1972), bowel-cancer mortality is highest in the northeast United States and lowest in the Southwest, and any factor with this kind of distribution will be correlated with bowel cancer. They also pointed out that other official publications give conflicting results for cadmium distribution. Nevertheless, the magnitude of this correlation should encourage further studies. These should be at the individual person level—both a case-control study and a follow-up study of persons with heavy industrial exposure are the next step, if such a group exists.

The other relationships that Berg and Howell (1974) found could likewise be pursued. Present knowledge of the carcinogenic potential of lead and nickel may be found in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volumes 1 and 2 (International Agency for Research on Cancer, 1972, 1973). They report no further positive evidence linking either of the metals to gastrointestinal cancers, and two industrial cohort studies showed no increased risk, although the populations studied were too small to detect small differences from the general population.

Shamberger (see below) makes a good case for selenium to be seriously considered as an anticarcinogen. Of all the trace elements suggested as having a relationship to cancer, selenium must now rank near first as warranting much further investigation.

After noting certain gross geographic negative correlations, Shamberger moved in the direction of narrowing down the problem and again found negative correlations

TABLE 25 Statistically Significant Positive Correlations between Metal Concentrations and Gastrointestinal Cancer Death Rates

| Metal | Site (ICD)[a] | *P*-Value[b] | Correlation[c] |
|---|---|---|---|
| Cadmium | Large bowel (153/154) | 0.00001 | 0.61–0.81 |
| Lead | Stomach (151) | 0.0026 | NG |
| | Small bowel (152) | 0.038 | NG |
| | Large bowel (153/154) | 0.009 | NG |
| Nickel | Large bowel (153/154) | 0.031 | NG |

[a] ICD, International Classification of Disease.
[b] Statistical significance.
[c] NG, not given by Berg and Burbank (1972).

between blood selenium levels in communities and their cancer death rates and also between the selenium concentrations in community milk supplies and their cancer death rates. Although the latter finding is contradicted by more accurate data (age-standardized cancer mortality data for 1950–1969), the approach is still acceptable, and a single finding of no relationship should not, and does not, destroy the general picture. This is especially so in light of the experimental animal data he has gathered to support his case. The more crucial case-control studies in man of selenium as a protective agent, however, are essentially uninformative. Shamberger and his colleagues found that the mean selenium level in blood of normals was approximately 23 μg/100 ml, while colon-cancer patients had a mean level of 16 μg/100 ml, stomach-cancer patients 15 μg/100 ml, and rectal-cancer patients 21 μg/100 ml. They also found that patients with "metastases to gastrointestinal organs had significantly lower blood-selenium values." The blood-selenium values may therefore simply be the result of the diseases.

In such a situation, where one wishes to study etiology using a case-control approach but where the variable to be studied may be affected by the disease, it is sometimes possible to get an indication of the patient's predisease levels by studying other persons living with them or related to them. In studying selenium, one would first need to establish the correlation of selenium levels between different members of nondisease control households. Then, if a significantly high correlation was found, a case-control study using other household members' selenium levels could be undertaken.

If selenium levels of different household members do not correlate well, then some other novel approach is needed—there is little to be gained from doing further geographical studies or of doing further measurements of selenium levels in cancer patients.

An excellent summary of current knowledge of selenium is given by Oldfield *et al.* (1974) in their report given at the Asilomar Workshop. One of their main recommendations for research is still valid:

> Baseline data should be established with reference to selenium levels in humans in health and disease. Much more extensive sampling of human material, such as blood, urine, and hair, might be done in attempts to correlate concentrations of selenium with disease incidence.

### *Summary*

In geographical-correlation studies, one wishes clearly to use measurements of trace elements actually consumed by people so that, for example, one would prefer to have measurements of trace elements in tap water rather than in lake and river water. Few such data exist at present, and it has been suggested that more effort should be made to collect them.

My prejudice is that such an effort would not be very productive of new leads and that emphasis should now be placed on studies to test the leads we have already. These studies can either be of the case-control type (with any necessary modifications as required by possible alterations due to the disease state itself) or of the prospective cohort type. Measurement of cancer incidence in individuals excessively exposed to some suggested causative elements would be especially worthwhile.

In any further geographical correlation studies, some attempt should be made to allow for other factors known, or suspected, to be related to disease incidence. For example, studies on carcinoma of the rectum should allow for differences in beer consumption.

## THE GEOCHEMICAL ENVIRONMENT AND CANCER EPIDEMIOLOGY—COMMENTS ON INTERNATIONAL DIAGNOSES AND STUDY DESIGN

(Leonard T. Kurland and John F. Annegers)

### *Problems in Evaluating the Geochemical Environment and Cancer*

During the past 25 years, clinicians and epidemiologists have noted associations between cancer and risk factors such as smoking, occupation, drug therapies, and certain individual characteristics such as the age at first pregnancy (Fraumeni, 1975). Although some associations have been demonstrated and many hypotheses have been developed, there has been considerably less work in the area of the relationship between cancer and the geochemical environment, i.e., soil, water, air, and food. Some of the difficulties that account for this apparent lack of progress have also been alluded to by Hopps (above):

- The latency period of most cancers is assumed to be long, perhaps 20 years or more. Thus, the geochemical environment of interest might be that which existed some time in the past. It may not be possible to determine the sources and content of the food and drinking water that were consumed during the period of interest.
- The free movement of populations within a country such as the United States affect the ability to relate local conditions to subsequent incidence or death rates. On the other hand, there are many populations in the third world that are closely tied to their local environment for food and other needs, but in these same areas reliable cancer incidence data are usually lacking.
- The diets of a large proportion of the population of the world are now assembled from the produce of many regions so that diet may not always reflect the local geochemical environment. In a single day we are likely to have orange juice from Florida, lettuce from California, bacon from Iowa, beef from Texas, potatoes from Minnesota, stringbeans from Michigan, bread (wheat) from the Dakotas, coffee from Brazil, Colombia, or Africa, and tea from India or Ceylon. It may still be possible to study general dietary characteristics, such as the amount of fiber

and the percentage and type of fat, in relationship to cancer. But it is also desirable to measure regional differences in terms of excesses or deficiencies of specific trace elements or particular compounds. In addition, it may be possible to investigate the quantity of known or suspected toxic substances in artificially treated or preserved foods.

- Even the most common cancer sites—e.g., carcinoma of the bowel—have relatively low incidence rates, of the order of 20–50 per 100,000 population per year. Relatively large populations are needed either to compare rates between localities or to observe associations between risk factors and the appearance of cancer in an exposed population. Therefore, proposed studies of a small population of even several thousand in a region carefully selected because of a detailed evaluation of the geochemical environment would be insufficient to provide adequate reliability.
- The etiology of most cancers is quite complex, with interaction occurring between numerous factors. With environmental factors, it is often difficult to elucidate the exact role of any single agent.

*Differences in Cancer Incidence Rates*

In recent years the statement has been made that 80–90 percent of all cancers in man are due to environmental factors (Doll, 1977). This statement is based on a strong association of certain cancers (e.g., lung) with specific risk factors. However, the suspicion that most other cancers (e.g., breast, colon, prostate) are due to environmental factors is derived largely from international differences in mortality.

Comparisons of international statistics on cancer are largely restricted to reports from Japan and the predominantly Caucasian populations of the United States and Western Europe. The available data often reveal large differences between countries, which may be due to differences in diagnosis and reporting but which are usually ascribed to genetic or environmental differences. Since migrants, after a generation or two, appear to have cancer at rates approaching that of others in their adopted country, it has been assumed that culture and/or environment rather than heredity account for most of the differences by country.

Another source of information that has been interpreted as suggesting that at least some cancers have important environmental causes are the changes in rates over time. Over the past few decades, in most western countries and Japan, the death rates from certain types of cancer, such as that of the lung, have increased greatly, whereas that of the stomach have been decreasing. In these instances, one might expect that changes in the environment accounted for the trends. However, for most major sites, available cancer registry data do not show dramatic secular changes.

The above statements are made with the realization that cancer diagnosis and reporting is not equally complete or accurate in different countries and may have changed in the same country over time. For sites such as breast, colon, and prostate, the rates in Japan are appreciably less than those in western countries, whereas the rates for stomach cancer are greater in Japan. The fact that the rates for those sites among Japanese migrants to the United States begin to approach the local rates and those of their offspring even more so, suggests that environmental differences account for the observed patterns. However, it is possible that social conditions and medical practice may also account for some of these differences. Specialty and group practices in Japan are relatively new, and most of the ill population are still seen by local physicians who emphasize treatment rather than specific diagnosis and are reluctant to arrange for referrals to advanced diagnostic centers. Tradition may influence the reported causes of death; furthermore, intensive medical work-up and autopsies, particularly for the elderly, occur infrequently outside the medical centers. As an example of these effects, one might examine the death rates for cerebral hemorrhage that have been reported as several times greater in Japan than that of the white population of the United States. In a recent prospective study of a small community, the staff of Kyushu University found that if intensive efforts were made and the autopsy rates approached 100 percent, the cerebral hemorrhage rates were comparable with those of the United States, although initially the frequency of clinical diagnosis and death certification of cerebral hemorrhage remained high. In Japan, cerebral hemorrhage has been considered by the laity as an indication of superior intellect; thus socially, it was desirable as a stated cause of death. The family physician may have often complied with family interests when there were other causes of stroke or the exact cause of death was uncertain.

The reported low rates for prostatic cancer in Japan could be due, in part, to failure to diagnose this lesion because of the reluctance of many Japanese physicians to subject their patients to routine rectal examinations and to the relatively low rates of autopsy. Thus, the continuing improvement of medical practice in Japan can be expected to influence reported mortality rates, although the changes will almost certainly be ascribed to environmental factors rather than to improved diagnosis. The change in rates among Japanese immigrants to the United States may thus partly reflect an increasing availability and acceptance of more intensive medical care by them and their descendants.

The changes in medical practice, which seem dramatic in modern Japan, are also present to varying degrees in the United States and other western countries. With increasing governmental-supported health services, the elderly are seeking and obtaining more intensive care and more specific diagnoses. It is quite possible that the apparent increase in cancer in recent years is instead a reflection of the increased utilization of health-care facilities by the elderly. As cancer is largely a problem of the elderly, it may help to follow cohorts and examine the age-specific rates in an effort to distinguish changes, which may be a reflection of environmental effects from those associated with improving diagnosis. The reduced stigma of cancer, which was so intense a few decades ago, the effect of better education, and the free discussion of cancer in public can be expected to improve the reporting of cancer in morbidity and mortality surveys. In the past, when an elderly patient, whose medical needs had gone largely unattended, died, "senility," "carcinomatosis," or some other vague term was frequently certified as the cause of death. In recent decades, the proportion of such certifications has decreased, thus adding to the number of cancers in general, as well as to some specific forms.

"Stomach" cancer has traditionally been regarded as the common abdominal cancer of adults, and the failure to distinguish "belly" from "stomach" or to localize the primary site specifically could conceivably have influenced the accuracy of diagnosis and death certification. In many countries, the colon cancer rate has risen as the stomach cancer rate has declined. Also, western countries, in recent decades, have shown higher rates for colon than for stomach cancer, whereas it is the reverse in many developing countries. It is conceivable that the geographic pattern and secular trends for colon and stomach cancer may be explained, in part, by semantics, as well as improving diagnosis of the less common abdominal cancers such as those of the pancreas.

### *Methods of Study*

Virtually all epidemiologic investigations are observational. For practical and ethical reasons it is impossible to have the ultimate design when studying disease in man. One cannot randomly allocate a potential carcinogen to an experimental group. Thus, the major chore of the epidemiologist is often to make the best use of available observational data.

Epidemiologic studies may be classified into three general categories, two of which—descriptive and analytic epidemiology—are primarily observational and reasonable to apply, whereas the third—experimental epidemiology—is generally avoided for ethical reasons (Lilienfeld *et al.*, 1967). An experimental situation may be simulated if one is fortunate enough to recognize a "natural experiment"—some circumstance for which exposure or nonexposure to a suspected carcinogen may be documented as having occurred in a specified population or in some random manner.

*Descriptive Epidemiology* Here one may use a variety of data sources on the occurrence of cancer, including mortality rates by state or nation and tumor registry data representing a defined population [e.g., Connecticut and other states, Scandinavian countries, or the SEER (Surveillance, Epidemiology and End Results) program]. The registries provide annual incidence rates—i.e., the number of new cases of cancer for a given site per 100,000 population. The rates can be specified by age, sex, time period, or other characteristics.

Official mortality resources provide annual death rates or the number per 100,000 per year by cancer site. Death certificate data are available for large parts of the globe, often over a period of years or even decades. For the period 1950–1969, mortality rates for major cancer sites are now available by state and for every county in the United States by sex and race (Mason *et al.*, 1975, 1976). Although mortality rates are a valuable resource, their limitations must be kept in mind. First, they reveal cancer deaths only and reflect incidence rates most accurately for malignancies with very high case fatality ratios. Also, they are more remote in time from the date of onset (to which incidence rates apply) and, therefore, may be less useful in the effort to identify preceding etiologic risk factors.

In many parts of the world, a cancer research worker may have available only a series of cases or deaths observed at a hospital. There is no information regarding the population at risk with which to estimate incidence; this information may be of limited usefulness by calling attention to the existence of the illness in that population or by measuring the population of hospitalizations or deaths due to that form of cancer in comparison with that of all hospitalizations or deaths. This provides an estimate of relative frequency and is often the only type of information available from certain areas. If differences are truly profound, such as the high proportion of esophageal and liver cancers and the low proportion of colon cancer in some African populations, they may provide useful leads in the identification of possible etiologic factors in the environment (Mulligon, 1970; Bradshaw and Schonland, 1974; Burkitt, 1971).

Similarly, case reports of an unusual concentration of a rare form of malignancy may arouse suspicion of a new or previously unsuspected etiologic agent. The relationship between vinyl chloride and angiosarcoma of the liver and *in utero* exposure to diethylstilbestrol (DES) and clear-cell adenocarcinoma of the vagina are examples of the importance of published case studies related to the effect of changes in the environment.

*Analytic Epidemiology* Analytical epidemiologic studies are designed either to examine many associations in order to generate etiologic leads or to test specific hypotheses of disease causation. There are two types of study design—the prospective cohort investigation and the retrospective case control study.

In prospective cohort studies, a group (i.e., cohort) of individuals exposed to suspected risk factor are followed and the occurrence of cancer is noted. The rate of occurrence is compared with that in a nonexposed control group or with the known rates of occurrence of cancer in the general population. Although a prospective study may be desired to see whether cancer does result in a group exposed to a suspected risk factor; such studies are rarely feasible because of the ethical considerations and because of the considerable period of follow-up that would be necessary. However, it is often impossible to identify a retrospective cohort for prospective studies, i.e., a group of individuals who were exposed in the past who can then be followed to determine the occurrence of a subsequent disease. If the incidence rates or mortality rates of the population are known, it may not be necessary to have a specified control group. In this situation one can apply the known incidence or mortality rates to the cohort under study and devise an expected number of cancer cases that would have occurred if the experience of the cohort with respect to the disease was the same as in the general population. Lanier *et al.* (1973) identified a large group of pregnancies in Rochester, Minnesota, in which DES had been administered and proceeded to check the daughters of these women. Although in that study no increased incidence of vaginal cancer was observed, those children had an increased incidence of benign vaginal epithelial changes referred to as adenosis. The exact relationship of adenosis to eventual development of vaginal cancer is unknown. Another example is an investigation of a cohort of asbestos workers by Selikoff *et al.* (1968). In that study, a retrospective cohort of asbestos workers were found to have considerably higher rates of lung cancer than the general population. There was a strong interaction with cigarette smoking, as the asbestos workers who smoked were at extremely high risk of developing lung cancer. Lower, but significantly elevated rates, of gastrointestinal cancer were also found in the asbestos workers.

Another type of design is that of the case-control study. Here one selects a series of cases of a disease and a series of controls, usually individuals of the same age and sex who come from the same population as the cases. One then determines exposure to factors of interest in both groups. The relative risk of exposed individuals can be estimated by the odds ratio. That is the product of the exposed cases and nonexposed controls divided by the product of the exposed controls and nonexposed cases. This method has commonly been used in cancer epidemiology over the past 25 years to establish such relationships as that between breast cancer and parity and bladder cancer among dye workers.

There are two major difficulties with the case-control approach. First, the choice of suitable controls is difficult but essential. (Ideally, one should have a random sample of persons from the population at risk matched by age and sex.) In some cases one may wish to match for other variables such as race or socioeconomic status. The process of matching is designed to ensure comparability of cases and controls and eliminate "spurious" associations with factors that are not related to etiology. Since control groups often are difficult to select from the population at large, they may be chosen from other hospitalized patients or persons in the community with a given disease. The problems of hospitalized controls are essentially that they are not representative of the general population and that the antecedents to their disease processes may relate to the risk factors in some confounding manner. Two or more such control groups may be selected so that comparisons with each other can help to determine whether they are likely to be appropriate for comparison with the cohort of cases.

A second problem is that there may be differences in recall between cases and controls regarding past exposure. This may be due to selective recall on the part of patients or some previous knowledge of a possible association on the part of the cases or the controls or simply diminishing recall over time.

The retrospective case-control method has definite advantages in that studies can be done more quickly and cheaply than prospective studies, but one must weigh the advantages and disadvantages.

It should be clear that there is no simple and generally no single mechanism for epidemiologic studies of cancer. The results of any single study, even though dramatic in its etiologic implication, must lead to investigations in other populations or with other techniques. Concordant results can enhance the impression of disease association with the suspected risk factor; lack of agreement may lead to the rejection of the proposed association.

## SOME OBSERVATIONS ON THE EPIDEMIOLOGY OF COLORECTAL CANCER

(James E. Enstrom)

There are large differences between countries in the incidence of colorectal (colon and rectal) cancer (Figures 27 and 28). These differences have led to a great deal of epidemiological research on colorectal cancer, which has produced a number of etiologic hypotheses. These hypotheses are environmental (dietary) rather than genetic, because when people from low-risk countries move to high-risk countries, for example, when Japanese migrate to Hawaii and the U.S. mainland, their bowel-cancer rates rise to the level of that of the inhabitants of the host country. Currently, the two most-favored explanations relate increased rates of the disease to (1) increased beef and/or fat consumption and (2) decreased intake of fiber.

### *Beef and Fat Hypothesis*

Wynder and Reddy (1975), Hill (1974), Berg and Howell (1974), and others have stressed the relation of fat and/or beef intake with bowel cancer, particularly colon cancer. This hypothesis is based largely on correlations that show that incidence and mortality rates for colorectal cancer are low in parts of the world with a low-fat, low-beef diet, such as Africa and Japan, and are high in westernized countries with a high-fat, high-beef diet, such as the United States, Canada, and parts of Europe. Also, a study of Hawaiian Japanese (Haenszel *et al.*, 1973) showed a significant difference in beef consumption between colorectal cancer cases and controls and suggested that the risk of colorectal cancer was about 2.5 times as high for those who ate beef frequently as for those who did not, thereby providing some direct evidence on individuals to support the geographical observations. The fat and beef relationships must be considered as independent hypotheses at present; however, beef provides about 20 percent of the animal fat in the American diet.

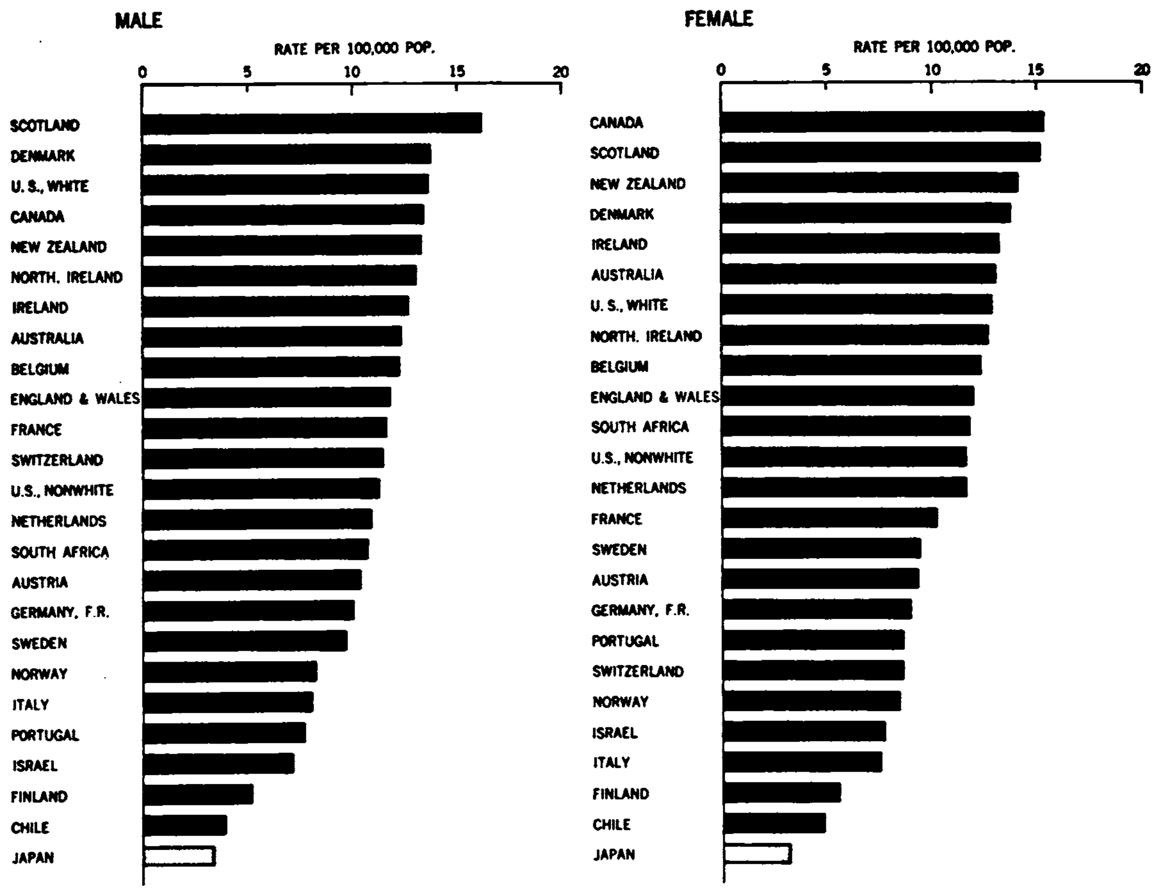


FIGURE 27 International comparison of 1964–1965 age-adjusted colon cancer mortality rates (Segi *et al.*, 1969). (Lighter shading was used for Japan because figure was originally published there.)
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*Fiber Hypothesis*

Burkitt (1975) and others have argued that the prolonged retention of feces in the intestine, resulting from intake of mainly refined carbohydrates, might account for the anatomical distribution of cancer in the colon as well as for its geographical distribution. Dietary fiber has been shown to regulate the speed of transit, bulk, and consistency of stools and together with other dietary factors is probably also responsible for the geographical differences in the bacterial flora of feces (Hill, 1974). It is suggested that carcinogens are produced by the *abnormal* bacterial flora in persons on a western diet, and they are then held for a prolonged period in contact with the bowel mucosa. However, the world distribution of colonic cancer correlates best with high intakes of dietary fat and protein together with other indices of affluence, and poorly, if at all, with dietary fiber. In particular, the pastoral tribes of East Africa, especially Kenya, eat an essentially fiberless diet, and, although accurate data are not available, colon cancer appears to be rare among these people. It has also been shown that Hawaiian Japanese have a much shorter bowel transit time than Hawaiian whites, yet these two groups have very similar colon-cancer incidence rates (Glober *et al.*, 1974).

In this paper, U.S. figures on colorectal cancer rates and *per capita* beef and fat consumption are examined in a variety of ways and shown to give no support to the beef/fat hypothesis. However, the cancer rates are shown to correlate well with *per capita* beer consumption.

These observations on dietary factors that may be causally connected with cancer of the colon and rectum do not appear to relate directly to geochemical environment. They do, however, illustrate a type of epidemiologic approach that should be quite useful in studies to determine relationships between the geochemical environment and cancer.

*Materials and Methods*

The materials for this analysis consist of food- and beer-consumption data and colorectal cancer morbidity and mortality rates. U.S. *per capita* food-consumption data are based on U.S. Department of Agriculture statistics for annual U.S. consumption of beef and fat, on their household

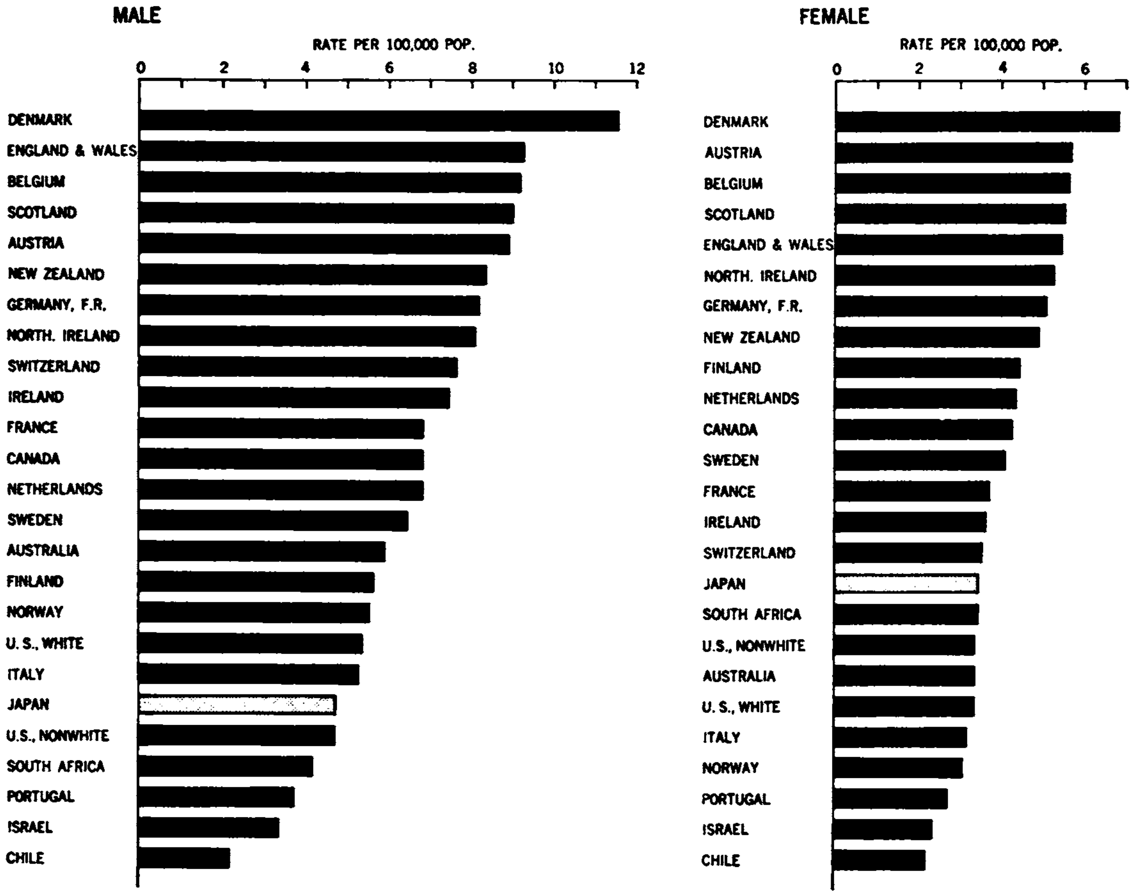


FIGURE 28 International comparison of 1964–1965 age-adjusted rectal cancer mortality rates (Segi *et al.*, 1969). (Lighter shading was used for Japan because figure was originally published there.)
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food-consumption surveys conducted on a small sample of the noninstitutionalized U.S. population over the past 40 years and on estimated *per capita* food consumption by state (Agricultural Research Service, 1956, 1966). In this paper, animal-fat consumption is defined to be the combined fat content in beef, pork, poultry, fish, eggs, milk, butter, margarine, and cheese. These items contain about 80 percent of the animal fat and about 60 percent of the total fat in the American diet. Other meats, oils, and lard are the components of animal fat not included here.

The U.S. cancer-incidence data were collected by the National Cancer Institute in a 1947 survey of ten cities and a 1969–1971 survey of nine metropolitan areas covering samples of about 4 percent and 10 percent of the U.S. population, respectively (Cutler, 1973). The regions covered in the two surveys overlap only in part, and neither survey attempted to cover a representative sample of the total population. Annual mortality data for the United States is collected and analyzed by the National Center for Health Statistics and the National Cancer Institute (Burbank, 1971; Lilienfeld *et al.*, 1972).

All incidence and mortality rates are age-adjusted to the 1950 U.S. population. Data are presented for colon and rectal cancer rates, sometimes separately, at other times combined. The poor definition of the colon–rectal junction makes analysis of separate colon- and rectal-cancer time trends somewhat unreliable (Berg and Howell, 1974). Given this inaccuracy, comparisons are probably most meaningful for colon- and rectal-cancer rates combined. Colon and rectal cancer may have different etiologies (Wynder and Shigematsu, 1967), but their mortality rates are highly correlated (correlation coefficient, $r \sim 0.9$) both between countries and between states of the United States, and no compelling reasons have been put forth concerning why these two parts of the intestines should have greatly different etiologies.

### *Results*

*Geographical Differences* The correlation coefficient between the 1950–1967 age-adjusted colorectal-cancer mortality rates (Burbank, 1971) and the estimated 1965 *per capita* beef consumption (Agricultural Research Service, 1966) in the 48 contiguous states of the United

States, excluding the District of Columbia, is about $r = 0.3$ (Enstrom, 1975, 1977). Approximately the same coefficient is obtained for animal-fat consumption. The proportion of the variance of mortality between states for which each correlate could account, is thus only about 10 percent. The correlations for colon and rectal cancer for whites and nonwhites, analyzed separately, vary by less than $\pm 0.1$ from the overall figures.

The reason that these correlations are positive at all is that colorectal cancer rates and beef and animal-fat consumption are uniformly low in the South. If Alabama, Arkansas, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, and Tennessee are eliminated, then the colorectal cancer correlations in the remaining 40 contiguous states are $r = -0.1$ for beef and $r = 0.1$ for animal fat. If the entire South, as defined by the Bureau of the Census, is eliminated, then the colorectal cancer correlations in the remaining 32 states are negative both for beef ($r = -0.5$) and for animal fat ($r = -0.1$). Data available for the four regions of West, South, North Central, and Northeast shows that total fat consumption throughout these regions is the same to within 5 percent, being the highest in the South and the lowest in the Northeast (Agricultural Research Service, 1956, 1966). However, in the South the colorectal cancer rate is 25 percent lower and in the Northeast it is 25 percent higher than the national average (Lilienfeld *et al.*, 1972).

The correlation between the 1950–1967 age-adjusted colorectal-cancer mortality rates (Burbank, 1971) and the 1960 *per capita* consumption of beer (Brewers Association, 1972) is, however, much larger ($r = 0.7$) for the 47 contiguous states of the United States, excluding Nevada and the District of Columbia (Breslow and Enstrom, 1974; Enstrom, 1977). (Nevada and the District of Columbia have been excluded because of heavy alcohol consumption by transient nonresidents.) The largest single correlation is between beer consumption and white male rectal cancer, where $r = 0.81$.

Correlations have also been calculated with the average cumulative beer consumption from 1941 to 1960. (The correlation coefficient between the cumulative average and the 1960 consumption is very high, $r = 0.97$.) In almost all cases these new correlations are increased in relation to their values obtained with the 1960 data alone. The maximum correlation coefficient is again obtained with white male rectal-cancer mortality ($r = 0.87$); a scattergram showing this relation is given in Figure 29.

*Secular Trends* Figure 30 compares changes in the colorectal-cancer rates in the United States with changes in beef consumption for the period 1940–1970 (Enstrom, 1975). Whereas *per capita* beef consumption has more than doubled over the 30 years (Agricultural Research Service, 1956, 1966), the age-adjusted colorectal cancer-mortality rate decreased from 21 to 19 per 100,000 during the same time period (Dorn and Cutler, 1959; Lilienfeld *et al.*, 1972). For colon cancer, the white mortality rates have remained constant and the nonwhite rates have increased by about 50 percent; whereas for rectal cancer,

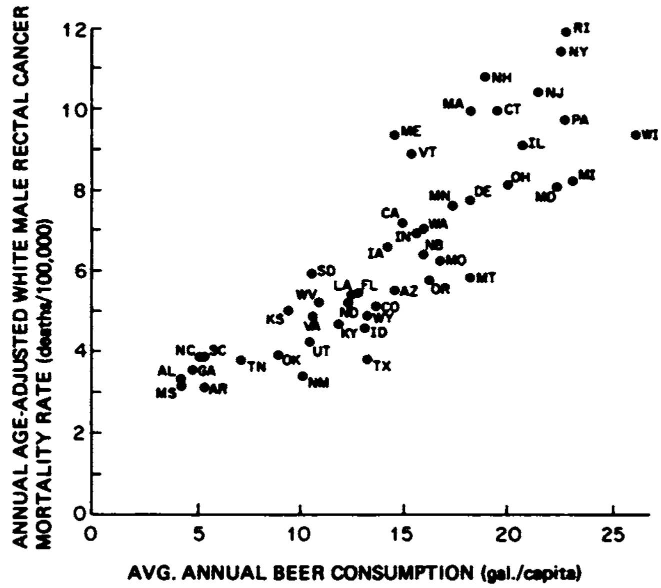


FIGURE 29 Scattergram showing relationship between 1941–1960 average annual *per capita* beer consumption and the 1950–1967 average annual age-adjusted mortality rate for white male rectal cancer in 47 states of the United States (Enstrom, 1977).

Reproduced from the *British Journal of Cancer*.

the white and nonwhite rates have both decreased by about 30 percent. A comparison of the national cancer-incidence surveys suggests that the age-adjusted colorectal cancer-incidence rate decreased from 44 to 39 per 100,000 from 1947 to 1970 (Cutler, 1973). Other compari-

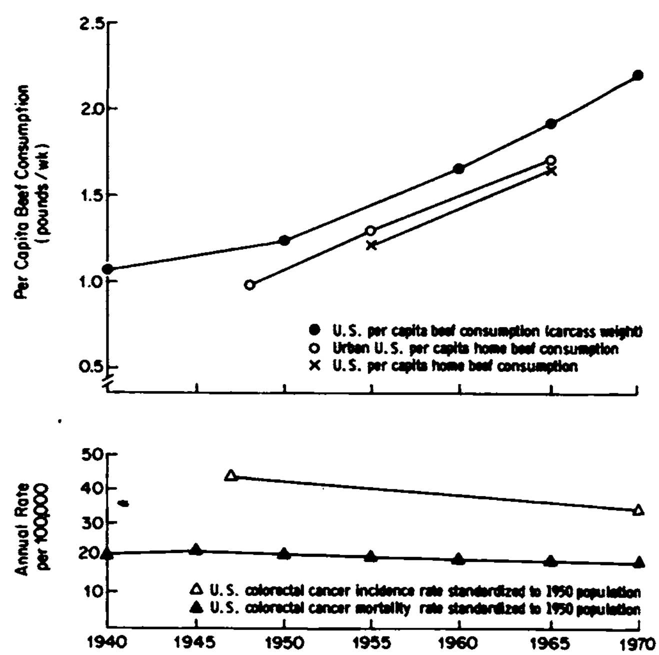


FIGURE 30 Secular trends in U.S. beef consumption and colorectal cancer rates (Enstrom, 1975).

Reproduced from the *British Journal of Cancer*.

sons over the 1947–1969 time period indicate that the colorectal cancer-incidence rate in different parts of the country has remained about constant. [Moreover, there was essentially no change in the survival rate for colorectal cancer from 1950 to 1970 (National Cancer Institute, 1972), so that incidence rates can essentially be considered to be about twice mortality rates.]

There has, however, been little change in *per capita* beer consumption over the period 1945–1960 (Brewers Association, 1972; Enstrom, 1977), in agreement with the lack of change in colorectal-cancer mortality rates during the period 1950–1967 (Figure 31). Between 1933 and 1945, there was a rapid rise in all alcoholic-beverage consumption based on taxed sales, reflecting the end of prohibition in 1933, but the increase in true consumption may not have been nearly so great (Department of Health, Education, and Welfare, 1971).

*Socioeconomic Gradients* Morbidity data from ten U.S. areas in 1947 show no significant gradient in incidence of colon or rectal cancer for whites or nonwhites when grouped by income level (Dorn and Cutler, 1959); and 1960 U.S. mortality data show a slight negative association between colorectal cancer and educational level for adult (25+ years) whites (Lilienfeld *et al.*, 1972; Kitagawa and Hauser, 1973; Enstrom, 1975). The 1950 U.S. mortality data for middle-aged (20–64 years) whites show a slight positive gradient for colon cancer and a slight negative gradient for rectal cancer and no gradient for colorectal cancer when plotted against increasing occupation levels (Guralnick, 1963).

These near-zero gradients for colorectal-cancer rates are in sharp contrast to the steadily increasing beef consumption with increasing income shown in Figure 32 (Agricultural Research Service, 1956, 1966; Enstrom, 1975). They are in somewhat better agreement with the

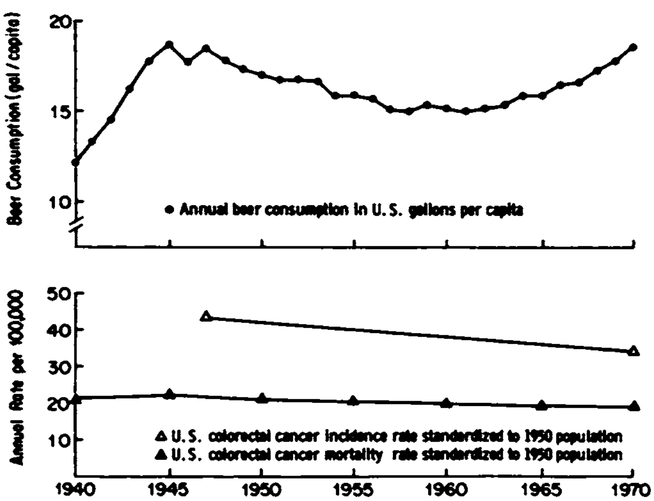


FIGURE 31 Secular trends in U.S. beer consumption and colorectal cancer rates (Enstrom, 1977).
Reproduced from the *British Journal of Cancer*.

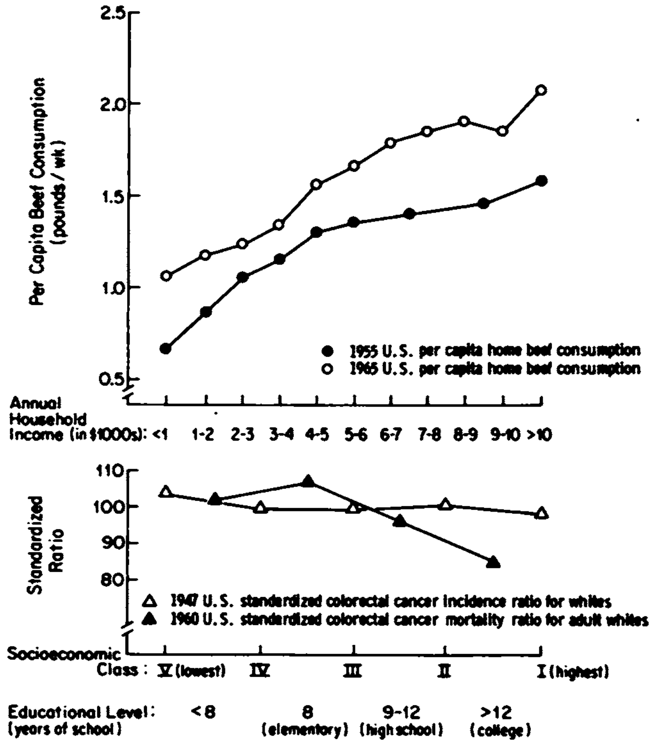


FIGURE 32 U.S. beef consumption and colorectal cancer rates as a function of socioeconomic status (Enstrom, 1975).
Reproduced from the *British Journal of Cancer*.

data on beer consumption shown in Figure 33 (Agricultural Research Service, 1966; Enstrom, 1977). Aligning the socioeconomic level of the food/alcohol consumption surveys to the cancer-rate data is clearly unsatisfactory, and more data on cancer rates by socioeconomic level are needed.

*Urban–Rural Differences*

A substantial urban–rural difference exists in colorectal cancer rates. The ratio of 1959–1961 age-adjusted colorectal cancer death rates for U.S. urban to rural counties was 1.4 (Lilienfeld *et al.*, 1972). For colon cancer, the ratio was 1.3 for whites and 1.5 for nonwhites; and for rectal cancer, 1.4 for whites and 1.7 for nonwhites. The 1955 and 1965 food-consumption surveys, however, showed that the urban-to-rural ratio for *per capita* beef and animal-fat consumption was almost exactly 1.0 (Agricultural Research Service, 1956, 1966; Enstrom, 1975), whereas the ratio was 1.7 for *per capita* beer consumption (Enstrom, 1977).

*Sex Ratios*

There is a strong correlation between the ratio of white male to white female 1950–1967 colorectal-cancer mortality rates (Burbank, 1971) and 1960 *per capita* beer consumption (Brewers Association, 1972) for the same 47 states previously mentioned under Geographical Dif-

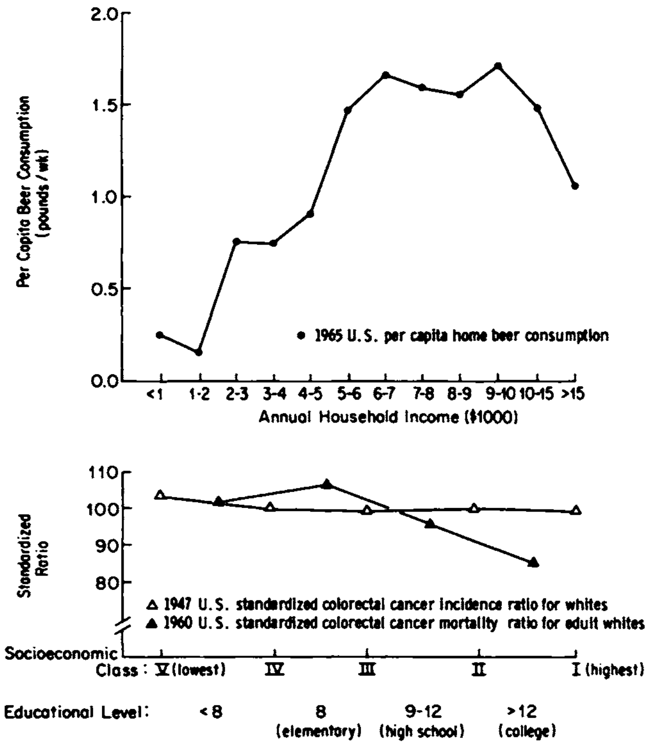


FIGURE 33 U.S. beer consumption and colorectal cancer rates as a function of socioeconomic status (Enstrom, 1977). Reproduced from the *British Journal of Cancer.*

ferences (Enstrom, 1977). The correlation coefficients are as follows: for rectal cancer, $r = 0.77$; for colon cancer, $r = 0.56$; and for colorectal cancer, $r = 0.73$. The correlations are even stronger when 1941–1960 average cumulative beer consumption data are used. The maximum correlation is obtained for rectal cancer ($r = 0.82$); a scattergram showing this relation is given in Figure 34. These sex-ratio correlations are consistent with heavier beer consumption among men compared with women, as shown in U.S. surveys (Department of Health, Education, and Welfare, 1971). For example, for rectal cancer in the areas with very little beer consumption, the ratio becomes essentially 1, but for heavy beer consumption regions, the ratio approaches 2. This relation is only suggestive, because precise figures on beer consumption by sex throughout the country are not available.

### *Discussion*

A review of the secular trends since 1940 shows that *per capita* beef consumption in the United States has risen significantly. If beef consumption has a substantial effect on colorectal cancer and it takes approximately 20 years for the disease to develop, then the incidence and mortality rates should have increased. They have, on the contrary, declined substantially for both white and nonwhite rectal cancer, remained constant for white colon cancer, and increased only for nonwhite colon cancer. There has always been a pronounced socioeconomic gradient in U.S. beef consumption, which is not present in available colon or rectal cancer-rate data for whites or nonwhites; and there is an urban–rural ratio in colon and rectal cancer rates, which is not present in beef or fat consumption. In addition, there is no significant correlation between *per capita* beef and fat consumption and colorectal cancer-mortality rates in the United States either regionally or on a state-by-state basis.

In addition to these gross observations (Enstrom, 1975), case-control studies in the United States (Higginson, 1966; Wynder and Shigematsu, 1967) and in Finland (Pernu, 1960) have shown no increased beef-fat consumption or socioeconomic gradient in colon- and rectal-cancer patients compared with controls. Similarly, a Norwegian study (Bjelke, 1971) showed no case-control differences in meat or dietary fat consumption or other aspects of diet. A study among native Japanese (Wynder *et al.*, 1969) showed a possible relation with milk but none with meat, eggs, or other fat. The Hawaiian Japanese study (Haenszel *et al.*, 1973) is the only one showing any significant relation of beef to colorectal cancer, and it did not show a dose–response relation. This study also found that Hawaiian Japanese actually have fairly low beef consumption: only 25 percent of the cases and 18 percent of the controls ate beef at least 16 times a month. This rate of consumption contrasts with that in Kansas City, where

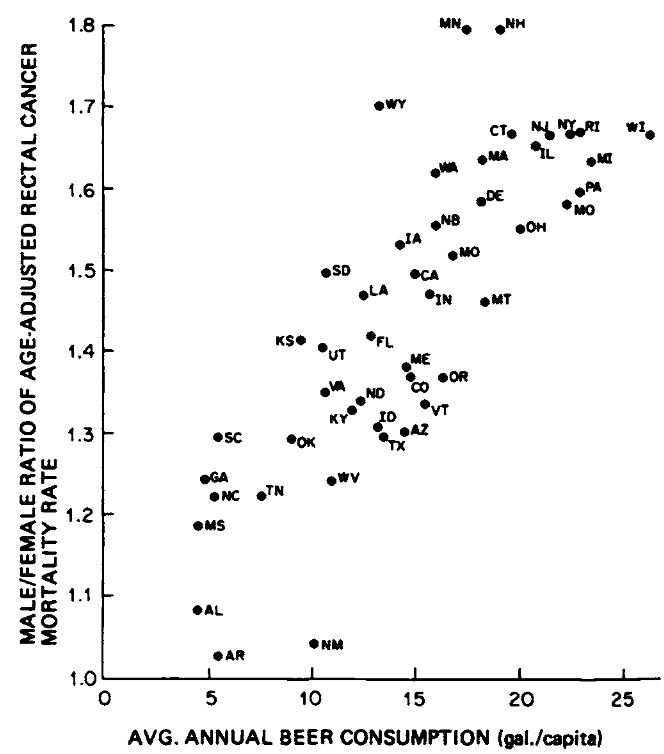


FIGURE 34 Scattergram showing relationship between 1941–1960 average annual *per capita* beer consumption and white male-to-female ratio of 1950–1967 average annual age-adjusted mortality rates for rectal cancer in 47 states of the United States (Enstrom, 1977).
Reproduced from the *British Journal of Cancer.*

Higginson (1966) found that 52 percent of the cases and 56 percent of the controls ate beef at least daily. Yet the colon- and rectal-cancer incidence and mortality rates (Burbank, 1971; Doll *et al.*, 1970) for Hawaiian Japanese are the same as the respective rates for Hawaiian whites and Kansas whites.

All these observations appear to contradict the suggestions that beef and fat consumption may largely explain colorectal cancer, particularly colon cancer (Haenszel *et al.*, 1973; Berg and Howell, 1974; Wynder and Reddy, 1975).

U.S. data showing an association between beer drinking and colorectal cancer have been given (Enstrom, 1977); international comparisons also show a similar strong positive association (Breslow and Enstrom, 1974). Experiments on animals, however, are largely inconclusive, and epidemiological studies on individuals have produced inconsistent results. Wynder and Shigematsu (1967) showed a significantly higher proportion of beer drinkers in the male colon and rectal groups (31 and 35 percent, respectively) compared with 19 percent in one control group, but there were no significant differences from another control group. In a case-control study, Stocks (1957) showed a significant association of increased beer drinking with intestinal cancer in British males. In addition, Bjelke (Breslow and Enstrom, 1974), in a prospective study of Norwegian men, found a relative risk of 2.7 for colorectal cancer among men who drank beer six or more times per month compared with men who drank beer less than three times per month. However, his earlier retrospective study (Bjelke, 1971) showed no differences in beer consumption. Other studies have produced equally conflicting and confusing results. A detailed discussion of these findings is given in Enstrom (1977).

If beer drinking is causally related to colorectal cancer, one possible mechanism is through carcinogenic agents in the form of geochemical contaminants in the beer. However, before any conclusions can be drawn regarding beer or any other factors, much further work is needed on the epidemiology of this disease.

## THE ETIOLOGY OF GASTRIC CANCER

(Pelayo Correa, William Haenszel, and Carlos Cuello)

The etiology of gastric cancer has been intensively studied by many investigators for many years, and several in-depth reviews are available (Barrett, 1946; Doll, 1956; Haenszel, 1958; Wynder *et al.*, 1963; Boyd *et al.*, 1964). This paper summarizes the etiology of gastric cancer in 1964 and reviews progress that has been made in the last dozen years.

### *Facts about the Epidemiology of Gastric Cancer*

The epidemiology of gastric cancer in 1964 was characterized by:

- A marked intercountry variation in mortality rates, with rates in the high-risk countries being approximately five times greater than those in the low-risk countries. Japan has always been first in gastric-cancer mortality, followed closely by Chile, Costa Rica, Iceland, Finland, and Poland. The U.S. white population has always shown the lowest rate, with Australia and New Zealand as a close second.
- Marked variations in mortality rates were found for different regions within several countries, in general showing that the northern and colder regions have a higher rate. In Yugoslavia, the mountainous region of the interior displayed a markedly higher rate than the coastal area.
- The sex ratio of the mortality rates showed little variation, the female rate being 50–67 percent of the male rate.
- A marked socioeconomic gradient was well established; rates of lower classes were approximately two and one half times greater than those of the higher classes.
- No clear urban–rural differential was established.
- Migrants to the United States had higher rates than natives.
- The premalignant role of pernicious anemia was well established.
- No race was exempt from stomach cancer, and in all of them, groups could be identified with very high, and very low, rates.
- Also, mortality was declining. This was first noticed in the United States and then in several European countries.

### *Other Epidemiologic Evidence*

At the time that these facts were accepted, many other less well-defined pieces of epidemiologic evidence were the subject of discussion. Some of the most prominent were the following:

- The role of genetic predisposition was suggested by the clustering of the disease in families and by the known excess in subjects of blood group A. But the familial aggregation could have resulted from exposure to a similar environment, and the excess of blood group A was very small, the relative risk being around 1.2 in most studies.
- The role of precancerous conditions was the subject of debate. Several international authorities were of the opinion that chronic atrophic gastritis and intestinal metaplasia of the gastric mucosa were precancerous conditions.
- No occupation was found specifically associated with high gastric-cancer risk. Miners, fishermen, and agricultural workers were implicated in several studies. The belief was widely held that professions characterized by actual contact with the soil carried a higher risk.
- Some studies suggested that the composition of the soil was a determinant of gastric-cancer risk. Peaty soil and a high content of organic matter was blamed in Great

Britain; peat and sea-clay soils in The Netherlands; peaty, ill-drained alluvial and acidic soil in Japan. Trace elements were also under suspicion. In north Wales, an excess of chromium and a deficiency of nickel, vanadium, and lead in soil was found associated with high mortality rates. By contrast, in Devonshire nearly all the trace elements gave high mean values in the high-mortality area, with highly significant excesses of cobalt, nickel, and iron. When the soils of gardens of persons with gastric cancer were compared with controls, higher risks were associated with chromium, cobalt, and zinc (Stocks and Davies, 1960).

- Although not systematically explored, the countries with the highest rates have many volcanoes. This is the case for Japan, Chile, Costa Rica, and Iceland.
- Most epidemiologists were of the opinion that environmental factors involved would most probably be related to the diet. The findings of several studies of dietary habits related to gastric cancer are not easy to interpret. Rice was suspected in Japan, fried foods in north Wales, potatoes in Slovenia, grain products in Finland, spices in Java, smoked salmon and trout in Iceland. Some epidemiologists saw starchy foods as the common denominator of many studies. Haenszel (1958) noticed that the decline in gastric mortality in the United States was associated with a decrease in the consumption of cabbage and an increase in the consumption of lettuce and citrus fruits. He recognized the weakness of some of the studies at the time, which partly resulted from the design of the studies and also partly from dietary factors that might have been exerting their influence many years before being interpreted, as well as possibly inaccurate recall by the persons being studied. He proposed that dietary effects might be the result of the presence of a carcinogen in food, the introduction of carcinogens during food preparation, and/or the absence of protective factors in some foods.
- Although there were no well-structured etiologic hypotheses offered at the time, there was a general feeling of helplessness because an experimental model was lacking, and the glandular mucosa of the stomach of experimental animals resisted even the most potent carcinogens, such as methylcholanthrene.

### *Recent Accomplishments*

During the last dozen years, the following have been major accomplishments:

- New statistical material became available, especially incidence figures for selected cancer registry areas on five continents (Doll *et al.*, 1966; Waterhouse *et al.*, 1976).
- The natural experiment of massive human migration has been skillfully exploited to advance our knowledge of gastric cancer epidemiology (Haenszel and Segi, 1967).
- The histology of gastric carcinoma, previously considered homogeneous, was found to encompass at least two epidemiologic entities (Järvi, 1961; Laurén, 1965; Muñoz *et al.*, 1968).
- Studies combining epidemiology and pathology have brought considerable additional evidence on the role of premalignant lesions (Correa *et al.*, 1970).
- The fiber-optic gastroscope was developed and has become a popular instrument, making possible epidemiologic studies of earlier stages of neoplastic transformation of the gastric mucosa.
- Experimental models of gastric cancer have been developed (Sugimura *et al.*, 1970).

### *Significant Changes in Epidemiological Knowledge*

The following are ways in which the foregoing accomplishments have modified our knowledge of the epidemiology of gastric cancer.

*Variations between Countries* As expected, incidence figures have confirmed mortality figures for gastric cancer. The disease continues to show high lethality. The only improvement in this area has been the report of a very favorable survival rate in early carcinomas found by mass population screening in Japan (Kuroyanagi, 1968). Proximity to the equator, however, no longer seems to be a protective factor. Low-latitude cities, such as Bogota, Guatemala City, Cali, and Lima, reported high mortality rates (Puffer and Griffith, 1967). Subgroups of populations of Cali and Hawaii were also found to be at high risk (Correa *et al.*, 1970). The very high mortality rate in Costa Rica was confirmed (Strong *et al.*, 1967). In contrast, a low mortality rate was found for Mexico City (Puffer and Griffith, 1967).

*Regional Variations* New intercountry contrasts have been described. The Central Andean region was found to be at high risk, while the coasts of tropical America were areas at low risk. The excess is mainly the result of one histologic type, originally described by Järvi (1961) and Laurén (1965) in Finland, as the so-called *intestinal type*, which seems to correspond to the epidemic type. In Cali, Colombia, the incidence rate for this type is approximately seven times greater in immigrants from the mountains than in immigrants from the coast (Correa *et al.*, 1970).

*Sex Ratio* The male/female sex ratio for gastric cancer was shown by Griffith (1968) to be age-dependent. The ratio was around 1 for younger ages, climbed to values of 2 or more around age 55, and then declined to values between 1.3 and 1.7 after age 70. It was suggested that this peculiar pattern might reflect age-related patterns of food intake and calorie consumption, which could help to determine the ingested dose of a hypothetical food-borne carcinogen.

Another explanation based on the different age and sex-specific incidence of the two histologic types has been offered. At younger ages, the incidence of intestinal and diffuse type is similar or slightly greater for the diffuse type. Since the latter is relatively more frequent in females, the sex ratio in young ages is around 1. Around age 55 there is a considerably higher incidence rate for the intestinal type, which dominates the picture and shows its well-known male predominance. In the late years, the ratio tends to decline somewhat because the diffuse type, which is more predominant in females, shows a steady rise in incidence and the intestinal type shows a greater number of female survivors, because of their well-known advantage in prognosis (Correa *et al.*, 1973).

*Economic Status* The negative relation of socioeconomic gradient to cancer has persisted, and gradual improvement of the economic standards of many populations has been considered an explanation for the decline in cancer rates. The intestinal or epidemic type is declining much faster than the diffuse type (Muñoz and Asvall, 1971; Muñoz and Connally, 1971).

*Studies of Migrants* Migrant studies have provided one of the most important contributions to gastric-cancer epidemiology, namely, the finding that migrant populations carry the risk of the place where the individuals have spent the first years of life. It is not well known how long a person has to be in a high-risk area to develop a high risk. But it is suspected that the first decade of life is the most important (Correa *et al.*, 1976). This means that the search for etiologic factors should be concentrated in that age. First-generation migrants moving from an area of high risk to an area of low risk, keep their high frequency of intestinal-type carcinomas, the epidemic type. The second generation fails to develop most of the expected numbers of cancer of this type, and therefore a greater proportion of the diffuse type is found. This is the type that has the tendency to predominate in populations at low risk (Haenszel *et al.*, 1976).

*Genetic Factors* It has been shown that the excess of blood group A is only present in the endemic or diffuse type of tumors. This observation was originally made in Colombia (Correa, 1970) and later found to be true in Japanese and other populations (Correa *et al.*, 1973). No real evidence of genetic susceptibility has been found for the intestinal type of tumors.

*Precancerous Conditions* New evidence has accumulated to point to chronic atrophic gastritis and intestinal metaplasia as a precursor (Correa *et al.*, 1970, 1976). This is especially true for the intestinal type of tumors. The new endoscopic technology has allowed us to study populations at high and low risk for gastric cancer. Table 26 shows the results for several healthy populations of Colombia. The prevalence of atrophic gastritis with or without intestinal metaplasia is below 25 percent in the low-risk areas and close to 50 percent in the high-risk areas. The comparison between the inhabitants of the high-risk area of Nariño and the immigrants from Nariño to the low-risk area of Cali is interesting. It suggests that the prevalence of atrophic gastritis may diminish somewhat but that intestinal metaplasia is not affected by the migration.

*Nitrate* Hill *et al.* (1973) found a correlation between high nitrate ingestion and high gastric-cancer rates in England. Our studies of the high gastric-cancer area of Nariño, Colombia, have led us to delimit subregions with different risks to gastric cancer as estimated by the study of discharge diagnoses from the hospitals serving these populations. The map of Figure 35 shows areas A and B to have relatively higher risks than area C. The prevalence of intestinal metaplasia in the population was estimated by gastric biopsies and shows correlation with the gastric cancer risk (Table 27). The nitrate content of wells was found to be higher in the areas of higher risk, but the nitrate content of aqueducts was not different. The data suggest a positive correlation between nitrate ingestion, premalignant lesions, and gastric-cancer risk (Cuello *et al.*, 1976). Studies of urinary excretion of nitrates in towns with high and low risk (Table 28) show that the median values are higher in areas at high risk and lower in areas of low risk. The average, however, shows no difference. This is because there are individuals excreting high levels of nitrate in areas of low risk. High values of nitrate excretion have been found in areas of high risk in patients who are not being supplied by high nitrate wells, apparently indicating other sources (probably locally grown foods) of nitrate ingestion. Although much new work is needed before reaching a definitive conclusion, our re-

TABLE 26 Histologic Findings in Gastric Biopsies from Unselected Populations

| Area | Number | Cancer Risk | Normal (%) | Superficial Gastritis (%) | Atrophic Gastritis (%) | Intestinal Metaplasia (%) |
|---|---|---|---|---|---|---|
| Coast | 30 | Low | 70 | 16.7 | 6.7 | 6.7 |
| Cali natives | 57 | Low | 45.6 | 29.8 | 17.5 | 7.0 |
| Cali (Nariño immigrants) | 44 | High | 36.4 | 29.6 | 13.6 | 20.5 |
| Nariño | 463 | High | 29.8 | 22.2 | 30.0 | 17.9 |
| Cauca | 27 | High | 25.9 | 7.4 | 40.7 | 25.9 |

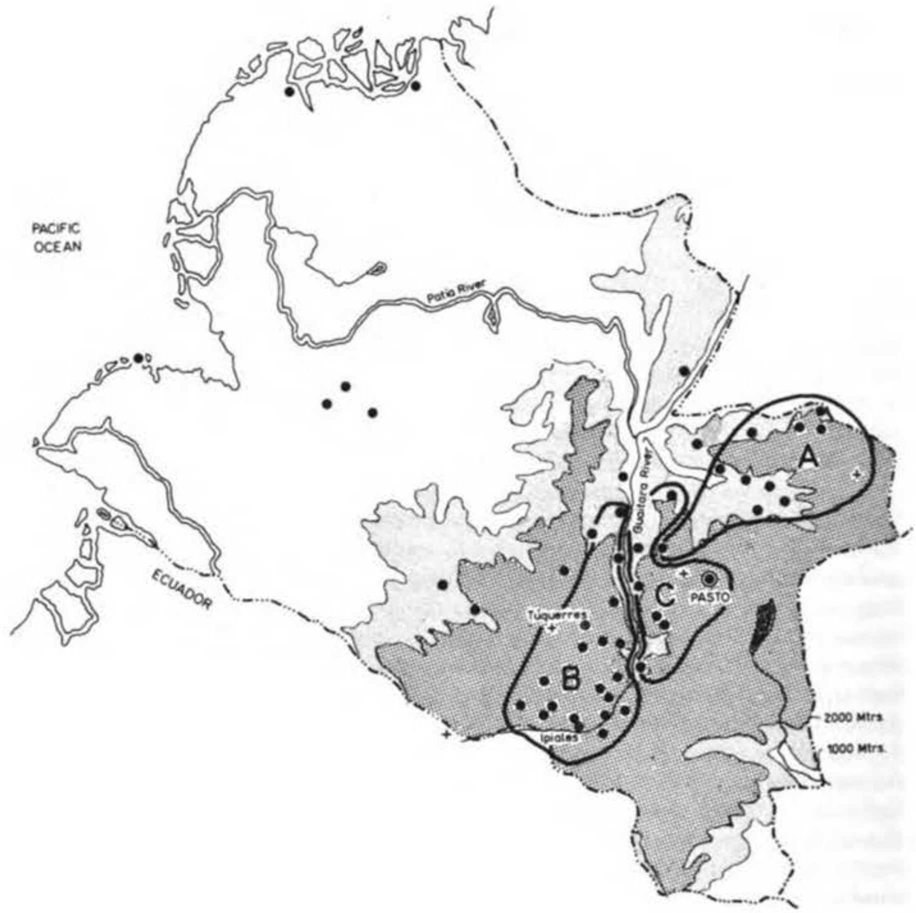


FIGURE 35 Map of Nariño, Colombia, showing areas of highest gastric cancer risk (A and B) and areas of relatively lower risk (C).

sults seem to indicate a general correlation between nitrate ingestion and the risk for gastric cancer and atrophic gastritis. We have found many individuals excreting high levels of urinary nitrate in low-risk areas, which is indicative to us that high nitrate ingestion alone cannot be held as capable of inducing the disease.

TABLE 27 Gastric Cancer Risk, Prevalence of Intestinal Metaplasia and Nitrate Content of Drinking Water in Four Areas of Nariño, Colombia

| Area | Population (Thousands) | Gastric Cancer Relative Risk[a] | Prevalence of Intestinal Metaplasia (%) | Average $NO_3^-$ (ppm) | |
|---|---|---|---|---|---|
| | | | | Wells | Aqueduct |
| A | 114 | 2.14 | 58.4 | 12.5 | 0.8 |
| B | 129 | 1.82 | 53.6 | 42.6 | 3.8 |
| C | 69 | 0.47 | 41.3 | 1.9 | 2.8 |
| D[b] | 215 | 0.58 | 25.9 | ? | ? |

[a]Relative risk of gastric cancer for all four areas combined is equal to 1.
[b]Pacific coast area where studies are less complete and less reliable (not identified on map).

*Diet* Dietary surveys have failed to find any food item associated with cancers that is common to all the high-risk areas of the world. In Japanese populations, salted dry fish and pickled vegetables carry a high relative risk (Haenszel *et al.*, 1972).

Dietary surveys have been conducted in patients with precancerous gastric lesions—chronic atrophic gastritis and intestinal metaplasia. Table 29 shows the proportion of patients with atrophic gastritis according to their dietary patterns. In the high-risk geographic area, the prevalence of atrophic gastritis in people is the same, regard-

TABLE 28 Concentration of Urinary Nitrates in Persons of Four Villages of Nariño, Colombia, by Gastric Cancer Relative Risk

| Town | Cancer Risk | Arithmetic Average $NO_3^-$ (ppm) | Median $NO_3^-$ (ppm) |
|---|---|---|---|
| Tambo | Low | 35.4 | 6.6 |
| Tangua | Low | 30.2 | 8.8 |
| Guaitarilla | High | 27.7 | 26.4 |
| Guachucal | High | 31.5 | 17.6 |

TABLE 29 Prevalence (in Percent) of Atrophic Gastritis in Nariño, Colombia, by Frequency of Use of Certain Foods

| | High-Risk Areas | | Low-Risk Area | |
|---|---|---|---|---|
| | Above-Average Use (%) | Below-Average Use (%) | Above-Average Use (%) | Below-Average Use (%) |
| Corn | 56 | 55 | 41 | 29 |
| Lettuce | 52 | 72 | 33 | 42 |
| Lima Beans | 57 | 51 | 35 | 29 |
| Moras | 58 | 45 | 38 | 20 |

less of whether their corn consumption is above or below average. In the low-risk area, however, above-average use of corn is associated with higher prevalence of gastritis (41 percent versus 29 percent). In both areas, higher lettuce ingestion is associated with a lower prevalence of gastritis (52 percent versus 72 percent and 33 percent versus 42 percent). Higher-than-average ingestion of lima beans and moras (local berries) correlates with an excessive prevalence of gastritis in both areas.

Table 30 illustrates the effect of different food combinations. When the ingestion of corn is high, there is practically no difference in the prevalence of gastritis between persons consuming high or low amounts of lettuce (53.8 percent versus 50.8 percent). If the amount of corn consumed is not excessive, the prevalence of gastritis in persons consuming higher than average amounts of lettuce is significantly lower (28 percent) than in those consuming lower than average amounts of lettuce (53 percent). This suggests a protective effect of lettuce, when the consumption of corn is not excessive. The prevalence of gastritis in persons consuming higher than average amounts of moras is higher than in those consuming lower amounts of the same fruit. In both situations, a higher-than-average consumption of lettuce is associated with lower prevalence of gastritis. Eating above-average amounts of corn and moras results in a higher prevalence of gastritis than in any other combination of the two foods, which suggests some synergistic effect. The protective role of lettuce and fresh vegetables has been found in previous studies (Haenszel, 1958). Weisburger (1975) has recently pointed out that ascorbic acid or refrigeration blocks the nitrosamine formation in stored food. It may be that lettuce inhibits the formation of some carcinogen. Or it may be that chronic atrophic gastritis and, by implication, cancer are deficiency diseases preventable by fresh green vegetables such as lettuce. Its inability, in the Colombian situation, to overcome the effects of high corn ingestion points to a crucial role of the combination of foods in the gastric microenvironment leading to cancer induction that should be further investigated.

TABLE 30 Combined Prevalence of Intestinal Metaplasia and Chronic Atrophic Gastritis (per 100 Individuals Examined) by Combinations of Level of Use of Corn, Lettuce, and Moras in Nariño, Colombia, 1973–1974

| | | Lettuce | |
|---|---|---|---|
| | | High | Low |
| Corn | High | 53.8 | 50.8 |
| | Low | 28.0 | 53.1 |
| | | Lettuce | |
| | | High | Low |
| Moras | High | 45.5 | 55.2 |
| | Low | 29.4 | 35.3 |
| | | Corn | |
| | | High | Low |
| Moras | High | 54.6 | 41.7 |
| | Low | 35.6 | 30.4 |

### *Results and Hypotheses*

In considering the result of these studies, it must be recognized that we are dealing with at least two epidemiologic entities. Cancer of the epidemic type is of most concern because it is the only type showing evidence of environmental influence. The continuing gradual decline in cancer rates obviously indicates that the epidemic type is preventable. The cancer itself is preceded by a chronic condition, which leads to atrophy of the mucosa, first seen in the body–antrum junction as multiple small foci, which are confluent and gradually extend over a large area of the mucosa. This change brings about a mutation in the gastric epithelium, which results in something similar to a chimera. The muscle of the stomach is covered by an intestinal type of mucosa. This ectopic epithelium gradually becomes more atypical and finally breaks the barriers of dependency and invades the submucosa and thence travels the rich lymphatic network eventually to produce the death of the host. Once this process has started, most probably in the first decade, there is no known way to reverse it, except perhaps by surgical ablation.

What initiates this process in childhood? We know so little about this, all we can do is speculate, based on a few isolated facts. For example, the stomach of a child in a high-risk area seems to be subjected to the following influences (Figure 36):

- Carcinogens. A series of mutations are most probably involved, and we tend to agree with Sugimura *et al.* (1970) that most carcinogens are mutagens.
- Abrasive foods. The child in our example is probably eating abrasive foods, such as hard-coated cereals and

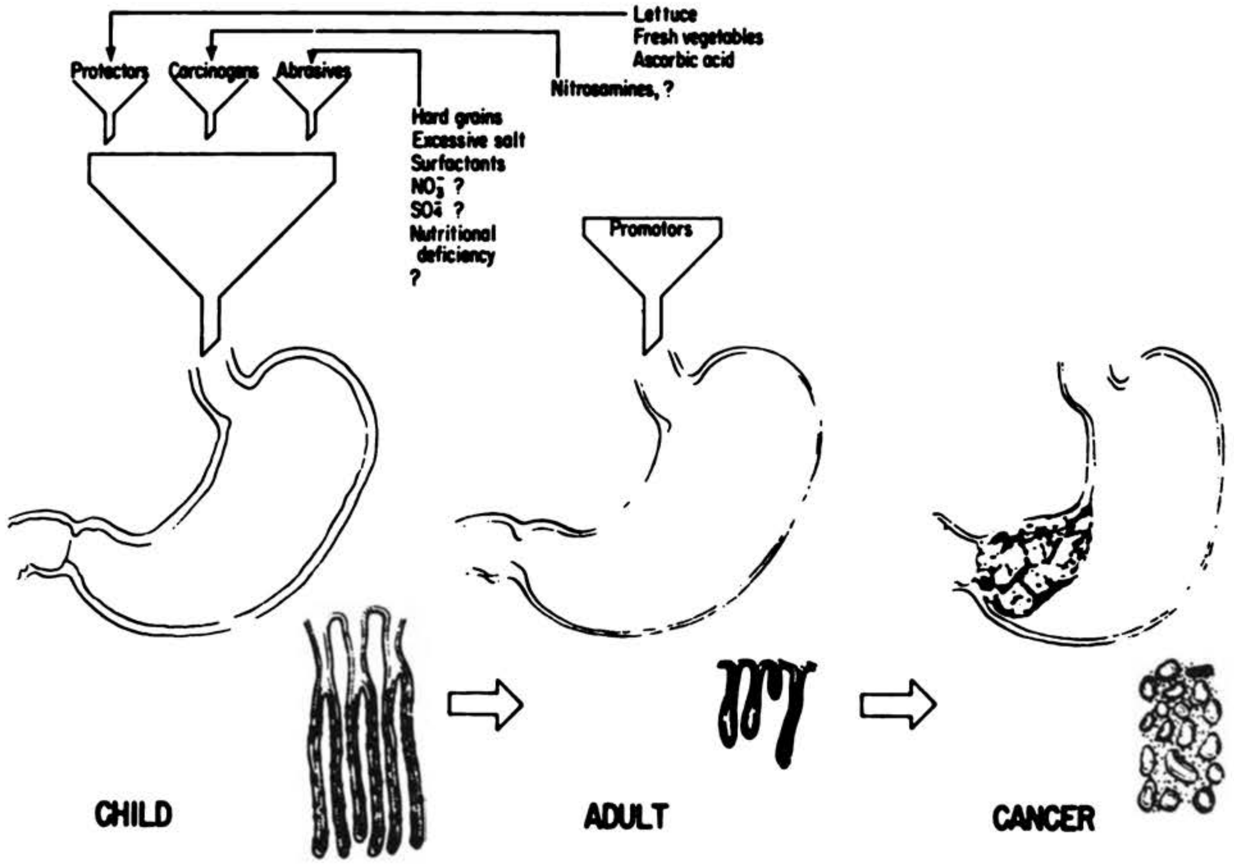


FIGURE 36 Diagrammatic representation of etiopathogenic model of gastric cancer. Gastric glands are shown below.

grains, like corn in some countries, or perhaps salty fish or pickled vegetables, in others. Other things may also act as abrasives with surfactant qualities, breaking down the mucus barrier. It is possible that acid radicals, such as the nitrates and sulfates, may exert their influence by thus producing superficial erosion in the mucosa.

• Insufficient protective food. Our child is probably getting insufficient quantities of protective foods, such as lettuce and other fresh vegetables. Such foods could be inhibitors of the synthesis of carcinogens; they might also be needed as nutrients for the integrity of the gastric mucosa, in which case a deficiency disease could be involved.

If the balance of the interaction of the three groups of factors tends toward production of chronic atrophic gastritis and intestinal metaplasia, the result is a population of high risk. A significant percentage of this population will eventually develop cancer of the stomach. Competing risks for other diseases may prevent more of them from showing the cancer. If so, two situations are possible: either there is a carcinogen in everybody's environment that is ineffective in the absence of a very abnormal gastric mucosa, or the process of metaplasia itself may have enough intrinsic energy to break the barrier of dependency without added stimuli. If the multiple-mutation hypothesis is accepted, the first alternative is more likely.

*Conclusions*

In the circumstances described, we are concerned with a disease that is mainly related to environmental factors. There is a consensus that diet is the determining factor. Because there is no incriminating food common to all countries, certain foods are probably acting as carriers of a carcinogen. The nature of the carcinogen is totally unknown, and it may respond differently in different populations. Nitrosamines are now being considered because they are found in the environment; are synthesized from nitrites and secondary amines in the soil, in food, or in the organism; and are used in the best animal models of the disease.

No specific element has proven to be carcinogenic with respect to the stomach. If geochemical elements were solely responsible for the current rates of stomach cancer in Japan, Costa Rica, Chile, or Iceland, rather high doses would have to be postulated. Such elements may, however, influence the microenvironment on the gastric cavity and thus favor the formation of a carcinogen.

The epidemiology of gastric cancer has advanced to the point where the collaborative efforts of laboratory workers are needed. If trace elements are involved, it should be possible to resolve the nature of their implication through the coordinated efforts of laboratory specialists and epidemiologists.

## SOME EFFECTS OF SELENIUM AND ZINC ON CANCER IN EXPERIMENTAL ANIMALS AND IN HUMANS

(Raymond J. Shamberger)

### *Selenium and Cancer*

Diets of torula yeast containing added sodium selenite significantly reduced the incidence of tumor in mice in three experiments (Shamberger, 1970; Harr *et al.*, 1972; Clayton and Baumann, 1949). The number of animals with skin tumors was reduced in the group treated with 7,12-dimethylbenz-γ-anthracene croton oil ($p < 0.05$) and the number of animals with benzo-γ-pyrene-induced skin tumors decreased ($p < 0.001$) (Shamberger, 1970). Harr *et al.* (1972) and Marshall *et al.* (1978) observed a significant reduction in liver tumors induced by the administration of *N*-2-fluorenylacetamide; Clayton and Baumann (1949) observed a reduction in the incidence of liver tumors induced by diethylaminoazobenzene. Griffin and Jacobs (1977) reported a decrease of liver tumors induced by 3[1]-methyl-4-dimethylaminoazobenzene. Schrauzer and Ishmael (1974) observed a lower incidence in spontaneous mammary tumors in $C_3H/St$ mice (a strain originated in 1920 by L. Strong) supplemented with 2 ppm of selenite in the drinking water for 15 months than in unsupplemented animals. Several significant reductions in tumor incidence by the topical administration of selenium have also been summarized (Shamberger, 1970; Riley, 1968).

At toxic levels, selenium is claimed to have caused some low-grade liver tumors in rats (Volgorev and Tscherkes, 1967; Nelson *et al.*, 1943). The experiments of Volgorev and Tscherkes (1967) had no controls, and those of Nelson *et al.* (1943) were poorly controlled. In a recent evaluation of the carcinogenicity of selenium by the World Health Organization (1975), Volgorev's experiment was considered invalid because of the lack of controls.

Jacobs *et al.* (1977) have observed a marked reduction in the number of colon tumors per animal and the total number of tumors induced by 1,2-dimethylhydrazine when 4 ppm of selenium (sodium selenite) was added to the drinking water. In a similar experiment, using methylazoxymethanol, 4 ppm was added to the drinking water; Jacobs noted a reduction in the total number of tumors per animal but not in the number of animals with tumors. This effect of selenium on colon tumors induced in animals is consistent with epidemiologic evidence showing substantially lower colon cancer death rates in the high-selenium areas of the United States (Shamberger *et al.*, 1976) and Canada (Shamberger *et al.*, 1974a) than in the low-selenium areas of the United States and Canada. Colon-cancer death rates per 100,000 males in the United States were 12.4 in the high-selenium areas versus 18.5 in the low-selenium areas. In Canada, the 1966 colon cancer death rate (males) was 11.6 in the high-selenium area and 18.4 in the low-selenium areas.

*Environmental Availability of Selenium* Kubota *et al.* (1967), after determining the selenium content of various forage crops, constructed a map of the United States showing the generalized regional distribution pattern of selenium in forage crops (Figure 22). The states were divided into three groups by Shamberger (1970): those containing 0.02–0.05 ppm, 0.05–0.09 ppm, and 0.1+ ppm or more of selenium in their forage crops. Alaska was not included in the study. The states and their selenium-in-forage classifications appear to be related to cancer deaths for U.S. white males age 55–64 per 100,000 population (Figure 37). The District of Columbia is included in the low-selenium group. The classifications and groupings of states in our studies are similar to those of Kubota *et al.*

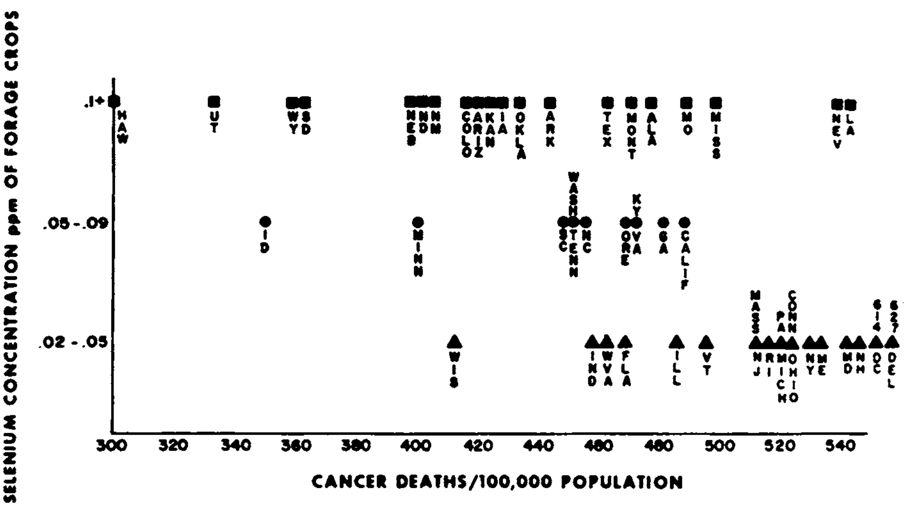


FIGURE 37 The 1968 age-specific cancer death rates for white males 55–64 years of age for states located in different regions of selenium occurrence (Shamberger *et al.*, 1976). For the District of Columbia and for Delaware the off-scale values were 614 and 627, respectively.

Reproduced from Archives of Environmental Health.

(1967), who had four categories of selenium concentration instead of three. In their lowest category there was only one state, so it was combined with the next lowest group. It is important to realize that the classification of mortality by state or political boundaries does not always correspond to the agricultural boundaries. The transitional states mostly appear in the intermediate classification. In some instances, the traditionally very high-selenium states (Colorado, Kansas, Nebraska, North Dakota, South Dakota, and Wyoming) were separated for comparative purposes.

*Human Cancer Mortality in Different Areas of Selenium Bioavailability* The 1968, 55–64 age-specific cancer death rate in the 19 high-selenium states (excluding Hawaii) was 429.9 ± 12.8 deaths per 100,000 (Table 31 and Figure 37). The differences between the high-, medium-, and low-selenium states are highly significant ($p < 0.001$). The six extremely high-selenium states (Colorado, Kansas, Nebraska, North Dakota, South Dakota, and Wyoming) showed the smallest age-specific cancer death rate (392.0 ± 11.6). The chi-square statistic using the U.S. average mortality of 484.0 is 28.08 ($p < 0.001$).

*Human Selenium Blood and Breast-Milk Levels* The selenium blood levels in 19 cities (Table 32) were reported by Allaway *et al.* (1968). In general, people in high-selenium areas had high blood selenium, whereas people in low-selenium areas had low blood selenium.

The correlation coefficient between the selenium blood content (Shamberger *et al.*, 1976) and the 35–74 age-specific death rate for 19 cities for males and females was −0.49 ($p < 0.05$; Table 32).

Because many foods are widely distributed throughout the United States, geographic variations in blood selenium levels may be difficult to explain. Although there may be a tendency for foods from high-selenium areas to contain more selenium, large amounts may also be absorbed from inhalation of dust. In addition, small amounts of selenium enter the atmosphere from biological processes within some plants. Dimethyldiselenide is a volatile product of *Astragalus racemosus* (Evans *et al.*, 1968), and volatile selenium is also released by such nonaccumulator plants as alfalfa. The amounts of selenium released are related to the amounts of volatile compounds within the plant (Lewis *et al.*, 1966).

Human breast milk contains greater selenium levels in the high-selenium areas than the low-selenium areas (Shearer and Hadjimarkos, 1975). This latter study confirms the study of Allaway *et al.* (1968), whose results were similar in that individuals in high-selenium areas tended to have high-blood-selenium levels.

TABLE 31 The 1968, 55–64 Age-Specific Cancer Death Rates for White Males in States Located in Regions of Selenium Occurrence. Standard Errors and Probability Are Indicated[a]

| No. of States | Selenium Level (ppm) | Cancer Death Rates/100,000 | Probability of Significance[b] |
|---|---|---|---|
| 6 | Very high 0.26+ | 392.0 ± 11.6 | $p < 0.001$ |
| 19[c] | High 0.10+ | 429.9 ± 12.8 | $p < 0.001$ |
| 11 | Medium 0.05–0.09 | 450.0 ± 12.2 | $p < 0.001$ |
| 19 | Low 0.02–0.05 | 516.0 ± 10.7 | — |

[a]Source: Shamberger *et al.* (1976).
[b]Each value was compared statistically to the low value with a Student *t* test (Lewis, 1966). The chi-square statistic (Lewis, 1966) using the U.S. average mortality of 484.0 and three degrees of freedom is 28.08 ($p < 0.001$).
[c]Also includes the six very high states. If the six states are excluded, the mean of the remaining 13 would be significantly different than the low ones. The probability of significance of both the *t* and the chi-square statistical tests would be $p < 0.001$.

TABLE 32 Selenium Concentration in Human Blood in the White Male and Female, 35–74, Age-Specific Cancer Death Rates (ICD 140–205)[a] in Various Metropolitan Statistical Areas, 1959–1961[b]

| City | County | State | Blood Se (μg/100 ml) | Cancer Deaths per 100,000[c] |
|---|---|---|---|---|
| Rapid City | Pennington | S.D. | 25.6 | 221.0 |
| Cheyenne | Laramie | Wyo. | 23.4 | 189.0 |
| Spokane | Spokane | Wash. | 23.0 | 229.6 |
| Fargo | Cass | N.D. | 21.7 | 220.0 |
| Little Rock | Pulaski | Ark. | 20.1 | 236.8 |
| Phoenix | Maricopa | Ariz. | 19.7 | 232.9 |
| Meridian | Lauderdale | Miss. | 19.5 | 225.4 |
| Missoula | Missoula | Mont. | 19.4 | 192.1 |
| El Paso | El Paso | Tex. | 19.2 | 229.8 |
| Jacksonville | Duval | Fla. | 18.8 | 280.6 |
| Red Bluff | Tehama | Calif. | 18.2 | 255.2 |
| Geneva | Cayuga | N.Y. | 18.2 | 271.0 |
| Billings | Yellowstone | Mont. | 18.0 | 257.1 |
| Montpelier | Washington | Vt. | 18.0 | 249.0 |
| Lubbock | Lubbock | Tex. | 17.8 | 198.3 |
| Lafayette | Tippecanoe | Ind. | 17.6 | 241.8 |
| Canandaigua | Ontario | N.Y. | 17.6 | 235.6 |
| Muncie | Delaware | Ind. | 15.8 | 243.5 |
| Lima | Allen | Ohio | 15.7 | 280.7 |

[a]ICD, International Classification of Diseases.
[b]The data have a correlation coefficient of $r = -0.49$ ($p < 0.05$).
[c]Unpublished data from Herbert I. Sauer, University of Missouri, Columbia, 1975.

*Environmental Selenium and Cancer Death Rates by Site and Sex* Age-adjusted cancer-death rates by body site and sex are presented in Table 33. For white males, significantly lower cancer-death rates from sites or types of cancer, such as tongue, esophagus, stomach, intestine, rectum, liver, pancreas, larynx, lung, kidney, bladder, Hodgkin's disease, and lymphoma, were observed in the high-selenium states than in the low-selenium states.

For white females, significantly lower cancer-death rates in the high-selenium states were observed at sites or types of cancer, such as esophagus, stomach, intestine, rectum, liver, pancreas, larynx, lung, bladder, thyroid, Hodgkin's disease, and lymphoma, than in the low-selenium states; breast and uterine (cervix, corpus, and ovarian) carcinoma were also lower in the high-selenium states.

TABLE 33 The Age-Adjusted Cancer Death Rate by Site and Sex in States Located in High-, Intermediate-, and Low-Selenium Areas (Shamberger *et al.*, 1976). Standard Errors Are Indicated

| | | Male | | | Female | | |
|---|---|---|---|---|---|---|---|
| Cancer Type | ICD[a] | High | Medium | Low | High | Medium | Low |
| Lip | 140 | 0.41 ± 0.017 | 0.38 ± 0.042 | 0.32 ± 0.023 | — | — | — |
| Salivary gland | 142 | 0.42 ± 0.019 | 0.40 ± 0.022 | 0.47 ± 0.021 | — | — | — |
| Nasopharynx | 146 | 0.35 ± 0.018 | 0.34 ± 0.030 | 0.34 ± 0.023 | 0.11 ± 0.012 | 0.11 ± 0.011 | 0.12 ± 0.0062 |
| Tongue | 148 | 3.27 ± 0.25 | 3.73 ± 0.39 | 5.20 ± 0.34 | 1.02 ± 0.083 | 1.29 ± 0.150 | 1.06 ± 0.040 |
| Esophagus | 150 | 2.63 ± 1.12 | 3.00 ± 0.28 | 4.73 ± 0.28 | 0.78 ± 0.052 | 1.07 ± 0.100 | 1.06 ± 0.035 |
| Stomach | 151 | 9.17 ± 1.43 | 12.72 ± 1.25 | 15.81 ± 0.63 | 7.13 ± 1.35 | 6.47 ± 1.55 | 8.00 ± 1.33 |
| Intestine | 153 | 12.39 ± 1.45 | 12.42 ± 0.81 | 18.50 ± 0.64 | 14.11 ± 0.62 | 15.36 ± 1.45 | 15.88 ± 0.76 |
| Rectum | 154 | 4.93 ± 0.26 | 5.17 ± 0.64 | 9.00 ± 0.43 | 3.73 ± 0.24 | 4.57 ± 0.69 | 4.62 ± 0.26 |
| Liver, biliary tree | 155 | 4.74 ± 0.15 | 4.41 ± 0.26 | 5.31 ± 0.13 | 4.91 ± 0.18 | 4.69 ± 0.44 | 5.49 ± 0.19 |
| Pancreas | 157 | 9.19 ± 0.20 | 9.35 ± 0.26 | 9.61 ± 0.14 | 5.47 ± 0.10 | 5.61 ± 0.13 | 5.99 ± 0.11 |
| Nose | 160 | 0.45 ± 0.02 | 0.44 ± 0.018 | 0.44 ± 0.018 | 0.23 ± 0.11 | 0.24 ± 0.015 | 0.21 ± 0.011 |
| Larynx | 161 | 1.85 ± 0.13 | 1.95 ± 0.20 | 2.95 ± 0.16 | 0.20 ± 0.015 | 0.23 ± 0.024 | 0.27 ± 0.019 |
| Lung, trachea, bronchus | 163 | 32.27 ± 1.86 | 33.25 ± 2.54 | 40.06 ± 1.18 | 5.45 ± 1.26 | 5.73 ± 0.41 | 6.33 ± 0.16 |
| Breast | 170 | 0.25 ± 0.013 | 0.34 ± 0.023 | 0.30 ± 0.015 | 21.66 ± 0.54 | 22.18 ± 1.26 | 27.02 ± 0.74 |
| Uterus, cervix | 171 | — | — | — | 7.43 ± 0.33 | 8.25 ± 0.75 | 8.28 ± 0.40 |
| Uterus, corpus | 174 | — | — | — | 5.43 ± 0.16 | 5.42 ± 0.20 | 6.57 ± 0.18 |
| Ovary, fallopian | 175 | — | — | — | 7.55 ± 0.24 | 7.56 ± 0.46 | 8.91 ± 0.21 |
| Prostate | 177 | 17.95 ± 0.33 | 17.80 ± 0.51 | 18.15 ± 0.34 | — | — | — |
| Testis | 178 | 0.80 ± 0.030 | 0.78 ± 0.063 | 0.83 ± 0.02 | — | — | — |
| Kidney | 180 | 3.50 ± 0.11 | 3.40 ± 0.24 | 4.09 ± 0.095 | 1.94 ± 0.10 | 1.87 ± 0.11 | 2.06 ± 0.036 |
| Bladder | 181 | 5.42 ± 0.22 | 5.17 ± 0.47 | 7.62 ± 0.270 | 1.92 ± 0.069 | 2.15 ± 0.10 | 2.63 ± 0.080 |
| Skin melanoma | 190 | 1.56 ± 0.092 | 1.59 ± 0.15 | 1.45 ± 0.061 | 1.18 ± 0.069 | 1.24 ± 0.13 | 1.00 ± 0.038 |
| Skin cancer | 191 | 1.77 ± 1.14 | 1.61 ± 0.23 | 1.36 ± 0.047 | 0.81 ± 0.078 | 0.79 ± 0.13 | 0.62 ± 0.021 |
| Eye | 192 | 0.24 ± 0.014 | 0.25 ± 0.018 | 0.21 ± 0.010 | 0.21 ± 0.011 | 0.22 ± 0.015 | 0.19 ± 0.0069 |
| Brain | 193 | 4.16 ± 0.12 | 4.56 ± 0.20 | 4.28 ± 0.078 | 2.76 ± 0.080 | 2.96 ± 0.14 | 2.86 ± 0.069 |
| Thyroid gland | 194 | 0.40 ± 0.026 | 0.36 ± 0.022 | 0.42 ± 0.016 | 0.60 ± 0.021 | 0.61 ± 0.043 | 0.68 ± 0.026 |
| Other endocrine glands | 195 | 0.31 ± 0.019 | 0.29 ± 0.022 | 0.31 ± 0.019 | 0.19 ± 0.016 | 0.18 ± 0.013 | 0.20 ± 0.010 |
| Connective tissue | 197 | 0.62 ± 0.017 | 0.63 ± 0.033 | 0.62 ± 0.035 | 0.45 ± 0.016 | 0.48 ± 0.032 | 0.47 ± 0.014 |
| Hodgkin's disease | 201 | 2.22 ± 0.052 | 2.21 ± 0.10 | 2.38 ± 0.069 | 1.20 ± 0.050 | 1.21 ± 0.086 | 1.43 ± 0.050 |
| Lymphoma | 202 | 4.43 ± 0.14 | 4.44 ± 0.24 | 4.96 ± 0.085 | 3.04 ± 0.090 | 2.94 ± 0.22 | 3.27 ± 0.070 |
| Multiple myeloma | 203 | 1.75 ± 0.050 | 1.84 ± 0.11 | 1.74 ± 0.035 | 1.21 ± 0.042 | 1.25 ± 0.072 | 1.21 ± 0.030 |
| Leukemia, aleukemia | 204 | 8.90 ± 0.14 | 8.71 ± 0.31 | 8.59 ± 0.13 | 5.71 ± 0.095 | 5.69 ± 0.17 | 5.68 ± 0.085 |

[a]ICD, International Classification of Disease number. Note: ICD 205 was excluded because the number of deaths was not significant.

Significantly higher cancer mortality was observed in the high-selenium area in lip (male), skin (male and female), skin melanoma (female), eye (male and female), and aleukemia (male) than in the low-selenium areas. Eye, skin, and lip cancers are associated with the ultraviolet rays from sunlight. Because the high-selenium states are located in the areas of lower rainfall and greater sunlight, it is likely that the increases in eye, lip, and skin cancer are due to greater amounts of sunlight in the high-selenium areas.

If selenium protects humans against environmental carcinogens in the same way that it protects mice or rats, then one would expect a lower mortality from cancer in the body areas concerned with assimilation, metabolism, and excretion of selenium. Selenium is concentrated by the kidney, liver, and pancreas. Lower cancer mortality was observed in the high-selenium areas in each type of cancer for both males and females. Esophageal, stomach, intestinal, and rectal cancer death rates were also lower in the high-selenium areas for both males and females. Similarly, less age-adjusted gastrointestinal cancer has been observed in the high-selenium provinces of Canada (Shamberger *et al.*, 1974a). The entire gastrointestinal and urinary tracts are known to be exposed to selenium

(Thomas, 1972; Thomson and Stewart, 1974). In this study, bladder-cancer mortality is also lower in both males and females in the high-selenium areas.

This might explain why mortality from cancer of the larynx and the lung appears to be lower in the high-selenium areas. However, the high-selenium areas in this study also have less air pollution as well as less population density, less industrial development, less humidity, different ethnic makeup, and hard versus soft water. Certainly the lower cancer mortality in the high-selenium areas could be the result of factors other than selenium bioavailability.

Mortality from some types of cancer, such as breast, uterine, and ovarian, unexpectedly was also less in the high-selenium areas. Schrauzer and Ishmael (1974) observed a considerable decrease of a spontaneous strain of $C_3H$ mammary tumors in mice supplemented with selenium.

In New Zealand, the cancer mortality is slightly greater in the South Island than the North Island. The South Island also has lower selenium bioavailability than the North Island (Shamberger, 1974a). In this case, a very low selenium bioavailability is being compared with a selenium bioavailability that is only slightly better.

The inverse relationships for several types of cancer mortality and selenium in blood are consistent with the several dietary experiments showing an anticarcinogenic effect of selenium in animals and a protective effect against carcinogen-induced chromosome damage (Shamberger *et al.*, 1973a). Selenium could be protective against formation of a product of peroxidative tissue damage (Shamberger and Willis, 1971), malonaldehyde, which is carcinogenic (Shamberger *et al.*, 1974b). Selenium is a component of glutathione peroxidase, which breaks down peroxides that can cause peroxidative tissue damage (Rotruck *et al.*, 1973). Selenium in the high-selenium areas might also stabilize the malonaldehyde present in food, particularly in beef and other meats (Shamberger and Willis, 1975). Selenium is also found in lower concentrations in the blood of many cancer patients (Shamberger *et al.* 1973b), an observation that has been confirmed by McConnell *et al.* (1975) but that may also represent an effect of, rather than a cause of, cancer. Schrauzer *et al.* (1977) have observed an inverse relationship between dietary intake of selenium or blood selenium and human cancer mortality in several countries.

### *Zinc and Cancer*

Zinc also seems to have a nutritional role in the cancer process. Subnormal plasma zinc levels have been reported in patients with malignant tumors (Addink and Frank, 1959; Addink, 1960). Vikbladh (1950) has reported similar findings on serum zinc levels. Addink's work states in general that the zinc content of *whole* blood and serum of cancer patients is subnormal unless the tumor in tissue is relatively rich in zinc, when an elevated level was found. Rosner and Gorfien (1968) reported that, in general, plasma zinc was subnormal, whereas erythrocyte zinc was elevated in leukemia, myeloma, and lymphomas.

Smith *et al.* (1973) reported that contrary to previous reports serum zinc in bronchogenic carcinoma patients did not differ from controls. Marked changes occur in zinc content of leukocytes in patients with chronic leukemia. Zinc concentration in peripheral leukocytes is greatly reduced and cannot be increased by injections of zinc. In clinical remission, a rise to normal levels occurs (Gibson *et al.*, 1950). The zinc content of the leukocytes also decreases in patients who have a variety of neoplastic diseases, and this difference has been suggested as a diagnostic test for cancer (Szmigielski and Litwin, 1964). Zinc plays a role in the transformation of lymphocytes by phytohaemagglutinin (Chesters, 1972; Berger and Skinner, 1974).

Poswillo and Cohen (1971) reported the inhibition of chemical carcinogenesis in the hamster cheek pouch by dietary zinc deficiency. Petering *et al.* (1967) and DeWys *et al.* (1970) have reported the inhibition of Walker 256 carcinosarcoma (a transplantable sarcoma) by dietary zinc deficiency. Similar results were reported by McQuilty *et al.* (1970). Because zinc is necessary for growth of normal tissue, it may also be necessary for tumor growth. Zinc deficiency depressed the growth of P 388 leukemia (a transmissible leukemia) in weanling mice after the third post-transplantation day (Barr and Harris, 1973). Growth of a transplantable heptoma induced by $3^1$-methyl-4-dimethylaminoazobenzene was significantly reduced in rats maintained on a low-zinc diet of 0.4 μg/g (Duncan *et al.*, 1974). On the other hand, high-zinc diets, 500 μg/g, had a protective effect as compared with the control diet of 60 μg/g. Their results indicate that zinc may have a bimodal effect on cancer; that is, protective against cancer under some circumstances, and supportive of its growth under others, thus making its use dangerous where cancer is already present. Zinc levels are higher in certain types of human cancer tissue (Mulay *et al.*, 1971).

EDTA (ethylenediaminetetraacetic acid) inhibits the synthesis of DNA (deoxyribonucleic acid) by chick embryo cells in tissue culture, and this inhibition can be reversed only by zinc (Rubin, 1972). In contrast, EDTA did not significantly inhibit DNA synthesis in Hela (a human uterine cervical carcinoma in culture) and L (cultured mouse fibroblast cells) cells (Lieberman and Ove, 1962), ascites tumor cells (Weser *et al.*, 1969), or chick embryo cells transformed by Rous sarcoma virus (Rubin, 1972).

Although zinc at normal dietary levels also inhibits rhinovirus (Korant *et al.*, 1974), which can cause the common cold, there are enough untoward effects to indicate that appropriate caution should be used in taking it as a dietary supplement. Perhaps zinc may also inhibit certain viruses that cause animal tumors and possibly may cause certain human tumors. Zinc is an important cofactor for reverse transcriptase (Poiesz *et al.*, 1974) and DNA-dependent RNA (ribonucleic acid) polymerase (Terhune and Sandstead, 1972).

## RECOMMENDATIONS FOR RESEARCH

• Much more information is needed on the time, place, and circumstances in which specific (human) cancers begin their development.

• Much more information is needed on the origins, chemical forms, and distribution patterns of those trace elements in the geochemical environment that are suspected to affect the occurrence and behavior of cancer.

• Considerable additional research and development remains in the broad area of data evaluation, manipulation, and output, including computer production of maps.

• Additional research is required to develop mathematical models that will further elaborate factors and parameters that connect geochemical environment with occurrence and behavior of specific cancers.

• In terms of cause of or protection from cancer, much more information is required about differences in the biological action of individual trace elements, depending on whether they are derived from water, vegetable, or animal foods.

• There have been many suggestions that certain types of soil "favor" occurrence of human cancer. Such relationships need to be explored in much greater depth.

• Additional information is needed concerning those trace elements that have significant effects on intestinal microflora, including whether they act to affect the *in vitro* production or destruction of carcinogens or cofactors.

• More information is required about the factors that effect conversion of nitrites to nitrosamines, in the context of significant human exposure, and the mechanism of their action.

• A great deal more work needs to be done to determine effects of geochemical environment, particularly deficiency of certain trace elements, on production of carcinogenic intermediary metabolities by microorganisms under natural conditions, e.g., *Aspergillus flavus*/aflatoxin.

• Additional information is necessary to determine whether the apparent protective action of selenium (and zinc) against cancer is real, and if so, the optimal intake of these elements, the optimal tissue levels, the most effective chemical forms, and, finally, to determine the significance of the relationship between (available) selenium content of the soil and prevalence of different types of human cancer occurring in the region.

• More information is needed about the role of certain trace elements that present rather consistent, marked variations in concentration in the blood and tissues of patients with cancer, e.g., copper. Some of these elements may have significant effects on metabolism of the tumor that can be exploited in prophylaxis or therapy.

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(James E. Enstrom)

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# VII

# *Cardiovascular Disease*

GARDNER C. McMILLAN, *Chairman*

*H. Mitchell Perry, Jr., Harold H. Sandstead, Herbert I. Sauer, A. Richey Sharrett*

## GENERAL CONSIDERATIONS

(Gardner C. McMillan)

The present discussion has been arbitrarily limited to arteriosclerosis, hypertension, and such consequent diseases as coronary heart disease, stroke, or peripheral vascular disease. We recognize that other cardiovascular disease states can be associated with disorders of trace-element metabolism; for example, hemochromatosis heart disease can be associated with iron accumulation and myxedema heart disease with iodine deficiency. However, our considerations were guided by the great prevalence of arteriosclerotic and hypertensive disease, together with the associations with trace-element metabolism that have been suggested. We know also that calcium, sodium, potassium, and phosphorus influence the function of the cardiovascular system in the most fundamental ways by affecting its contractile proteins, bioenergetics, cell membranes, electrical behavior, and fluid balance. Such elements are not, however, usually regarded as trace elements and are therefore beyond the principal interests of this Workshop.

A number of trace elements have been associated with arteriosclerosis, hypertension, or heart attack by fragmentary data. Their metabolism is virtually unknown or poorly understood, and cogent hypotheses with which to explore the associations that have been reported are usually lacking. One of the more robust associations that has been reported is between an accumulation of cadmium in the kidney examined at autopsy and some cases of hypertension. Another association is between drinking-water softness and a relatively increased susceptibility to heart attack. If we are to understand thoroughly the possible roles of trace elements in arteriosclerotic or hypertensive disease, information about them will also need to be congruent with other known aspects of the natural history of these disorders.

We have limited information about the nature and causes of hypertension. Only a small proportion of cases can be causally associated with other known disorders such as kidney disease, tumors of the adrenal glands, or stenosis of a renal artery. The remaining causes are "essential" or of unknown cause. Some aspects of the disorder and its mediation through vasopressor substances have been studied in detail, and it is possible to develop subclassifications of essential hypertension using such descriptors. Hypertension is not equally prevalent in all countries; for example, it is more prevalent in Japan than in the United States. In the United States, it is more prevalent among black than among white Americans; geographical differences also exist. There appears to be an important genetic component to the disorder. Its prevalence increases with age. Hypertension is a major cause of stroke and an important risk factor for both stroke and coronary heart disease.

Arteriosclerosis is a basis for both heart attack and stroke. It is a major factor in the former, and few heart attacks occur unless arteriosclerosis of the coronary arteries is at least moderately severe. Fatal heart attacks occur because a deficient supply of blood through the coronary arteries to the heart leads to death of some of the heart muscle or because it precipitates electrical instability of the heart's rhythm and sudden death.

Major factors that have been associated predictively with coronary heart disease and arteriosclerosis are increasing age, male sex (particularly before age 65), cigarette smoking, hypertension, elevated blood cholesterol, and several other conditions such as diabetes mellitus and a coronary-prone behavioral pattern. It would appear, however, that these conventional risk factors, some of which are continuous variables and appear to be "dose-related" to their effect, can be invoked to explain only about 50–75 percent of heart attacks. Although they are powerful predictors of liability to future attack, an appreciable number of attacks in a given age and sex group (perhaps 20–30 percent) occur in their absence, as judged by conventional criteria. Consequently, additional explanations and perhaps additional risk factors can be postulated. Indeed, since this Workshop was held, it has been shown that a class of lipoproteins in the blood known as high-density lipoproteins are inversely and independently associated with risk of heart attack. Their measurement allows an explanation of an additional fraction of the unexplained variance noted above. The prevalence of arteriosclerosis and coronary heart disease varies widely in different parts of the world. There are also appreciable rate differences at various locations within the United States. Individuals who migrate from a country of low prevalence to a country of higher prevalence tend to conform to the higher prevalence. Most countries that had low rates relative to the United States rates 3 or 4 decades ago have manifested considerably higher rates in the past 1 or 2 decades. On the other hand, recent data for the United States developed by the National Center for Health Statistics have shown a decline in the very high rates experienced in the early 1960's. Declines in death rates between 1970 and 1975 have been about 13.6 percent for coronary heart disease and about 17.5 percent for stroke. When analyzed by decade of age, sex, and race, declines are found in both sexes, in blacks and whites, and in each 10-year age group from age 35. Consequently, these prevalences are malleable, and, although subject to genetic influences, they are also clearly subject to environmental conditions.

If trace elements play roles in the major cardiovascular diseases that we have been considering, then it will ultimately be necessary to show that their roles are congruent with the manner in which the diseases manifest themselves. That is, their roles must have meaning in terms of the descriptions of the diseases given above. In that context, however, it would be possible to consider that they had an independent function, or an independent but synergistic one, or that they operated through one of the conventional risk-factor or pathogenetic mechanisms. For example, because the electrical stability of the heartbeat depends on the cationic microenvironment of the cardiac muscle fibers, one might speculate that a particular trace element or ratio of elements could determine whether an individual with coronary heart disease would suffer sudden cardiac death. Chromium appears to have an effect on carbohydrate metabolism, which in turn impinges on systemic lipid metabolism, so that impaired glucose tolerance may be accompanied by hypertriglyceridemia and often also hypercholesterolemia. It is possible to speculate that chromium could affect arteriosclerosis indirectly through lipid metabolism as a conventional risk factor. Or, one might speculate that lithium could affect heart attack through some effect on the coronary-prone behavior pattern. Again, trace elements that can be shown to affect contractile protein can be related speculatively to atherogenesis and to hypertension through an influence on vascular smooth-muscle cells. They can also be linked to atherosclerosis through a possible effect on the contractile protein of vascular endothelium or of blood platelets. We can also speculate that trace elements may influence the proliferation of the vascular mesenchymal cells that build up plaques or that they influence the extracellular products of mesenchymal cells such as collagen and mucopolysaccharides in plaques or in the arterial wall.

Such speculations have little value at present. In general, our knowledge of the absorption, balance, turnover, active and inactive pools, interactions, and functions of the trace elements of current interest is inadequate to allow meaningful speculations. We seriously lack fundamental understanding of the metabolic roles of such elements as magnesium, lithium, cadmium, selenium, copper and molybdenum, zinc, vanadium, chromium, and manganese, although there may be experimental or epidemiological evidence to bring them to our attention. Indeed, we are often uncertain whether we should regard them in terms of excess or deficiency, as having a threshold value, or in the context of some ratio in relation to the pathogenesis of cardiovascular disease.

Clearly, much fundamental metabolic research remains to be done. At the same time, it may also be possible to advance and strengthen our correlative descriptions of the association of trace elements and cardiovascular disease in man. Studies in several countries have shown association between the measured softness of local drinking water and deaths from coronary heart disease. This surprising finding has been obtained repeatedly. There are no satisfactory concepts or theories within which to consider the finding. The studies have varied greatly in the precision of their observations and, indeed, even in the definitions and meanings of the terms "hard" and "soft" water. Most of the studies have failed to measure the water actually consumed or to analyze it in great detail or with stringent control of analytic quality; other sources of drinking fluid, such as milk and bottled drinks, have not been measured; the trace elements contributed by raw, cooked, and packaged foods and their bioavailability have not been evaluated. Most studies have not attempted to separate the incidence of fatal heart attack into sudden and nonsudden death. Other conventional risk factors have not been measured, and the data are not suitable for multivariate analysis of risk.

The present state of information is unsatisfactory because of the apparent strength of the association and the obvious weaknesses of the data in which the association is found. It is also unsatisfactory because we are presented with the possibility of using such information to change public water supplies to help to prevent arteriosclerosis and heart attack, but we lack both the necessary strength of data and the essential understanding of the elements involved to warrant consideration of such an action.

A positive association has been found *post mortem* between the amount of cadmium accumulated in the kidney and hypertension. Again there is no satisfactory conceptual framework or metabolic hypothesis within which to consider the association. Because hypertension has a severe effect on the public health, and the etiology of almost all cases of hypertension is unknown, it becomes important to ascertain the prevalence of the cadmium–hypertension association and to understand its meaning, both in terms of the disease process and for hypertension in general.

The associations observed between softness of water and coronary heart disease and between renal cadmium and hypertension (and to a lesser extent other elements and cardiovascular disease) have undergone preliminary study. It will now be necessary to reapproach them with greater methodological sophistication. Both geochemical and disease-associative studies, as well as fundamental metabolic studies, will be essential if useful understanding is to be gained. Methodological problems are severe. The Workshop participants judged it to be practical now to conduct studies that can provide data of markedly superior resolution to those now available, data that would allow greater certainty in drawing conclusions and that would provide a conceptual *modus operandi* for at least some of the elements.

## EXCESS CADMIUM IN RELATION TO HYPERTENSION

(H. Mitchell Perry, Jr.)

Excess environmental cadmium has been suggested as a possible contributing cause of essential (unknown cause) human hypertension (Schroeder, 1965; Lener and Bibr, 1971; Voors *et al.*, 1975), which in turn is a major but indirect contributor to our current epidemic of degenerative cardiovascular disease, manifested primarily by myocardial infarction and cerebrovascular accident. Two observations seem to provide the best evidence for the involvement of cadmium in human hypertension: first, hypertensive subjects are reported to have elevated levels of renal cadmium; second, chronic feeding of low doses of cadmium to rats induces an increase in blood pressure.

The distribution of cadmium in the human body is quite different from the largely random distribution of most other nonessential trace metals. Cadmium is distributed in a definite and unique pattern; the kidney has about ten times the concentration present in the liver, which itself has five times the concentration present in other organs (Perry *et al.*, 1961). Most renal and much other cadmium is bound to metallothionein, an unusual small protein with a molecular weight of 6000 to 10,000 grams, which contains 33 percent cystein (Kägi *et al.*, 1974), an amino acid, which may have a storage, transport (Bremner and Marshall, 1974), and/or detoxification (Piscator, 1964) function. At birth, the renal-cadmium concentration is less than 1 percent of its adult value, with the metal being largely accumulated during the first three or four decades of life and reaching a maximum concentration at about age 35 (Schroeder, 1960), close to the age at which most essential hypertension appears. Negroids in nonindustrialized parts of Africa have been found to have lower renal cadmium concentrations than the average Caucasoid American; whereas Mongoloids from several parts of Asia, particularly Japan, were found to have higher concentrations than the average Caucasoid American (Perry *et al.*, 1961). This pattern very roughly approximates the prevalence of human hypertension.

Subject-to-subject variability of renal-cadmium concentration is less than that of other nonessential trace metals; in fact, it is in a range more characteristic of essential trace metals (Perry *et al.*, 1962). Biologic variability, however, remains considerably larger than the variability of the analytic methods, both of the early emission spectrographic and dithizone extraction methods and of the current more accurate atomic absorption methods. Despite the intersubject variability, which makes such data difficult to evaluate, several studies have suggested that hypertensive subjects have significantly more renal cadmium than otherwise similar, but normotensive, subjects. Schroeder (1965) compared 117 normotensive Americans, who died sudden accidental deaths, with 17 hypertensive Americans, who died similarly. The normotensive group had an average of 2.9 mg of cadmium per g of kidney ash, whereas the hypertensive group had 4.2 mg, a highly significant difference (probability $< 0.005$). Schroeder (1965) also found a larger, but less significant, difference when he looked at smaller numbers of subjects from 10 different countries. Thus, 23 normotensive and 17 hypertensive subjects had averages of 3.2 and 5.1 mg of cadmium per g of kidney ash, respectively, with $p < 0.025$. Lener and Bibr (1971) reported that 10 normotensive and 12 hypertensive subjects from Czechoslovakia had averages of 27 and 36 $\mu$g of cadmium per g of fresh kidney, respectively, a difference they found significant. Morgan (1969), on the other hand, did not find a significant difference when she studied subjects from Alabama, but her subjects died in the hospital as a result of their hypertension or from other nonaccidental causes and thereby differed from Schroeder's American subjects. She noted that the 25 normotensive and the 12 hypertensive subjects both had averages of 2.5 mg of cadmium per g of kidney ash; however, the median values for the two groups were 2.2 and 2.7 mg, respectively. It should be emphasized that Schroeder (1967) reported *low* renal-cadmium levels in patients with "malignant" hypertension, who died of renal failure. Moreover, this observation of Schroeder's is consistent with Friberg's (1950) observation that cadmium-exposed workers have high renal-cadmium levels if they do not have renal failure, but low levels when renal failure has supervened.

Both injected and ingested cadmium have been noted to raise the blood pressure of rats. The hypertensive responses to intravenous (Perry *et al.*, 1970) and intraperitoneal (Perry and Erlanger, 1971) cadmium were rapid and marked. Of more practical interest, however, was hypertension induced by cadmium-feeding, since most accumulated human cadmium is thought to be ingested. Schroeder and Vinton (1962) were the first to report the hypertensive effect of long-term, low-dose cadmium-feeding, and they reported a marked effect. The hypertensive effect of cadmium-feeding was confirmed by Perry and Erlanger (1974), although they apparently observed a smaller effect than Schroeder. A major part of the difference, however, was related to the manner of expressing results (Perry, 1976). Other investigators (Lener, 1973; Sorenson *et al.*, 1973; Ohanian *et al.*, in press) have also confirmed the hypertensive effect of chronic cadmium-feeding. Some workers have failed to induce hypertension with cadmium (Lener and Bibr, 1970; Friberg *et al.*, 1974; Doyle *et al.*, 1975), but their experimental conditions were significantly different. A careful evaluation of the currently available data indicates that chronic cadmium-feeding can produce a signficant increase in blood pressure, but the animals must be healthy; no hypertensive effect is observed in the presence of serious infection or in response to large and overtly toxic amounts of cadmium.

Two to 12 months' exhibition of drinking water containing from 0.1 to the original standard 5 parts per million (ppm) of cadmium used by Schroeder and Vinton (1962) has induced an increase in average blood pressure (Perry *et al.*, 1977a). The magnitude of the effect was largely independent of the dose, with the average increase in systolic pressure ranging from 15 to 20 mm of mercury. This increase was consistent and highly significant statistically; moreover, it was marked for some animals, with the systolic pressure of a quarter of the exposed animals exceeding the average control value by more than two standard deviations (about 30 mm of mercury) (Perry and Erlanger, 1974). Although most work on cadmium-induced hypertension has been done with female Long-Evans rats, cadmium-feeding has induced comparable hypertension in both female Sprague-Dawley rats and in male Long-Evans rats (Perry *et al.*, 1976). Supplementing fed cadmium with selenium (Perry *et al.*, 1974), zinc, or copper, Perry and Erlanger (1977) inhibited the induction of hypertension in rats by cadmium. Dissolving cadmium in hard water also inhibited the hypertensive effect of cadmium (Schroeder, 1967; Perry *et al.*, 1974), apparently because the cadmium was quickly precipitated and hence was not available. Unlike the other metals tested, lead was unique in that it not only induced an increase in systolic pressure comparable with that induced by cadmium, but, when the two metals were exhibited together, their effect was additive (Perry and Erlanger, 1977).

The minimum daily dose that induces hypertension in rats (Perry *et al.*, 1977b) is of the same order of magnitude (on a weight-for-weight basis) as the amount ingested by the *average* American adult with no specific cadmium exposure (Perry, 1976). Moreover, the renal-cadmium concentrations of rats with cadmium-induced hypertension (Perry *et al.*, 1977a) bracket the range of renal-cadmium concentrations found in the *average* American adult without specific exposure (Perry *et al.*, 1961).

The mechanisms of the cadmium-induced hypertension in rats remain unknown, although there is some evidence for two likely mechanisms. Following chronic cadmium-feeding, both Doyle's (1975) group and Perry's group (unpublished, 1976) observed an increased sodium retention remininscent of that originally observed following injection of cadmium into one renal artery (Vander, 1962). Cadmium has also been found to produce vasoconstriction by a direct effect on vascular smooth muscle (Perry and Erlanger, 1975). Either of these effects could explain the hypertension induced by cadmium. In addition, significant hyperreninemia has been observed following cadmium exposure (Perry and Erlanger, 1973); however, renin does not seem to be critical to the induction of hypertension by cadmium since tying off the kidneys failed to diminish the hypertensive effect, although the circulating renin level fell to abnormally low values (Perry and Erlanger, 1975). Finally, the immediate elevation in pressure following intra-arterially administered cadmium has been directly correlated to an increase in cardiac output (Perry *et al.*, 1967); however, there is no evidence that cadmium-feeding induces any change in cardiac output.

If cadmium is involved in human hypertension, an excess of hypertension might be expected among those with high occupational exposure; however, any such excess might be extremely difficult to document. Hypertension has certainly been noted in industrially exposed populations, but the limited available data do not indicate whether the incidence differs from an unexposed but otherwise similar population. To illustrate the problem, Friberg and Mystrom (1952) observed that approximately one third (14 of 43) of a group of workers exposed to cadmium for more than nine years had systolic pressures of 160 mm of mercury or more and that approximately one fifth (9 of 43) had diastolic pressures of 100 mm of mercury or more. In an earlier publication, apparently involving the same 43 workers, Friberg (1950) compared them with 15 somewhat younger workers with cadmium exposures of four years or less. None of the 15 had systolic pressures as high as 150 or diastolic pressures as high as 100 mm of mercury. This difference in blood pressure is difficult to interpret because of the small numbers involved and because of the difference in the ages of the two groups (mean ages were 44 and 35 years). In more general terms, the limiting factor in drawing any conclusions from the blood pressures of exposed workers is the difficulty in obtaining a *comparable* unexposed population.

Environmental cadmium has been incriminated in a peculiar Japanese syndrome, "itai-itai disease," which apparently involves an imbalance in other metals as well as an excess of cadmium (Tsuchiya, 1969). The terminal stages of this syndrome are not associated with hypertension, and characteristically there are small, scarred, end-stage kidneys with little remaining parenchyma or cadmium. The absence of hypertension in subjects with itai-itai disease is cited as evidence against the involvement of cadmium in human hypertension. This argument is not entirely convincing. Exposing animals to excessive cadmium produces toxicity but not hypertension; however, there is a critical intermediate range of cadmium exposure that is associated with elevated blood pressure but no other recognizable effect (Perry *et al.*, 1977a). Thus, it is important to know whether hypertension occurs during the early stages of itai-itai disease, when there presumably is a high concentration of renal cadmium. There are no clear-cut data on this point, although the limited available studies report no excess of hypertension in asymptomatic subjects living in and near the itai-itai areas (Nogawa and Kawano, 1972).

There are obvious difficulties in proving a causal relationship between a ubiquitous environmental pollutant, which all human beings accumulate in their kidneys, and a very common, slowly progressive and initially asymptomatic condition. What data then are needed to determine whether cadmium does play a role in essential human hypertension? If cadmium is involved, hypertensive subjects should have an excess of cadmium in some tissue compartment or at least an increased ratio of cadmium to some other substance. As indicated, the current data on this point are not conclusive and should be expanded. In addition, for cadmium to be accepted as causal in human hypertension, the details of a reasonable mechanism for the effect need to be worked out, presumably in the laboratory with an animal model.

It seems that it should be simple to test whether hypertensive subjects have increased renal-cadmium concentrations; however, there has been no adequate collection of satisfactory tissue samples from two populations contrasting in blood pressures but matched for all other important characteristics. To find and recognize subjects with relatively early asymptomatic hypertension and to match them with otherwise similar individuals has proved to be very difficult. Healthy individuals who die suddenly in accidents would seem to constitute the optimum group of subjects, but antecedent histories for such subjects are often unavailable, and meaningful blood-pressure measurements are particularly difficult to obtain. To define hypertension, possible, but perhaps impractical and certainly not ideal, alternatives to actual blood-pressure measurements might rely on anatomic evidence of hypertension: e.g., the combination of cardiomegaly (manifested by cardiac weight greater than 3/4 percent body weight without anatomic cause) plus arteriolar nephrosclerosis (on microscopic examination), with the *absence of both* being indicative of normotension. There are, however, confounding difficulties: deaths from automobile accidents might seem to provide a good source of matched normotensive and hypertensive subjects; however, automobile accidents are apparently more common among smokers than among nonsmokers (Waller *et al.*, 1971), and there are data suggesting that cigarettes are a major source of cadmium in man (Lewis *et al.*, 1972).

It seems appropriate to recommend efforts to obtain the tissue samples needed to compare the renal cadmium concentrations of hypertensive and normotensive subjects. It might be possible to use current large hypertension screening and follow-up programs as sources of matched normotensive and hypertensive populations that could be followed until a significant number of fatal events made renal tissue available from subjects with known blood-pressure histories. Because of the geographic differences in renal-cadmium concentrations, geographic origin should be considered during matching.

An additional complementary epidemiologic study should be considered, namely, an investigation of blood pressures of asymptomatic individuals with high environmental exposure to cadmium such as populations living near alkaline accumulator factories in Scandinavia or in areas adjacent to the itai-itai areas of Japan. The critical blood-pressure data for such high-exposure populations are not currently available; moreover, defining a satisfactory control population presents major difficulties.

## SOME INTERACTIONS AMONG ELEMENTS AND BINDING LIGANDS THAT MAY RELATE TO CARDIOVASCULAR DISEASE

(Harold H. Sandstead)

This discussion is, of necessity, speculative. Most of the relevant information comes from experiments conducted on animals. In full recognition that extrapolation from such studies to man is hazardous, incompletely understood observations on animals, which might have implications for human cardiovascular disease, have been included. For purposes of this discussion, the term "interactions" is used in a broad sense. Some of the known and suspected interactions between elements are shown graphically in Figure 38. Of these interactions, some that may be of significance for the cardiovascular system will be discussed. Although our understanding of the molecular basis for many of the interactions is incomplete, it is known that chemically and physically similar elements often interact competitively for a specific ligand, i.e., the ion or substance to which they can bind (Hill and Matrone, 1970). Not all interactions between elements are competitive, some are additive or synergistic and others are indirect. In some instances, the elements act at different steps in a metabolic cycle.

Some interactions within the intestine, involving nonabsorbed organic ligands may be important for the cardiovascular system. The formation of an insoluble complex by zinc and phytate is an example of such an interaction. As a result, the intestinal absorption of zinc is decreased (Oberleas, 1973; Klevay, 1977). Calcium appears to facilitate the formation of this insoluble complex. In contrast, phytate does not appear to inhibit severely the absorption of copper (Klevay, 1977). Zinc can appar-

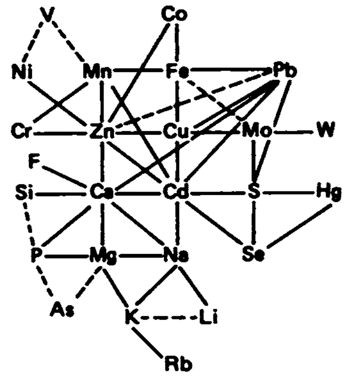


FIGURE 38 Interactions among the elements. Some illustrative interactions are shown. Known interactions are indicated by solid lines, while suspected interactions are indicated by broken lines. Many of the interactions are competitive. Others are either additive or synergistic. Interactions between two elements may be influenced by other elements that are present and can interact with the two elements in question. Some interactions are indirect in that the elements in question influence different steps in a metabolic pathway (after Sandstead, 1976).

ently form an insoluble complex with dietary fiber (Reinhold, 1975; Ismail-Beigi *et al.*, 1977). Thus, dietary fiber may affect the availability of zinc for intestinal absorption.

High levels of dietary zinc can impair the intestinal absorption of copper (Starcher, 1969), presumably by induction of the synthesis of metallothionein in the intestinal mucosal cells (Cherian, 1977) and the subsequent displacement of the zinc by copper, which has a higher binding affinity for thiolate sulfurs (Hartman and Weser, 1977). It appears that metallothionein regulates the absorption of copper in a manner analogous to the regulation of iron absorption by intestinal mucosal cell ferritin (Evans and Johnson, 1978). Impairment of copper homeostasis by high intakes of zinc has also been observed in humans (Prasad *et al.*, 1978).

The above-cited effects of phytate and dietary fiber on zinc absorption and the inhibitory effects of high levels of zinc on copper metabolism might have implications for the cardiovascular system because experimental studies have shown that an increased intake of zinc relative to copper will increase the serum cholesterol concentrations of rats (Klevay, 1973, 1977) and mice (Jacob *et al.*, 1977), and copper deficiency has been found to increase serum cholesterol, impair formation of aortic elastin, and cause myocardial necrosis and rupture (Allen and Klevay, 1978a). Impaired copper nutriture apparently causes increased cholesterol synthesis in the liver and increased clearance of cholesterol into the plasma and bile (Allen and Klevay, 1978b; Klevay and Allen, 1978). Abnormalities in elastin (Hill *et al.*, 1967) and collagen (Chou *et al.*, 1969) caused by copper deficiency have been well described. The abnormalities in the myocardium are less well understood, although electron microscopic findings have been described (Leigh, 1975).

In cattle, interactions between copper and molybdenum are important for health (Bremner and Davis, 1973); apparently, they can react with each other to form an insoluble complex within the rumen. In addition, low concentrations of molybdenum in the rumen apparently can lead to the generation of sulfide, which precipitates copper. It therefore seems possible that molybdenum nutriture might play a role in the occurrence of cardiovascular abnormalities related to impaired copper homeostasis.

Zinc and calcium can apparently interact *in vivo*. Increased dietary calcium will cause a shift of zinc from the liver to the bone (Heth *et al.*, 1966). Such a shift presumably decreases the ratio of zinc to copper in liver. In this regard, it has been shown that supplementation of human diets with calcium decreases the serum concentration of cholesterol (Albanese *et al.*, 1973).

Zinc may interact indirectly with chromium and manganese through its influence on carbohydrate metabolism. Zinc appears necessary for the release of insulin from the beta cells of the pancreas (Huber and Gershoff, 1973) and for normal glucose tolerance (Hendricks and Mahoney, 1972), while manganese is essential for the integrity of the islet tissue. A diabetes-mellitus-like syndrome can be produced in guinea pigs by manganese deficiency (Everson and Shrader, 1968; Shrader and Everson, 1968). Chromium seems to have a role in the utilization of glucose and amino acids by peripheral tissues. It is particularly potent when it is present as part of an organic complex, which has been called "glucose tolerance factor" (Mertz *et al.*, 1974). Chromium deficiency in humans has been shown to impair carbohydrate metabolism severely (Jeejeebhoy *et al.*, 1977). The above observations on the effects of zinc, manganese, and chromium deficiencies on the metabolism of carbohydrates might have implications for the cardiovascular system because the findings suggest an interference with the insulin-mediated aspects of carbohydrate metabolism. Such an interference may be somewhat analogous to what occurs in diabetes mellitus. The adverse effects of diabetes mellitus on the cardiovascular system are well known.

Zinc and chromium also appear to interact within intestinal epithelial cells. Both metals seem to bind to the same low-molecular-weight ligand (Hahn and Evans, 1975), which has been found to facilitate the intestinal absorption of zinc (Evans *et al.*, 1975). The zinc nutriture of rats seems to influence the intestinal absorption of chromium. Zinc-deficient rats were found to absorb more chromium (Hahn and Evans, 1975), which is an interesting finding in view of the roles of these two metals in carbohydrate metabolism.

Interactions of cadmium with essential elements that might be of significance for the cardiovascular system are those with zinc, copper, calcium, selenium, sulfur, and sodium. Some of these have been reviewed by Fox (1974).

Cadmium–zinc interactions have received the most attention. An increased ratio of cadmium to zinc in the renal cortex has been associated with increased blood pressure

(Schroeder, 1967; Lener and Bibr, 1971) and/or increased atherosclerosis (Voors *et al.*, 1973) in humans and increased blood pressure in rats (Schroeder and Vinton, 1962; Perry and Erlanger, 1974). In addition, it has been suggested, but not proven, that increased levels of cadmium in water or foods may contribute to the occurrence of essential hypertension in man (Schroeder and Perry, 1956; Perry, 1973).

Under proper dietary and environmental conditions, it is possible to induce increased blood pressure in rats by adding cadmium to their drinking water (Schroeder and Vinton, 1962; Perry and Erlanger, 1974, 1976; Perry *et al.*, 1977). The level of cadmium required is relatively low (0.1–10 ppm), and the duration of exposure long (6–12 months). With increased length of exposure (12 months), lower levels of cadmium (0.1–2.5 ppm) cause the blood pressure to continue to increase, whereas the higher levels (10–50 ppm) do not. It seems that the level of zinc in the diet or drinking water must be within a specific range for increased blood pressure to occur. In one study, the feeding of 12.5 ppm zinc in the diet along with 5 ppm cadmium in the drinking water did not result in increased blood pressure after 14 months (Doyle *et al.*, 1975), although sodium retention was increased. In contrast, increased blood pressure occurred in rats fed 12.5 ppm zinc in drinking water with 22.3 ppm zinc in the diet when 2.5 ppm cadmium was added to the drinking water for 12 months (Perry, cited by Sandstead, 1976). A higher intake of zinc, 50 ppm in drinking water plus 22.3 ppm in the diet, along with 2.5 ppm cadmium in drinking water, caused the blood pressure to increase significantly after 6 months. In contrast, 100 ppm zinc in drinking water, plus the above diet, prevented an increase in blood pressure when either 2.5 or 10 ppm cadmium was given. At a level of 200 ppm zinc in drinking water, plus the above diet, the rats developed increased blood pressure, although no cadmium was given. Subsequent work has confirmed the finding that high zinc intakes without added cadmium caused increased blood pressure (Perry and Erlanger, 1978) and prevented cadmium-induced increased blood pressure when given with cadmium. Thus, it appears that the interaction between cadmium and zinc is dependent on the relative amounts of the two elements. At low levels of cadmium, increased blood pressure will not occur unless the amount of zinc is within a specific range, and zinc alone, when given in sufficient amounts, will cause increased blood pressure. It seems possible that induction of metallothionein by cadmium (Winge and Rajagopalan, 1972) and zinc (Bremner and Davis, 1975) and the relative binding of cadmium and zinc to metallothionein may contribute to this phenomenon.

Cadmium, zinc, and copper interact in the arterial wall (Hill *et al.*, 1963). Increased intakes of cadmium cause histologic abnormalities that resemble those of copper deficiency. When increased zinc is given along with the cadmium, the abnormalities are even more severe. The findings suggest that cadmium and/or zinc interfere with the copper mediated cross-linking of elastin (Hill *et al.*, 1967) and collagen (Chou *et al.*, 1969).

Cadmium, zinc, and copper also interact in the liver. When 1 ppm cadmium and 30 ppm zinc were fed to rats, a 58 percent decrease in serum ceruloplasmin activity was observed along with a decline in the liver and blood copper and a thinning of cortical bone. The effect of cadmium was exacerbated when the amount of either cadmium or zinc was substantially increased (Mills, 1974). The effects of these interactions on hepatic cholesterol metabolism have not been defined. It might be expected that increased zinc or cadmium would increase cholesterol synthesis through an interference with copper metabolism. Both cations induce the synthesis of metallothionein (Bremner and Davis, 1975; Winge and Rajagopalan, 1972). Copper will displace both zinc and cadmium from metallothionein (Hartman and Weser, 1977). Copper bound to metallothionein can apparently be taken up by lysosomes (Porter, 1974) from which copper is excreted into the bile (Evans, 1973). The resulting decrease in liver copper might alter hepatic cholesterol metabolism (Klevay and Allen, 1978) causing increased levels of plasma cholesterol (Allen and Klevay, 1978a,b).

Cadmium and calcium interact in the intestine and elsewhere in the body. A low dietary intake of calcium is associated with an increased intestinal absorption of cadmium in rats (Larsson and Piscator, 1971), whereas increased dietary calcium decreases cadmium absorption. Cadmium can inhibit the absorption of calcium. While direct inhibition seems possible, cadmium has been shown to inhibit the synthesis of the vitamin D derivative, 1-25 $(OH)_2$ cholecalciferol (Suda *et al.*, 1974) by the renal tubule. When cadmium inhibits calcium absorption, a mobilization of calcium and zinc from bone, mediated by parathormone, presumably occurs (Hurley and Tao, 1972). Mobilization of zinc from the bone would increase the ratio of zinc to copper in the liver and might result in an increased concentration of serum cholesterol (Klevay, 1973; Klevay and Allen, 1978; Allen and Klevay, 1978a,b).

Cadmium interacts indirectly with sodium. A low intake of cadmium (5 ppm) will induce sodium retention in rats fed either 12.5 ppm zinc (Doyle *et al.*, 1975) or approximately 75 ppm zinc (Lener and Musil, 1971). Increased dietary sodium has been shown to increase body sodium and to induce hypertension in the rat (Meneely, 1973). It seems likely that the retention of sodium by cadmium-fed rats is at least in part responsible for the increased blood pressure that has been observed when rats were fed cadmium in drinking water for long periods of time (Schroeder and Vinton, 1962; Perry and Erlanger, 1974, 1976).

Cadmium interacts with selenium. Rats given 0.9 ppm selenium in drinking water along with 0.5 ppm in the diet do not develop increased blood pressure when given 2.5 ppm cadmium. This level of selenium given alone will induce increased blood pressure (Perry and Erlanger, 1974). The mechanism of this cadmium–selenium interaction is not known. Selenium will also protect from another toxic effect of cadmium, which might have cardiovascular implications. Cadmium has been shown to injure pancreatic beta cells and impair carbohydrate metabolism (Merali and Singhal, 1975); selenium prevents this injury.

Although we do not know whether any of the interactions noted in this section are of importance for the cardiovascular system of humans, the metabolic similarities between mammalian species suggest that investigation of this possibility may be appropriate.

## DESCRIPTIVE ASSOCIATIVE METHODOLOGY

(Herbert I. Sauer)

Experiments of nature and experiments that human beings unintentionally and unknowingly conduct on themselves are the concern of geographic pathology and epidemiology. Data on geographic differences in incidence of disease are most valuable but often not available. Prevalence is basically the cumulation of cases of nonlethal disease and thus, even when available, may be of limited value in measuring the frequency with which a chronic disease strikes in different geographic areas. Mortality data are widely available and useful when appropriate procedures are employed (Erhardt and Berlin, 1974; Kitagawa and Hauser, 1973; Moriyama *et al.*, 1971; Sauer and Parke, 1974; Sauer and Brand, 1971; Sauer *et al.*, 1973).

The risk of death from most chronic diseases varies widely by age and by sex and major ethnic group or race. Age–sex–race-specific rates are necessary for sound studies of geographic differences in the risk of dying. Because most readers will be overwhelmed by the quantity of rates thus generated, age-adjusted rates are usually desirable for purposes of summarizing. Age-adjusted death rates for all ages, however, tend to reduce or even obscure differences in risk in middle age. Death rates for ages 35–74, age-adjusted by the direct method by 10-year age groups, tend to produce a maximum contrast in rates between geographic areas consistent with reducing standard error to a minimum. In some instances, age groups 45–64 or 45–74, similarly age-adjusted, are more useful. For making comparisons of rates for ages 75 and over, 5-year age groups are more informative than broader age groups. Available evidence indicates that for whites in particular, age is entered accurately on death certificates (Hambright, 1968). In the western half of the United States especially, "black" (or "Negro") is a better definition of an ethnic group than "nonwhite" because the latter definition includes ethnic groups that are not at all homogeneous as regards death rates.

Because states tend to be heterogeneous in regard to death rates, much greater promise for research is offered by the use of metropolitan areas and nonmetropolitan groups of counties such as state economic areas (U.S. Bureau of the Census, 1963). When resources are available for adequately studying individual rural counties and census tracts of metropolitan areas, these smaller units give even greater promise.

The detection of (and, when necessary, correction for) systematic bias in data requires a knowledge of subject matter. For example, death rates are routinely calculated by place of usual residence, but two factors related to residence have been studied:

- *Migration.* Available evidence suggests that migration tends to reduce the amount of contrasts in mortality rates between geographic areas, rather than being the cause of such contrasts. An exception is the low rates for whites of retirement age in Florida areas, which are the result primarily of low rates for those born in the North now living in Florida.
- *Resident institutions.* Residents of mental hospitals and other resident institutions are enumerated by the Bureau of the Census as usual residents of the county in which the institution is located, whereas the accepted policy for deaths is to classify the people as having been residents of the county from which they were admitted. For areas with more than 3 percent of the adult population in resident institutions, an approximation method has been devised for producing rates useful for comparing geographic differences (Sauer *et al.*, 1966).

Problems in comparing cause-of-death categories between geographic areas are kept under better control by studying rates for all causes of death and for broad categories, such as the cardiovascular diseases (ICDA 390–448) as defined by the National Center for Health Statistics (1967) (or, for studies of long-term trends, the cardiovascular–renal diseases), before or simultaneously with the study of more specific categories, such as acute myocardial infarction (ICDA 410). Other chronic-disease categories may be used unevenly from area to area at times; e.g., in some instances there may be a need for caution in the use of a category even as broad as "hypertensive disease, ICDA 400–404" (Sauer, 1978). The category, "Symptoms and ill-defined conditions," is rarely used in some areas and very often in other areas. When analyzing data for a specific disease category, the usual procedure of ignoring such deaths is equivalent to assuming that none fell into the cardiovascular or other diseases category—which is like assuming that these deaths did not occur.

Undoubtedly many other variables are affecting the risk of dying and should therefore be kept under control, in order to have rates adequate for testing specific hypotheses in environmental geochemistry. At present, information about the relation of occupation, education, income, and many other variables to the risk of dying is incomplete and often confusing. It does not seem feasible, therefore, at this time to suggest methods for adjusting for such factors.

The objective is to design analytic approaches soundly to maximize differences that are both statistically significant and substantial. As a starting point in analytic methods, the numerical differences in rates and the percentage differences are both important, although at times some epidemiologists may look only at the latter. For example, for a common cause, such as ischemic heart disease, a 40 percent differential in rates may be both statistically significant and substantial, whereas for a relatively rare category such as acute and subacute endocarditis, a 400 percent difference may involve such a small number of deaths and such a small number of points in the rate per 100,000 population as to be of little importance.

Causation does imply correlation, although correlation or association does not necessarily imply causation (Buechley *et al.*, 1966). In instances in which there is no association or correlation between independent variables, such as a specified element in the drinking water and the risk of dying, at least two alternatives may be considered: (a) no correlation or causation actually exists, and (b) our present inability to make necessary adjustments for other variables of importance obscures the correlation and the causal relationship that exists.

Correlations and other techniques for studying the extent of association are valuable, but their usefulness is increased for other investigators when rates or other basic information are also published. The usual product-moment or Pearsonian correlation assumes that the distributions are normal; if a nonparametric measure such as a rank correlation produces a somewhat similar correlation, this suggests that the findings are not heavily dependent on the specific assumptions made.

Higher correlations provide greater opportunities for searching for causes of differences in risk, just as do the greatest differentials in rates, in numerical as well as in percentage terms. Even in such settings, the instances of lack of correlation may provide equally challenging opportunities for study. As an example, death rates for females repeatedly have correlations with male rates that are both statistically significant and substantial (the coefficient of correlation $r$ usually = +0.70 to +0.80). Yet in the Southeast, with some of the highest death rates in the nation for white males, the white-female rates tend to be more nearly average (Erhardt and Berlin, 1974, p. 119). From this observation one may increase the specificity of the research question: "What is causing the high rates in white males of middle age?" by adding to it, "without causing a similar increase in white-female rates?"

Thus many relatively simple relationships and ratios are being studied, even with limited resources. By so doing, more definitive hypotheses are being developed, thereby increasing the chances that multivariate analyses will be able to make a substantial contribution.

Mapping is another device for identifying associations of importance for further study. Geographic areas are often divided into quartiles or quintiles on the basis of their rates, a procedure providing valuable information. It has, however, been even more useful to identify the counties or other areas with extreme rates, such as the 3 or 5 or 12½ percent with the lowest and highest rates—that is, the areas in which the risk of death is either least or greatest for middle-aged individuals.

## TWO-HUNDRED EXTREME-RATE U.S. COUNTIES FOR DEATHS FROM CARDIOVASCULAR DISEASES

(Herbert I. Sauer)

In the United States, which 100 counties have the lowest death rates and which 100 have the highest for the diseases of the heart and blood vessels—the cardiovascular diseases?

Deaths that may be considered as "premature" include those occurring in middle age; broadly defined, that is ages 35–74, inclusive. For 1968–1972, tabulations have been made from the death-detail tapes of the National Center for Health Statistics for the cardiovascular diseases (International Classification of Diseases, Adapted (ICDA) Codes 390–448); also included are deaths ascribed to "symptoms and ill-defined" (ICDA 780–796), with the assumption, derived in part from several studies, that this procedure would introduce less error in the cardiovascular diseases rates than would be introduced by ignoring this latter category. Rates have been calculated, with the population at risk obtained from the Bureau of the Census revised tapes for the 1970 population, for white males aged 35–74, age-adjusted by 10-year age groups by the direct method. Rates are by county of usual residence; for four low-rate counties, there was evidence that "usual residence at death" was defined differently from the Census definition, sufficient to warrant postponing use of these rates until more definitive information could be obtained. (Rates for blacks and for white females present somewhat similar patterns, except that the latter group has few high-rate counties in the Southeast.)

Chance fluctuation or standard error presents a serious problem for counties with a small population. For counties with a high rate based on less than 100 deaths or with a low rate based on less than 50 deaths, the rates were accepted only if there were one or more confirming rates from three available sources: (a) cardiovascular diseases rates for white females aged 35–74 for 1968–1972; (b) rates for all causes, white males aged 35–74 for the 11-year period 1959–1969; and (c) cardiovascular-renal diseases death rates, white males aged 35–74 for 1959–1961. For extremely small counties with a high rate based on less than 20 deaths or with a low rate based on less than 10 deaths, at least two of the above confirming rates were required for acceptance. These procedures appear to identify the sections of the country with very low or very high rates, but work is still in progress to apply more thoroughly a multiplicity of approaches (Erhardt and Berlin, 1974; Sauer and Parke, 1974) for determining the counties for which rates are in fact persistently very low or very high.

The rates of the 100 highest-rate counties are about twice as high as those of the 100 lowest (Figure 39).

Of the 100 lowest-rate counties, 91 are in 14 contiguous plains and mountain states, and only 6 are east of the Mississippi River.

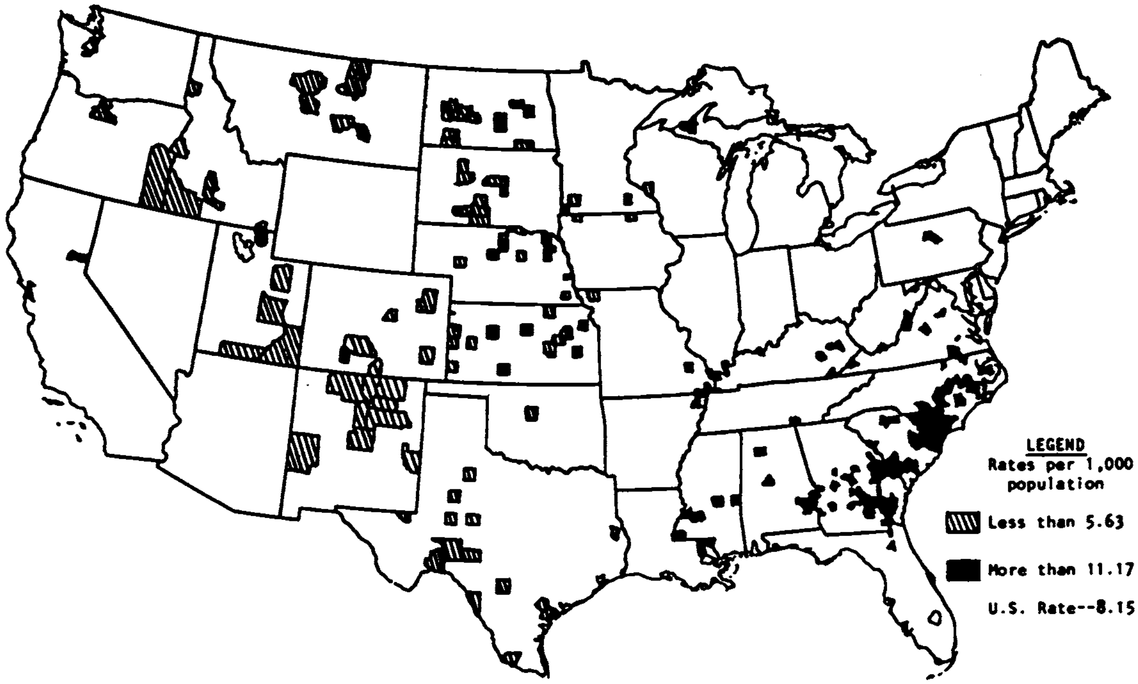


FIGURE 39 The 100 lowest and 100 highest death-rate counties, cardiovascular diseases, white males, age 35–74, 1968–1972.

Of the 200 lowest-rate counties, identified without regard to either standard error or systematic error, 83.0+ percent are in these same 14 plains and mountain states, and only 7.5 percent were east of the Mississippi River.

Of the 100 highest-rate counties, 84 are in the Coastal Plain or along or near the Fall Line in the Southeast; 64 of the highest-rate counties are in Georgia and the Carolinas. Geologically, the Coastal Plain extends up the Mississippi embayment as far north as southern Illinois; five of the highest-rate counties are in this northern part of the Mississippi Delta. Only four of the highest-rate counties are west of the Mississippi River, and two of these are in the Coastal Plain.

Of the 200 highest-rate counties, selected without regard to either standard error or bias, 71.5 percent are in the Coastal Plain and nearby areas, with 52.5 percent located in Georgia and the Carolinas alone; only 9.5 percent are west of the Mississippi River.

The methods of selecting the extreme-rate counties sharpen the patterns identified; however, even without the methodological refinements, there remains the concentration of lowest-rate and highest-rate counties in areas as shown in Figure 39, and listed in Table 34.

## DRINKING-WATER QUALITY AND CARDIOVASCULAR DISEASE

(A. Richey Sharrett)

Comprehensive reviews of the relation of drinking water to cardiovascular diseases have appeared recently (Neri *et al.*, 1974a; Punsar, 1973; Sharrett and Feinleib, 1975). The discussion here will be limited to general findings and commentary.

### *Water Hardness*

In major nationwide studies in the United States, the United Kingdom, and Canada, geographic areas with hard water were found to have lower cardiovascular mortality rates than areas with soft water (Crawford *et al.*, 1968; Neri *et al.*, 1972; Schroeder, 1966). Data were generally presented as correlation coefficients, and these were usually highly significant. Each of the major categories of cardiovascular disease showed similar negative correlations to water hardness, with the exception that in U.S. data cerebrovascular mortality was less closely related to water hardness than was arteriosclerotic heart disease mortality. In Britain, hard-water areas had 40 percent lower cardiovascular mortality rates than soft-water areas; in the United States the difference between areas was found in various studies to be closer to 15 percent. Studies of smaller nations or regions within nations have produced less consistent results (Biörck *et al.*, 1965; Lindeman and Assenzo, 1964; Mulcahy, 1966). One study sampled water consumed at home by individuals living in a single county (Comstock, 1971). The trend, though not statistically significant, was in a direction contrary to the water-hardness hypothesis: water drunk by decedents of arteriosclerotic heart disease was harder on the average than that drunk by matched controls.

The discovery of the relation between mortality and

TABLE 34 Counties with Extreme Rates, Cardiovascular Diseases, White Males Age 35–74, 1968–1972 (Average Annual Death Rates per 1000 Population, Age-Adjusted)

| States and "Lowest-Rate" Counties | Rate |
|---|---|
| California | |
| Sierra | 5.4 |
| Colorado | |
| Bent | 4.9 |
| Costilla | 3.2 |
| Douglas | 5.0 |
| Saguache | 5.6 |
| Washington | 4.7 |
| Idaho | |
| Camas | 4.9 |
| Franklin | 5.3 |
| Gooding | 5.2 |
| Jerome | 5.5 |
| Latah | 5.5 |
| Owyhee | 3.9 |
| Washington | 4.7 |
| Iowa | |
| Mitchell | 5.5 |
| Osceola | 5.0 |
| Kansas | |
| Coffey | 5.1 |
| Greeley | 5.1 |
| Jefferson | 5.4 |
| Kiowa | 5.0 |
| Lincoln | 5.3 |
| Marion | 5.3 |
| Morris | 5.4 |
| Scott | 5.4 |
| Stanton | 3.8 |
| Trego | 5.1 |
| Wabaunsee | 3.9 |
| Wallace | 5.4 |
| Washington | 5.4 |
| Kentucky | |
| Hancock | 5.6 |
| Jackson | 4.8 |
| Magoffin | 5.3 |
| Wolfe | 5.6 |
| Minnesota | |
| Dodge | 5.4 |
| Minnesota—Continued | |
| Murray | 5.5 |
| Rock | 5.5 |
| Missouri | |
| Nodaway | 5.3 |
| Montana | |
| Chouteau | 4.7 |
| Judith Basin | 5.6 |
| Musselshell | 5.2 |
| Phillips | 4.6 |
| Treasure | 4.7 |
| Nebraska | |
| Arthur | 2.6 |
| Blaine | 5.4 |
| Boyd | 5.5 |
| Cedar | 4.8 |
| Johnson | 5.1 |
| Rock | 4.2 |
| Sarpy | 5.5 |
| Stanton | 5.2 |
| Wayne | 5.3 |
| Wheeler | 5.3 |
| New Mexico | |
| Catron | 4.4 |
| Colfax | 5.4 |
| Mora | 5.6 |
| Rio Arriba | 5.4 |
| Roosevelt | 5.0 |
| San Miguel | 5.4 |
| Santa Fe | 5.5 |
| Taos | 4.9 |
| Torrance | 4.2 |
| North Dakota | |
| Adams | 5.5 |
| Dickey | 4.7 |
| Dunn | 5.4 |
| Eddy | 5.1 |
| Griggs | 5.6 |
| Hettinger | 5.5 |
| Kidder | 5.5 |
| Mercer | 5.5 |
| Oliver | 4.4 |
| Oklahoma | |
| Kingfisher | 5.3 |
| Oregon | |
| Malheur | 5.4 |
| Wasco | 5.5 |
| South Dakota | |
| Hyde | 4.6 |
| Jones | 2.4 |
| Mellette | 1.9 |
| Sully | 5.3 |
| Todd | 4.0 |
| Washabaugh | 5.1 |
| Zeibach | 5.6 |
| Texas | |
| Borden | 4.5 |
| Coke | 5.6 |
| Crockett | 4.9 |
| Dickens | 5.5 |
| Glasscock | 4.1 |
| Goliad | 5.0 |
| Loving | 5.1 |
| Maverick | 5.4 |
| Medina | 5.0 |
| Refugio | 5.6 |
| San Augustine | 5.3 |
| Starr | 5.0 |
| Sutton | 4.8 |
| Terrell | 4.1 |
| Utah | |
| Cache | 4.6 |
| Duchesne | 5.2 |
| Emery | 4.7 |
| Kane | 3.9 |
| San Juan | 4.1 |
| Virginia | |
| Highland | 5.2 |
| Wisconsin | |
| Buffalo | 5.4 |

| States and "Highest-Rate" Counties | Rate |
|---|---|
| Alabama | |
| Barbour | 11.4 |
| Bibb | 11.8 |
| Bullock | 11.3 |
| Russell | 13.1 |
| Winston | 11.3 |
| Colorado | |
| Mineral | 13.1 |
| Florida | |
| Bradford | 12.6 |
| Georgia | |
| Appling | 12.2 |
| Atkinson | 13.5 |
| Bacon | 12.8 |
| Baldwin | 12.5 |
| Ben Hill | 11.6 |

**TABLE 34**
Continued

| States and "Highest-Rate" Counties | Rate | States and "Highest-Rate" Counties | Rate | States and "Highest-Rate" Counties | Rate |
|---|---|---|---|---|---|
| Georgia—Continued | | Louisiana (Parishes) | | Pennsylvania | |
| Bibb | 11.3 | Tangipahoa | 11.7 | Clinton | 11.3 |
| Brantley | 12.5 | Washington | 11.2 | | |
| Burke | 12.8 | | | South Carolina | |
| Charlton | 11.4 | Michigan | | Allendale | 11.3 |
| Clay | 13.3 | Ontonagon | 11.6 | Barnwell | 13.0 |
| Coffee | 11.8 | | | Chester | 12.2 |
| Dodge | 15.2 | | | Chesterfield | 12.7 |
| Emanuel | 13.8 | Mississippi | | Clarendon | 12.5 |
| Jeff Davis | 12.2 | Claiborne | 12.7 | Colleton | 12.4 |
| Jefferson | 11.7 | Copiah | 11.9 | Darlington | 11.8 |
| Jenkins | 11.8 | Lauderdale | 11.2 | Dillon | 12.3 |
| Lamar | 11.8 | Scott | 11.2 | Florence | 12.1 |
| Long | 14.4 | Wilkinson | 12.5 | Georgetown | 11.6 |
| McDuffie | 13.9 | | | Hampton | 11.6 |
| Muscogee | 11.4 | | | Horry | 11.9 |
| Pierce | 12.3 | Missouri | | McCormick | 11.2 |
| Pulaski | 11.6 | Dunklin | 11.2 | Marion | 11.9 |
| Screven | 12.0 | Madison | 11.3 | Marlboro | 12.9 |
| Taylor | 11.3 | New Madrid | 11.4 | Sumter | 12.1 |
| Telfair | 12.2 | | | Union | 12.8 |
| Terrell | 12.0 | | | Williamsburg | 12.8 |
| Toombs | 14.1 | North Carolina | | | |
| Turner | 11.3 | Columbus | 12.5 | Tennessee | |
| Twiggs | 11.7 | Craven | 11.7 | Marion | 11.7 |
| Wayne | 11.5 | Cumberland | 11.2 | | |
| | | Duplin | 12.1 | Virginia | |
| | | Greene | 12.9 | Bath | 11.4 |
| | | Harnett | 13.0 | Brunswick | 12.9 |
| Illinois | | Johnston | 12.5 | Greensville* | 11.2 |
| Alexander | 11.9 | Northampton | 12.1 | Nelson | 11.7 |
| Pope | 11.6 | Pitt | 12.3 | Orange | 11.8 |
| | | Richmond | 12.7 | Petersburg City | 12.1 |
| | | Robeson | 12.8 | Wise* | 11.5 |
| Kentucky | | Scotland | 12.2 | | |
| Ballard | 11.3 | Tyrrell | 13.3 | West Virginia | |
| Bell | 11.6 | Vance | 11.8 | Mercer | 12.5 |
| Fulton | 12.0 | Washington | 13.2 | Mineral | 11.5 |
| Gallatin | 12.2 | Wilson | 11.5 | Morgan | 11.2 |

*Including independent cities within the county.

drinking water was serendipitous. Kobayashi (1957), an agronomist studying irrigation water, observed in 1957 that areas in Japan with high stroke mortality had very acid river water. Schroeder then assembled U.S. data and found that the association was with hardness rather than acidity and with all cardiovascular disease rather than just stroke (Schroeder, 1960), and this was the usual result in subsequent studies. Thus the relation is a result in need of an explanation. That the correlations achieve statistical significance gives them more credibility than it should. The significance of correlations among, say 100 cities, is tested on the assumption of a sample size of 100. But the assumption is incorrect because the cities are not statistically independent. For example, if 10 cities in the southeastern United States have both high mortality and soft water, this hardly is as convincing as would be 10 independent replications of an experiment with consistent results. The 10 cities tend to be similar to each other in many respects. Factors that can potentially confound the relationship of interest are distributed similarly among them. Therefore, in a sense, the results among cities in a single homogeneous region constitute only one experiment, and the results among 100 cities across the United States constitute only a few experiments. This argument, of course, bears on the significance of geographic correlations generally. Statistical significance can be expected to occur by chance more often than the statistical tables indicate, because geographic units are not independent.

The British Medical Research Council group has made an extensive investigation of possible confounding factors (Crawford *et al.*, 1968; Gardner *et al.*, 1969). The estimated effect of water hardness in Britain appears to be larger than in other parts of the world, and in these studies, the magnitudes of the correlation coefficients of water hardness and mortality are not appreciably reduced by the inclusion of a number of socioeconomic and climatic variables. Gardner, however, found a positive correlation between cardiovascular mortality and rainfall. Both this correlation and the negative correlation of mortality with water hardness remained strong in a multivariate analysis. In U.S. data, where the correlations between mortality and drinking water are less strong, rainfall has again been shown to be positively correlated with mortality. Its inclusion, along with other climate and socioeconomic variables, in multivariate analysis weakens the relation between mortality and drinking water but does not render it nonsignificant (Dudley *et al.*, 1969; Sauer, 1974).

This, perhaps, is substantially the conclusion to be drawn from the recent controversy in Britain over these relationships. Roberts and Lloyd (1972) stated their belief that the effect of the water hardness on mortality was "entirely dependent" on the association of soft water with high rainfall. They based their belief on an analysis of ischemic heart disease mortality rates in small localities in South Wales and mortality ratios in England and Wales, which showed that water-hardness correlations became nonsignificant when rainfall was included in the analysis. Crawford *et al.* (1972) showed that this did not occur for England and Wales if rates instead of ratios were used. West and Roberts with more recent data (West *et al.*, 1973) then found that with both rainfall and temperature included, the drinking-water correlation became marginally significant and stated that the correlation was "almost entirely" a result of the association of drinking water with climate.

In Dudley's work with U.S. metropolitan areas, low mortality was associated with low rainfall and humidity and extreme temperatures; high mortality with high temperatures and humidity (Dudley *et al.*, 1969). This could be well summarized by saying that the climate associated with low mortality is continental in type; that associated with high mortality is coastal. The association in the United States of soft water with coastal areas and hard water with the Central Plains is well known, and, of course, one suspects that important differences in the environment and in the ways people live and earn their living may be geographically distributed in a similar way. The effort to disentangle all these variables from each other by statistical means alone is perhaps futile. Certainly, the functional relationships between drinking water, climate, and mortality cannot be decided solely by whether geographic correlation coefficients are just at or above nominal levels of significance.

### *Water Hardness and Geochemistry*

Crawford *et al.* (1972) raised the relevant question of whether rainfall acts through water hardness. If heavy rainfall is associated with soft water causally, for example, by diluting and lowering the mineral content of ground and surface supplies, then soft water may be the reason for the relation of rain to poor cardiovascular health. But if so, why would rainfall correlate with mortality as well as it does—approximately as well as does water hardness? Perhaps because rain influences human mineral intake through food as well as through water.

Soil-mineral levels in the United States appear to follow rainfall patterns. Atlantic and Gulf coastal soils are relatively deficient in metals such as cobalt, manganese, nickel, and zinc, and dry soils in the western half of the country are high in calcium, magnesium, sodium, and potassium content (Shacklette, 1971). Rain and evaporation affect soil lithium, and lithium in drinking water can be seen to be low in the rainy northwestern and Atlantic coastal areas (Durfor and Becker, 1964). To the extent that the mineral content of plant and animal foods is affected by the content of soils, rainfall will have an influence on human nutrition through foods as well as through drinking water. If so, rainfall might correlate with mortality better than does drinking water.

A relation of rainfall to the mineral content of both food and water could explain why water hardness bears a more consistent relation to mortality in studies of nations than it does in studies of smaller geographic regions. Climate and soil have broad regional distributions. Within a country or small state or county, cities that differ in the mineral content of their water supplies, perhaps because some use groundwater and others use surface water, will generally still share common food supplies. Across a large nation, however, broad climate, soil, and water patterns emerge. Cities in one region with soft water, for example, and with food from the generally leached soils of the area will differ in both food and water from cities located at a distant region of the nation. The high correlation of drinking water and health in the nationwide study will in part reflect these associations. The lack of important health differences in communities that are adjacent geographically but have different water sources (Allwright *et al.*, 1974; Hadden, 1974) might indicate that water itself is a less important variable than are the associated geochemical variables. Birmingham, England, might serve as another example. It is located in a hard-water region and has low mortality but very soft drinking water (Roberts and Lloyd, 1972).

The issue of the health significance of minerals in drinking water versus the health significance of regionally distributed geochemical factors indexed by drinking water was subjected to an appropriate statistical analysis by Neri *et al.* (1972). They find, as do others, that drinking-water composition correlates with mortality less when municipalities are studied than when whole provinces are studied. Greater stochastic variability in death rates among municipalities than among provinces might explain that; but when the authors demonstrate a smaller average effect of water on mortality among cities than among provinces (they use the regression statistic for this), this finding is not the result of stochastic variability, and it can be taken as evidence in one part of the world of the importance of a regionally distributed factor associated with water.

Another type of approach to water as an index to the geochemical environment that has been only lightly explored (Masironi, 1970; Sauer *et al.*, 1971) is the study of untreated surface water. In these studies, raw water seemed to be related as closely to health as is finished drinking water, although it is finished water that humans drink. If raw water were clearly superior to finished water as a health predictor, its relation to the natural environment would be the probable reason. Another promising approach is the study of areas that change their water. In England and Wales, areas that switched to harder water had falling mortality rates; those with softer water tended to have rising rates (Crawford *et al.*, 1971).

None of these studies, however, has resolved the question of whether drinking water, as consumed, is of importance to health; whether water quality is an index of some important geochemical factor; or whether, as seems plausible, water and the other components of the geochemical environment may have related health effects. The failure to date to find socioeconomic confounding factors, and the fact that water hardness is not associated with lifestyle similarly in the various nations where it has been found to be related to health, indicates that the choice may lie within the above three alternatives.

TABLE 35 Association of Trace Metals with Hardness in Raw, Finished, and Tap Water, by Country Studied

| Metal | Continent or Country | Association of Metals with Hardness in: Raw Water | Finished Water | Tap Water |
|---|---|---|---|---|
| Copper | North America | +[a] | 0[f]<br>−[b] | −[b,c] |
| | Great Britain | | | +[d,e] |
| Zinc | North America | +[a] | +[b] | 0[b,c] |
| | Great Britain | | | 0[d]<br>+[e] |
| Cadmium | North America | +[a] | 0[b] | 0[b]<br>−[c] |
| | Great Britain | | | 0[d] |

[a]Source, Masironi, 1970.
[b]Source, Neri *et al.*, 1974b.
[c]Source, McCabe, 1970.
[d]Source, Crawford and Morris, 1967.
[e]Source, Elwood and Abernethy, 1974.
[f]Source, Durfor and Becker, 1964.
+, Metals found at higher levels or more often detected in hard water.
−, Metals found at lower levels or less often detected in hard water.
0, No clear association.

### *Hardness and Trace Metals in Drinking Water*

Work on the health effects of drinking-water constituents is clearly needed. Hard water usually has a high total-mineral content. In general, total dissolved solids, conductivity, and radioactivity, and the major minerals in hard water—calcium, magnesium, sodium, potassium, bicarbonate, sulfate, and silica—have correlated negatively with cardiovascular mortality (Masironi, 1970; Sauer *et al.*, 1971; Schroeder, 1960, 1966; Schroeder and Kraemer, 1974). In general, however, aside from calcium and magnesium, which we shall touch on later, interest in a specific water factor has centered on trace elements, but existing data are fragmentary. Copper, zinc, and cadmium are metals with hypothesized relationships to cardiovascular disease and will serve here to illustrate our point.

The relation of copper, zinc, and cadmium to hardness in drinking water depends on whether one is considering raw water prior to treatment at the public water plant, finished water at the plant, or distribution samples taken at home taps, as shown in Table 35.

In North American untreated supplies, zinc and cadmium, and to a lesser extent copper, appear to be highly associated with hard water. After treatment, this positive relationship may be weakened for zinc, absent for cadmium, and perhaps reversed for copper. However, there is great variation from city to city. In tap water, zinc shows no clear relation to hardness, cadmium is perhaps somewhat more frequently detected in the softest supplies, and copper has a definite association with soft water. In British studies of tap water, zinc, depending on the study, shows either no association or a positive association with hardness, cadmium is unrelated to hardness, and copper is at higher levels in harder water.

It is obvious that, for these metals, the softness of public water is not the only factor in its corrosiveness to domestic plumbing. Corrosiveness, measured by a modified Langelier's index, correlates with mortality better than does hardness in a recent paper by Schroeder and Kraemer (1974), indicating that the effect of domestic pipes on metal levels in tap water may be important. Because the principal types of metal pipe, those made from copper and galvanized iron, are both common in most communities, existing studies of mortality in communities and their average tap-water content (Elwood and Abernethy, 1974; Neri *et al.*, 1974b) will probably fail to resolve the issue.

The situation with respect to calcium and magnesium is different from that of trace metals, because these elements are not much affected by distribution systems (Neri *et al.*, 1974b). The published geographic correlations then bear directly on their relevance to health. Recent results, indicating that their concentration in human tissues may vary with the hardness of municipal supplies (Anderson *et al.*, 1973; Bierenbaum *et al.*, 1973; Crawford and Crawford, 1969; Neri *et al.*, 1974b), and existing knowledge of their relation to electrical properties of the heart, as well as results suggesting higher sudden-death rates in soft-water areas, make this an exciting area for research.

## RECOMMENDATIONS

### *Policy*

- Interagency and interscientist communication should be improved to optimize research opportunities.

### *Environment*

- Practical support mechanisms for research on the *chronic* effects of trace elements should be sought. Attempts should be made to ascertain the contribution of foods and geochemical environment as well as water to the trace-element environment of the individual.
- The mapping of food origins and consumption at local sites of interest should be undertaken.

### *Fundamental Studies of Metabolic Nature*

- Better understanding of the fundamental metabolism and functions of trace elements is needed. Studies of the bioavailability of elements of interest should be undertaken.
- Improved understanding and techniques for measuring these elements are needed with particular reference to stores, balance, and turnover. Interactions such as that between zinc and cadmium in relation to hypertension need to be elucidated.

### *Associative Studies of Cardiovascular Disease*

- Survey studies of relations of water composition to cardiovascular disease should be strengthened and refined.
- Opportunities should be sought to observe communities in which water hardness or other circumstances of trace-element exposure are anticipated to change or have recently changed.
- The data base of observations relating cadmium accumulation in the body (kidney) with hypertension should be improved. The prevalence of the association should be ascertained and an effort made to define incidence of cadmium-hypertension.

### *Descriptive Methodology*

- Health statistics should be collected in terms of total mortality as well as for the specific disease at issue.
- High- and low-extreme incidence rates should be collected on either a county or state-economic-area basis with due attention to corrections for such factors as resident institution populations and migration patterns. These should then be related to appropriate geochemical environmental maps.
- The obverse of this, i.e., high- and low-extreme maps, by county or economic area of interest, should be developed and related back to relevant diseases.
- Specific maps showing locations of high- and low-trace-element compositions in water and stratified according to multiple combinations of elements of interest, would be of special importance.
- An array of data that will minimize confounding by other environmental, socioeconomic, genetic, and measurement techniques should be sought.
- The numbers of samples, measurements, and individuals examined should be adequate to yield a significant conclusion according to prestated assumptions when specific comparisons are proposed. Measurements will require adequate specificity, sensitivity, and quality control.

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# VIII

# *Urolithiasis*

GEORGE K. DAVIS, *Chairman*

*Nancy B. Cummings, Birdwell Finlayson, John L. Meyer, M. J. Vernon Smith*

## RELATIVE IMPORTANCE OF UROLITHIASIS

The reported geographic distribution of urolithiasis, which is limited to kidney stones in this discussion, indicates high- and low-risk areas, with frequencies in some areas more than ten times those in others. This distribution is generally accepted as indicating that geochemical influences are important causative or preventive factors in the formation of urinary calculi (Anonymous, 1965). Identification of the geochemical factors has proceeded very slowly, although the available morbidity data indicate that much higher priorities should be given to urolithiasis research, because the incidence of urolithiasis ranks with that of hypertension and malignant neoplasms.

Inevitably the interrelations of such factors as culture, dietary habits, climate, race, and occupation with the geochemistry of the environment must be recognized in the occurrence of urinary calculi. Consequently, in making their recommendations, the Work Group on Urolithiasis emphasizes the need for evaluation of the possible confounding influences.

The available data suggest that diseases of the genitourinary tract occur almost as frequently as those of the respiratory tract or of the circulatory system. The number of recognized cases of urinary calculi of the kidney and ureters has been estimated by Ranofsky (1974) to approach in numbers and frequency the occurrence of hypertensive disease, but renal calculi are reported in hospital discharges only about half as frequently as malignant neoplasms. These data provide some perspective to the importance of this geographically distributed disease problem, but the data are inadequate because many more cases of urolithiasis occur than are hospitalized. The estimate that five times as many cases are not hospitalized as are admitted to hospitals seems to be supported by preliminary data from the program of health interviews being conducted by the National Center for Health Statistics (1974). These figures are even more startling when the morbidity information revealed in this report is considered.

The days of work lost by people, mostly young men, suffering from urolithiasis, have been reported as 14.7 million days per year. This characteristic distribution of cases of urinary calculi involving so many young males in their beginning productive years is particularly serious from a socioeconomic point of view, because they are, in general, less able to sustain this loss (Finlayson, 1974).

The data on the epidemiology of urinary calculi exhibit a real information gap, which further illustrates the need for definitive data on the occurrence in discrete areas, preferably logically identified geographic areas (Blandy, 1974; Butt *et al.*, 1952; Neri *et al.*, 1974). Areas the size of states are generally too large to be useful in terms of potential geochemical environmental relations (see detail available in Figures 40 and 19).

In the United States, the most common stones are calcium oxalate or calcium oxalate mixed with calcium phosphate, with calcium oxalate predominating (Herring,

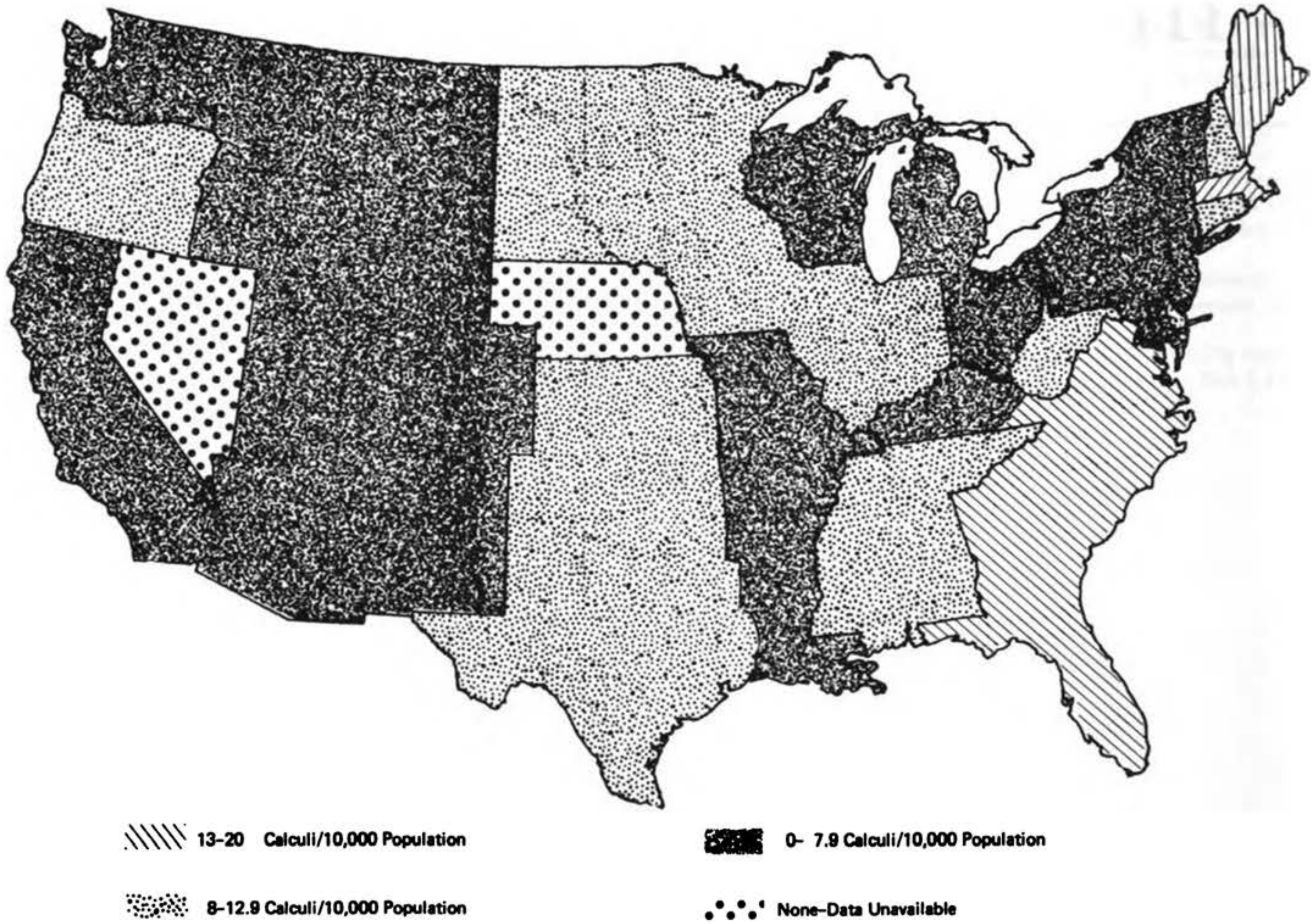


FIGURE 40 Geographic distribution of urolithiasis in the United States. (Map courtesy of Birdwell Finlayson.)

1962). This observation comes from the experience of general practitioners in North Florida and South Georgia (B. Finlayson, University of Florida, Gainesville, personal communication, 1974), who report that approximately 90 percent of the stones are calcium oxalate or calcium oxalate-calcium phosphate stones; by comparison, the reported U.S. average of calcium oxalate predominance is approximately 60 percent (Prien and Prien, 1968).

In examining the geochemical environment in relation to urolithiasis, it seems desirable to concentrate on a particular type of urinary calculi. The problem of pediatric urolithiasis is a real one in many parts of the world, but the incidence in the United States is much less than in other parts of the world, and it is a small proportion of the total (Ghayali *et al.*, 1973; Sanjad and Alterbarmakian, 1973; Paulson *et al.*, 1972; Chabal, 1972; Bennett and Colodny, 1973; Retief, 1974; Sadre *et al.*, 1973).

Because present epidemiological data, given in terms of state averages, are of such limited value for assessing relations to the geochemical environment, the possibility of reducing the geographic-area size as a base for reporting urolithiasis data is especially attractive. The Professional Standards Review Organizations (PSRO) Standards for Hospital Discharge Data, which was required to be operational for all areas by 1976, should be providing useful data by zip code area within a few years after that date (Dunphey *et al.*, 1974).

Zip code areas, of course, were established for postal service needs, quite unrelated to such objectives as accumulating epidemiological data, but it seems possible to group zip codes to permit relating urinary-calculi occurrence data to geological-geographic areas with the further possibility of defining the population characteristics, parameters of the geochemical environment, and relationships that may exist between them. Telephone area codes have also been suggested as a possible base, but many of the same criticisms apply as with zip codes.

At present, practically no data are available for an area more restricted than that of a state or region. Studies similar to that of Garrett and Shelley (1951) are conspicuous by their absence.

A number of reports have indicated that the soft-water areas have had an increasing incidence of urinary calculi as, for example, those of Anderson (1962, 1966, 1969) and Landes *et al.* (1977). However, in examining possible geochemical factors of the environment that might have an influence on the formation of urinary calculi, it seems desirable to consider those suspected conditions in stone formers that suggest a relation to food, water, and living conditions. The composition of stones and the known relation of chemical components in metabolism suggest the need for data regarding the ratios of calcium to phosphate, of calcium to magnesium, and of calcium to oxalate. Calcium:strontium ratios and absolute intakes of strontium should also be examined (Amin, 1973; Watts, 1973; Finlayson and DuBois, 1973; Takasaki, 1972; Westbury, 1974; Sutor *et al.*, 1974; Lonsdale *et al.*, 1968; Sutor and Wooley, 1971, 1972; Hodgkinson and Pyrah, 1958; Prien and Prien, 1968; King *et al.*, 1968). Bioavailability information is essential, because it is the urinary excretion and therefore concentrations in the urine that will determine the potential for calculi formation.

The need for oxalate data cannot be emphasized too strongly because of the predominance of calcium oxalate stones, but present methods used in clinical studies for detecting oxalate are poor. The need for a better, reliable oxalate detection method is acute, and support of efforts to develop such a method is strongly recommended.

The reported geographical variation in the incidence of urinary calculi, suggesting geochemical relations, places emphasis on the possible influence of drinking-water composition. The studies of Anderson (1969, 1973) mentioned above, suggest that a relation may exist between hard and soft water and stone formation. These studies indicate the need for evaluation of the role of sodium intake as a factor, because soft water may be characterized by low mineral content or softened by replacement of calcium and magnesium by sodium in water softeners.

The evidence for the role of trace elements as factors in the etiology of stone formation is so limited that any data on the intake of such elements as lithium, potassium, and zinc should be examined in the context of high-risk and low-risk populations with respect to calculi formation. The role of silicon and fluoride in calcification of bone and teeth suggests that these elements should also be considered in relation to calculi formation. Because of the similarity in chemical composition, the tendency toward dental plaque formation may be an indicator of individuals with a greater risk of being stone formers, and information of this nature would be valuable (Luoma and Nuuja, 1977).

Because the terms "hard" and "soft" water represent a wide range of chemical compositions, it appears that, when available, information on the total-dissolved-solids content of water should be examined, as well as the chemical makeup of the materials present in water ingested. The fact that water is consumed in food products, soft drinks, and other beverages that may influence urine composition should not be overlooked.

When data regarding urolithiasis can be made available on a scale that reflects limited geochemical environments, such as a river drainage area or areas with a reasonably discrete water supply, then the assistance of cartographers in showing the relation of geologic formations and water composition will be especially valuable for these areas. Their maps will be able to provide the bases for consideration of cause-and-effect relations that are not now available. Such other influences as cloud cover, and therefore relative rainfall, and sunshine exposure might then be better evaluated.

In any evaluation of geochemical factors it is essential that other interfering or contributing influences be recognized and evaluated. It is not now clear how much genetic and cultural backgrounds influence the incidence of urinary calculi. It has been suggested that black populations are essentially free of calcium oxalate calculi (Modlin, 1957, 1967). However, as blacks in the United States have become more affluent, and their cultural patterns have begun to resemble those of their Caucasian fellow citizens, the incidence of urolithiasis among blacks has begun to match that of others in their residential locality (M. J. Vernon Smith, Medical College of Virginia, Richmond, personal communication, 1974).

The examination of the body chemistry to ascertain possible differences between stone formers and nonformers indicates that a fairly large segment of the world population may be potential stone formers and that when the stress factor or insult occurs, then stones develop. The possibility that certain substances are present in the genitourinary tissues and in urine that prevent stone formation cannot be ignored. These substances may be trace elements, ratios of trace elements or macroelements (Elliot and Ribeiro, 1973), or organic compounds such as mucopolysaccharides (Robertson *et al.*, 1973). The search for peculiarities in body chemistry that may be present in stone formers needs constant support. The relation of urine concentration and its association with water consumption has often been considered important in the etiology of stone formation (Watson and Dale, 1966). It has been recognized that the urine of stone formers is commonly more concentrated than that of nonformers, although this is not universally true. The need is emphasized, however, to examine water intake and composition of that water as a factor, realizing that the water is often consumed in other forms, such as soft drinks, beer, and fruit juices.

There are other factors that need to be recognized and evaluated in consideration of cause-and-effect relations between calculi formation and the geochemical environment.

The time required for calculi formation may vary a great deal. In some individuals, stones may develop in a short period of weeks or months. In others, the process may take years. In general, experience appears to indicate that if there is a recurrence, it may be in 2 to 7 years. This emphasizes the need for time-of-residence information as a factor if geochemical relations are to be identified. Data are not now available to calibrate the importance of time of residence in an area of high-frequency stone occurrence as a risk factor.

Anatomical features that may be related to stone formation need to be examined. These would include height and weight, because there is some indication that overweight individuals are more likely to form stones. Age and sex also need to be evaluated as factors (Schneider and Bauerschmidt, 1973). The concentration profile of stone salts in the distal renal tubules has been considered a possible factor in stone formation.

The observation that people of Semitic origin appear to have a high proportion of uric acid stones suggests the possibility of a genetic relationship. The role of cultural background may, however, be the actual determining influence, because changes in the pattern of stone type occur as groups migrate from one environment to another (Vermooten, 1956).

For these reasons, both cultural and genetic relations must be considered when examining geochemical factors possibly related to calculi formation.

A relation has been noted repeatedly between the presence of a hypercalciuria condition and the occurrence of urinary calculi. The question may well be asked whether idiopathic hypercalciuria is a result of a genetic tendency to excess urinary excretion of calcium or of increased absorption efficiency (Henneman *et al.*, 1958; Morrison, 1974; Rose and Harrison, 1974).

Observations of the influence of carbohydrates, especially glucose and sucrose—causing increased absorption of calcium—suggest that dietary practices may be of great importance as factors in hypercalciuria (Lemann *et al.*, 1969). Because cultural patterns influence diet to a significant degree, this may be the basic factor behind certain apparent ethnic relationships. The practice of heavy cola-drink consumption with the accompanying sugar intake, for example, may be such a cultural factor in hypercalciuria and related calculi formation.

The socioeconomic status of patients forming calculi should be considered as a factor, because evidence has suggested that increasing affluence is paralleled by an increase in urolithiasis (Schneider *et al.*, 1973). This is perhaps related to occupation, because sedentary individuals appear to be more frequent stone formers than people in more active occupations.

There may well be climatic factors involved, which in turn may relate to water consumption, because there is evidence that individuals migrating to tropical areas or working in hot environments have an increased incidence of calculi. This increase may even be related to seasonal changes with a higher incidence occurring in the warmer seasons (Baleson, 1973).

The relation of cigarette smoking to other diseases has suggested that this practice should be examined in connection with studies of the environment as related to urolithiasis (Watson and Dale, 1966; Westlund, 1973).

The great paucity of cause-and-effect information in relation to urolithiasis has suggested that any parameters of health interview information that can be readily secured should be examined with respect to urolithiasis so that potential geochemical effects may not be overlooked or confounded with influences not of geochemical origin.

Criteria should be developed that will result in more complete and more reliable information in the diagnosis of urolithiasis. The limited number of urologists may have produced a bias in the reporting of urolithiasis occurrence and the accuracy of such diagnoses (Rose, 1967).

The medical profession and biomedical research scientists concerned should be encouraged to give this problem their early attention. Radiological or actual observation information should be a part of reporting information. In this respect, information on recurrence is needed. The experience of the British, who report that 90 percent of those forming one stone will form a second, contrasts with the experience in the United States, where that ratio is nearer to 20 percent.

## RECOMMENDATIONS

- Epidemiological data on the incidence of urolithiasis and calculus composition should be routinely reported on a more discrete, local basis.
- The possibility of using grouped zip codes or telephone area codes in compiling (Professional Standards Review Organizations) PSRO information concerning urolithiasis should be evaluated.
- The urgent need for water-composition data to match the more discrete urolithiasis occurrence data should be established as a goal and fulfilled.
- The hard- and soft-water interrelations with urolithiasis, especially with calcium, magnesium, and sodium intakes, should be carefully evaluated.
- The potential influence of certain trace elements as potentiators or as inhibitors of urolithiasis should be examined in detail.
- A better oxalate-detection method is acutely needed, and support of efforts to develop such a method is strongly recommended.

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PART THREE

# *Data Collection, Manipulation, Display, and Analysis*

# IX

# *Geography–Cartography*

JESSE H. WHEELER, JR., *Chairman*

*Vincent P. Barabba, John B. Peterson, Richard H. Schweitzer*

## EFFECTIVE MAP EXPRESSION IN GEOMEDICAL RESEARCH

(Jesse H. Wheeler, Jr.)

Maps are indispensable tools in research that has a spatial dimension. But for the lay public, students, and even many scholars, cartography is a relatively unknown and arcane field. Therefore, a few guidelines, pointers, and sources of information are offered for geomedical researchers who might wish to enlarge their knowledge and effective use of maps. Excellent textbooks, monographs, and bibliographical aids, a large number of recent articles in professional cartographic and geographic journals, and a rich array of base maps, reference maps, and atlases are useful sources, and some are cited herein.

### *Purposes of Map Expression*

Maps enable data to be recorded in such a way that spatial patterns can be discerned. According to Robinson and Sale (1969, p. 94):

> A map is a system for coding a variety of kinds of information so that a trained reader can efficiently retrieve it. In addition to the variety of factual data that is normally included in a map, there is always a considerable amount of derivative information that arises because of the spatial relationships revealed by the locational arrangements of the primary data. This too is communicative information. The basic classes of marks and their numerous variations used for cartographic communication constitute a large body of symbols and method. Because the symbolism of cartography has developed over many centuries, numerous traditions and conventions regarding map representation have grown up, and in a sense, the symbolism of cartography has become somewhat standardized. On the other hand, the great possibilities for variation have effectively prevented any really rigid standardization, although in the case of large-scale reference maps, standardization is more nearly approached. Conversely, the cartographer who works with a thematic map must of necessity be more critical and imaginative so as to adjust the representation and symbolism to the special purpose of his map, since his precise objectives are likely to be unique.

Maps enable spatial patterns to be compared, with a view to establishing covariations and possible correlations among different spatial distributions. Howe (1970, p. 1) has written an effective summary of this use of maps in medical geography:

> When the data are mapped, mortality from different human diseases shows patterns of distribution which exhibit irregularities and apparent anomalies. Sometimes these patterns suggest an

> association with other distributions, physical or cultural, not previously apparent. The association may be with water supply, atmospheric pollution, type of soil, or micro-organisms and their insect and other vectors. Regional variations in the distribution of diseases may reflect the habits, the tempo, the mental tensions and the anxieties of our twentieth century existence, our diet, or the increasingly sedentary nature of our work. Predisposition to a particular disease on the part of certain people may be due to heredity, which may be indicated by a parallelism between its geographical distribution and those of some other gene frequencies, e.g. of particular blood groups. . . .
>
> In recent years epidemiological hypotheses relating exposure to ionising radiation to leukaemia, and cigarette smoking to cancer of the lung have been fruitful. Yet as long ago as 1855 John Snow demonstrated that cholera was a water-borne disease as a result of a very simple medical map which he drew around the Broad Street pump in London. . . .

Hopps (1970, pp. 35–36) comments as follows concerning pattern comparison, especially in regard to maps produced by computers:

> Our concern with mapping is because this offers the best way to present large amounts of complex data in a form that permits one to visualize the distribution of disease in relation to a wide variety of possible causal environmental factors (climatic, geochemical, occupational, etc.).
>
> Computer techniques have progressed to the point that, today, dot-type, shading-type, even contour-type maps can be produced by a computer quickly and accurately, assuming an adequate data base. . . . Such maps as these can be printed on transparent materials and overlayed on base maps that show topographic, political, or population data, etc. Moreover, multiple transparent overlays, each presenting different kinds of information, can be layered together to show relationships, including the extent of pattern match.
>
> Within such a system there is virtually no computer limitation as to map *scale*, because as the geographic area to be covered decreases (the size of the map remaining constant), the map scale varies inversely, and "resolution" increases. Variation in the kind of map *projection* poses more of a problem, but it is technically feasible to produce computer programs that can convert one projection form into another. Moreover, the same computer techniques that make possible direct map print-out also allow print-out of tabular and narrative data to provide specific yes/no or qualified answers, locations of things by latitude-longitude coordinates or political areas and the like, correlation coefficients, lists of references, or data sources, etc.
>
> Overlaying and visual pattern comparing is a very powerful process because it permits human detection of relationships so complex that standard mathematical methods may be unable to detect them. Thus, the kinds of maps that we are describing allow quick and clear correlations, serving an important need, even for the medical expert. The rapid production of maps by computer gives an additional advantage; the process is so fast that one can get an up-to-date or an historic presentation, within several hours. The fact that maps can be produced quickly and easily (once the computer system is in hand) means that there is little limitation as to the number and variety of maps that one can get, so the maps can be used freely as a means to display information in the course of studying disease situations rather than merely a way to record the end results of such study.

In a later section of this chapter, Barabba and Schweitzer discuss the interesting technique called cross-classification mapping, which enables two variables to be plotted simultaneously in multiple colors on a computer-produced map.

Of course, no matter how skillfully they are produced, maps cannot transcend the limitations of the data base, nor can they eliminate the factor of human judgment in manipulating the data. Hopps (1977) has considered some of the problems of compatibility of data in Volume II of this series. A recurrent problem discussed by Schofer (1975, pp. 337–338) is the selection of class intervals:

> One fundamental problem of map production and analysis is that of reducing discrete or continuous data sets to a limited number of class intervals. Although a continuous or infinite set of classes can be graphically represented, few users would find such a procedure practical or desirable. The creation of discrete classes of data and their representation by either the choropleth or point-interpolation method allows the cartographer to assign a particular spatial pattern to the map. The arbitrary determination of class intervals, which is acceptable in aspatial research, is impractical in cartography because every possible classification scheme has a unique spatial expression, a different map with a different meaning. The number of class intervals which can be selected is quite limited, of course, because map readers can seldom integrate more than about ten discrete surface symbols for pattern recognition.
>
> By manipulating class intervals, entirely different messages can be communicated on maps utilizing the same data. Gottman's maps of Megalopolis, for example, minimize the extreme concentration of social and economic phenomena in New York City by consistently including all "large" urban centers in one class—despite the fact that in some data sets the values for New York

City were larger than all of the other "large" cities combined. . . .

Further advice concerning the selection of class intervals is offered by Jenks and Coulson (1963, p. 120):

> Since classification is necessary, the objective of the map-maker should be that of selecting classes which retain all significant characteristics of the data. These class intervals should
> 1. Encompass the full range of the data.
> 2. Have neither overlapping values nor vacant classes.
> 3. Be great enough in number to avoid sacrificing the accuracy of the data, but not be so numerous as to impute a greater degree of accuracy than is warranted by the nature of the collected observations.
> 4. Divide the data into reasonably equal groups of observations.
> 5. Have a logical mathematical relationship if practicable.

Maps enable ideas connected with space to be presented sharply. The explicit presentation of ideas by means of maps might be termed *intellectual cartography.* Finding ways to do this more effectively is a challenging frontier of cartographic research.

### *Map Design, Symbolization, and Drafting*

This section applies particularly to the design of finished maps which are to be reproduced and disseminated to users. Even work maps involve design, however, and time can often be saved in preparing finished maps, if the design of the work maps has been good. Proper design enables the map to display the data effectively and to point up the ideas the map is intended to convey. This involves the following procedures:

- Choice or construction of a base map of an appropriate projection and scale. (Some useful base maps and reference maps are listed below.)
- Choice of line weights and letter styles and sizes.
- Choice of appropriate symbols. Effective symbolization is a major key to successful map-making. The symbols should be sufficiently bold to be effective but not so garish as to distract the map user's attention. Some commonly used symbols are as follows:

*Dots* The areal distribution of a phenomenon often can be portrayed effectively by dots, each representing the same quantity or percentage. Distributions of two or more phenomena can be shown simultaneously by using dots of different colors or by using open circles, squares, or triangles of approximately the same dimensions as the dots. On percentage dot maps, each dot represents a stated percentage of the total quantity shown in the distribution. Such maps can be extremely useful for examining concordance or discordance between areas of occurrence of different phenomena. Percentage dots can be used in conjunction with percentage circles to show distributional data that vary greatly in concentration (Mackay, 1953).

*Graduated Dots, Circles, Bars, and Other Symbols* The graduation may be done mathematically or subjectively. To avoid confusion, the number of graduations should not be more than ten, and the size of each symbol should be sufficiently distinct to be readily recognized.

*Graduated Three-Dimensional Volume Symbols* Robinson and Sale (1969, p. 128) describe a valuable use of cubes or spheres as volume symbols:

> It is not uncommon that a cartographer is faced with a range of data so large that with interval scaling he cannot effectively show both ends of the range by graduated circles or squares. If he makes the symbols large enough to be differentiated clearly in the lower end of the scale, then those at the upper end will overshadow everything else and ruin the communication. Many attempts have been made to surmount this difficulty by employing a symbol form drawn to simulate a volume rather than an area, such as pictorial cubes or spheres. . . . This has been done by scaling the symbols according to the cube roots of the data, that is, by making the sides of the front of a perspective cube or the circle bounding a sphere proportional to the roots. If the symbols were actually three-dimensional, their volumes would be in strict linear proportion to the numbers they represented. The cube roots of a series cover a much smaller range than the square roots, and this, of course, is what makes it ostensibly possible to portray graphically the larger range of data.

Such symbols are tedious to construct and create problems for readers who may have difficulty in visualizing the values where a tenfold increase in symbol size represents a thousandfold increase in the value represented. Nonetheless, for certain cartographic situations these volume symbols are indispensable.

*Simple Graphs* Bar graphs, pie graphs, or others may be placed in the map areas to which their data refer.

*Choropleths and Isarithms* The portrayal of quantitative areal distributions by using color patches or shading patterns and tones to represent data classes or by using lines connecting points with equal data values is described this way by Robinson and Sale (1969, p. 146) except for the explanatory material that has been inserted within the brackets:

> In the simple choropleth map the geographical locations of the class limits employed coincide with the boundaries of the unit areas [such as counties,

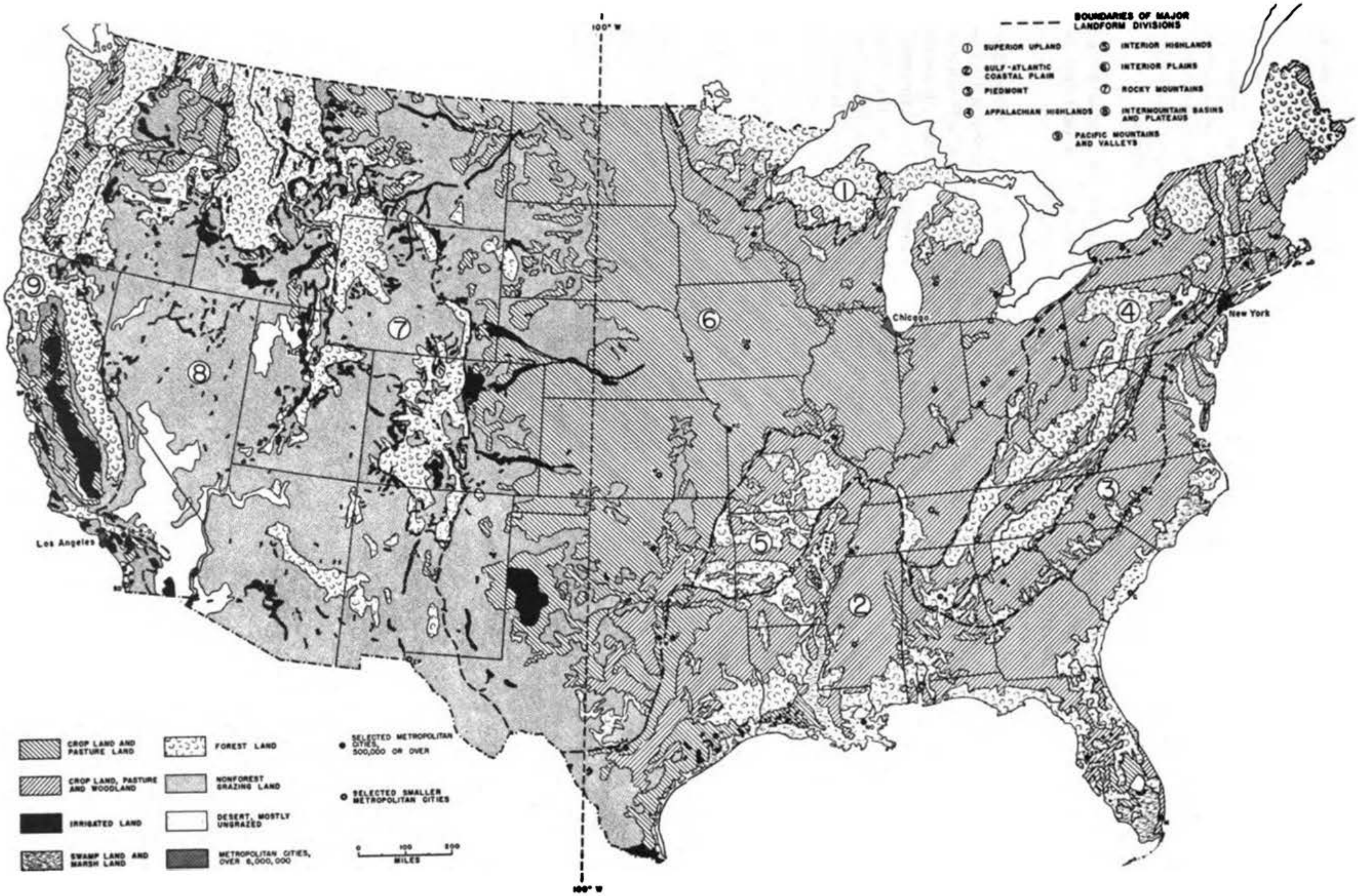


**FIGURE 41** Major uses of land in the United States. This map illustrates the use of reference points, in this case state boundaries, selected cities, boundaries of major landform divisions, and the meridian of 100° W. (Based on a map by F. J. Marschner in Wheeler *et al.*, 1961.)

> states, or other kinds of enumeration districts]. In the dasymetric map [another form of the choropleth map] the map positions of the class limits are independent of the boundaries of enumeration districts, but the lines separating one class from another have no numerical value. In the isarithmic map the geographical positions of the lines showing the class intervals employed are independent of the unit areas; they are lines along which the value is assumed to be constant.

The construction of choropleths and isarithms is too complex to summarize here. But standard texts, such as *Elements of Cartography* (Robinson *et al.*, 1978) contain discussions of cartographic symbolization, including the construction and use of some types of symbols not specifically referred to here. For an extraordinary display of possible symbols in black and white and color, consult a French work, *Sémiologie Graphique* (Bertin, 1967).

Shading of areas on choropleth and isarithmic maps can be done in colors, shades of gray, or a great variety of patterns (such as line, dot, crosshatch). It is easy to confuse and irritate readers by a poor selection of these area symbols. The mapmaker must strive for logic, order, and clarity. Especially to be avoided are shadings that are too similar in tone—a shortcoming of Figure 41, where the tone of the two pattern symbols for cropland is too similar to that for nonforest grazing land. However, the two cropland symbols themselves (diagonal lines turned in opposite directions) were deliberately selected as the same tone to convey an impression of the continuous sweep of cropland of all types, with or without woodland interspersed.

- Development of overall composition. Composition involves the placement of lines, lettering, and symbols in harmonious relation to each other so as to achieve clarity, emphasis, and pleasing effect. Presumably, the map user will be better able to receive the intended message if he is not offended by the appearance of the map. The exercise of imagination, ingenuity, and informed judgment by the mapmaker is very much in order, both in the choice of symbols and in the overall composition. Mapmaking is an open-ended process, and there is often some better way to present an idea, if one can only think of it when needed.

The effectiveness of maps is limited by the visual powers of the users. In general, bold and simple maps are apt to be more effective than cluttered and complicated ones. If words and symbols are too numerous and varied, the map may become a complete jumble. Where it is necessary to put numerous symbols on one map, care must be taken that the symbols be sufficiently distinct from each other. The more symbols, the more difficult the task. It is vitally important that the critical details of the map be emphasized sharply and that sufficient *points of reference* be provided. "Pattern maps" without reference points are more apt to provoke irritation than to contribute to understanding. Reference points may be states, cities, counties, rivers, parallels and meridians, or other features appropriate to the map (see Figure 41). They should be subdued to avoid cluttering the map and detracting from its impact. Transparent overlays are one means of providing reference points, as is done in the *National Atlas of the United States of America* and the *Atlas of Britain and Northern Ireland.*

Often it is better to make several maps than to try to put all the information on one map. This option was chosen in the accompanying panel of maps (Figure 42) showing the heavy concentration of truck-crop acreage in a relatively few counties of the United States. The purpose was to point up those counties that are the major producers of selected crops consumed directly for human food: asparagus, cantaloupes, carrots, dry onions, green peas, lettuce, snap beans, tomatoes, watermelons, and white potatoes. In each instance, a remarkably small number of counties represent three quarters of the national acreage for the crop concerned. Further maps could pinpoint specific soils within these counties to facilitate analysis of possible relations between trace elements and human diseases. In designing these maps, state boundaries and the Great Lakes were considered sufficient reference points. Inclusion of county boundaries permits identification of the counties through reference to an appropriate index map (see map list in a subsequent section). It was considered that inclusion of county names on the panel itself would create too much clutter and detract from the impact of the distributional patterns.

Drafting of the finished map is normally done with a view to reduction by photography to the final size, although modern professional drafting techniques often permit drafting at the final scale. Where drafting is done with reduction in mind, it is normal to work at twice, or two and a half times, the scale of the final product. This gives greater freedom in the use of base maps and reference maps from which data are to be taken, and it is often more convenient for drawing lines and placing letters and symbols on the map. If the drafting is done on too small a scale, it may not be physically possible to present all the information on the map in the manner desired. In addition, photographic reduction often improves the appearance of the final product by removing or minimizing drafting irregularities. However, care must be taken to use large enough lettering and bold enough lines and symbols to stand reduction well.

### *Useful Base Maps and Reference Maps*

Scientists and researchers seeking base maps and reference maps for cartographic expression of the kinds of data presented at the Captiva Island Workshop may be able to use some of the following map-products examples. Current listings of maps are issued periodically in such publications as the *Bibliographie Cartographique Internationale;* the *Publications of the United States Geological Survey;* the *Monthly Catalog of United States Government Publications;* the *Geography and Map Division Bulletin* of the Special Libraries Association; *Current Geographical Publications* issued by the American Geographical Society; *New Geographical Literature and*

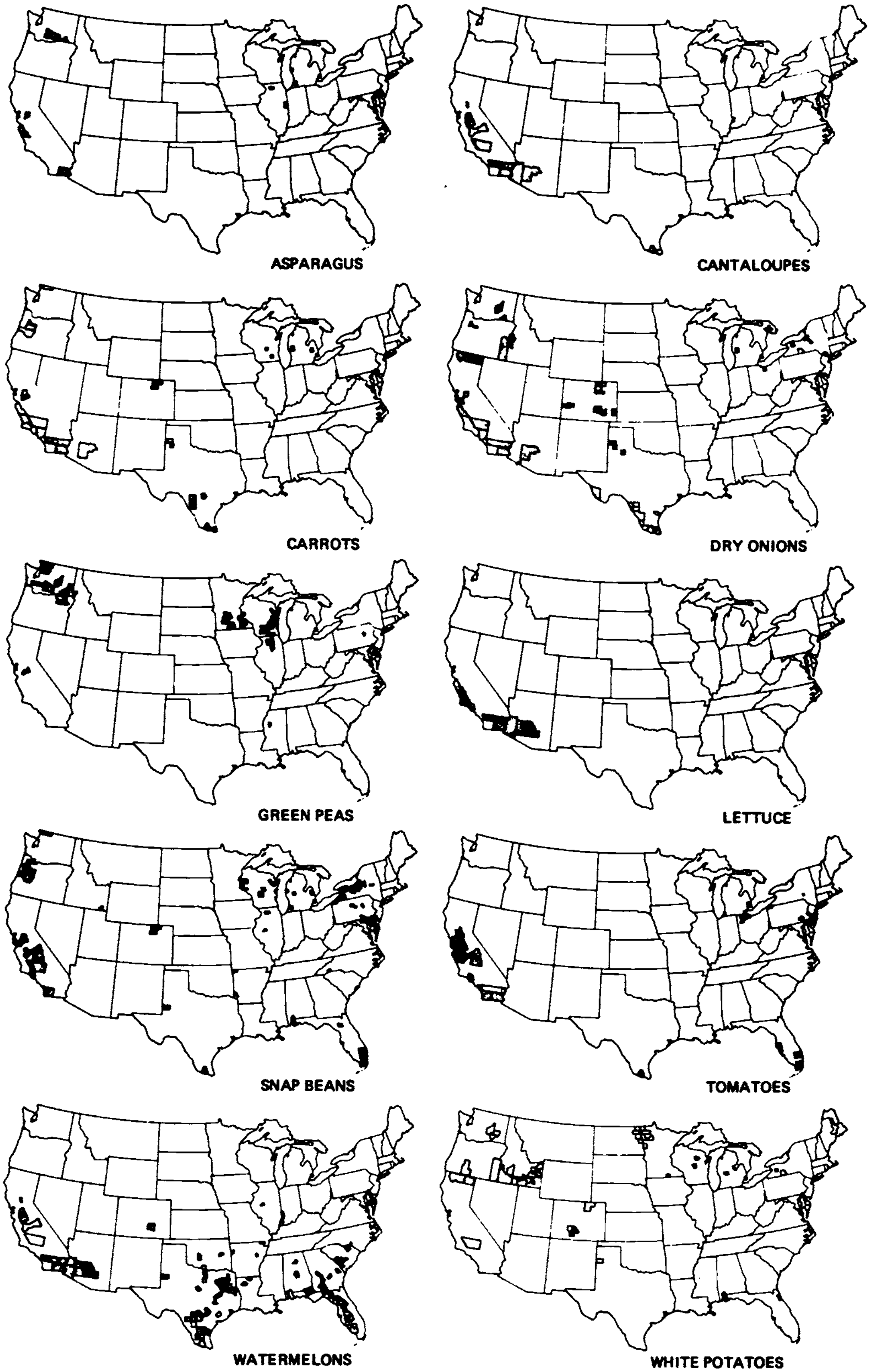


FIGURE 42 Concentration of truck-crop acreage in 1969. Each map shows, for the crop specified, the highest-ranking counties aggregating three fourths of the national acreage reported for that crop in the 1969 Census of Agriculture. Research by Belinda Young; cartography by Terry McBride, University of Missouri—Columbia. (Source of acreage figures, U.S. Census of Agriculture, 1969.)

*Maps* issued by the Royal Geographical Society, London; and the map catalogs of Edward Stanford Ltd., London. See also the *Index to Maps in Books and Periodicals*, Map Department, American Geographical Society, 10 volumes, published in 1968 and the *First Supplement, 1968–1971*, published in 1971.

*Maps on a Scale of 1/7,500,000*

• U.S. Geological Survey base map of the United States showing county boundaries and county names.

• Numerous maps in the *National Atlas of the United States of America*, many of which are available as separate sheets; transparent overlays in the pocket show county boundaries and names. Several specific *National Atlas* maps (some at other scales) of interest in the context of this Workshop are the following:

Geology
Salines
Karstlands and caverns
Shaded relief
Physical divisions
Land surface form
Forest types
Vegetation
Soils
Population distribution
Population density, 1960
Median age of population, 1960
Percent change in total population, 1950–1960
Daily traffic flow, interstate systems
Death rates, 1959–1961

• U.S. Bureau of the Census, "Population Distribution in the United States: 1970" (United States Maps, GE-70, No. 1); reference points are lacking, but the map can be used with the county-outline overlays from the *National Atlas*.

• National Resources Planning Board, "Livelihood Areas of the United States," 1943; county outlines, without names; 235 "livelihood areas" are distinguished.

• U.S. Department of Agriculture, Bureau of Chemistry and Soils, "Soil Associations of the United States," 1938; county outlines, without names; map accompanied *Soils and Men*, Yearbook of Agriculture, 1938.

*Maps on a Scale of 1/5,000,000*

• U.S. Bureau of the Census, county-outline base map of the United States, with county names (black print or blue print); also maps in the Population Series (GE-50).

• Erwin Raisz, "Landforms of the United States"; detailed pictographic representation of topography, available from Erwin Raisz, 130 Charles Street, Boston, Massachusetts.

• Edwin H. Hammond, "Classes of Land-Surface Form in the Forty-Eight States, U.S.A." Landform classes are delineated on a statistical basis. Published originally as Map Supplement No. 4, *Annals*, Association of American Geographers, Volume 54, No. 1 (March 1964). The same map on a scale of 1/7,500,000 appears in the *National Atlas of the United States* and is available as a separate sheet.

• F. J. Marschner, Bureau of Agricultural Economics, U.S. Department of Agriculture, "Major Land Uses in the United States," 1950.

• George F. Jenks, "Crop Patterns in the United States: 1959" and "Livestock and Livestock Products Sold in the United States: 1959." Detailed dot maps in multiple colors; county outlines shown. Each map was published by the U.S. Bureau of the Census as a sheet in the unbound *National Atlas of the United States*, a forerunner of the present *National Atlas*. These maps do not appear in the present atlas.

*Maps on Various Scales*

• Numerous maps in U.S. Bureau of the Census, *Graphic Summary*, 1969 Census of Agriculture, Volume V, Special Reports, Part 15.

• U.S. Bureau of the Census, "Type-of-Farming Areas in the United States, 1930," county boundaries shown; nearly 800 type-of-farming areas distinguished by name.

• Nevin M. Fenneman, "Physical Divisions of the United States" (1/7,000,000); a standard map published by the U.S. Geological Survey; elaborate descriptive breakdown of physical areas.

• U.S. Soil Conservation Service, "Land Resource Regions and Major Land Resource Areas of the United States (48 conterminous states) (1/10,000,000), 1963.

• U.S. Geological Survey, innumerable maps at national, regional, and local scales showing topography, lithology, surficial deposits, mineral deposits, radioactivity, nuclear reactor sites, elemental composition of surficial materials (e.g., nickel, molybdenum, lead, iron, copper, cobalt, chromium, calcium, beryllium, mercury, lithium, arsenic, fluorine, selenium), and maps of water resources as follows:

Dissolved minerals in surface water, United States
Dissolved solids in rivers (HA-61)
Dissolved minerals in groundwater (*National Atlas*)
Depth and quality of shallowest groundwater containing 1000+ ppm dissolved solids
Chemical types of water in rivers (*National Atlas*)
Chemical types of rivers
Composition of rivers
Suspended sediment in rivers
Sediment concentration of rivers (HA-61)
Annual runoff and productive aquifers in United States (HA-194)
Average annual runoff
Chloride in western U.S. streams (HA-189)
Sulphate in western U.S. streams (HA-189)
Sodium in western U.S. streams (HA-189)
Calcium in western U.S. streams (HA-189)
Chemical quality of public water supplies (HA-200)

Dissolved solids in untreated water supplies
Dissolved solids in finished water supplies
Hardness in untreated water supplies
Hardness in finished water supplies
Sodium in untreated water supplies
Sodium in finished water supplies
Fluoride in untreated water supplies
Fluoride in finished water supplies

### *Annotated General References*

The following general references contain much useful information on cartography:


Board, C. 1970. Maps as models. In Models in Geography, R. J. Chorley and P. Haggett, eds. Methuen & Co., London. pp. 671–725. Problems of communication between the map designer and the map user are examined. An extensive bibliography is appended.

Crawford, P. V. 1971. Perception of grey-tone symbols. Ann. Assoc. Am. Geogr. 61(4):721–735. The author maintains that well-chosen uniform grey tones used as map symbols do not differ significantly in visual effectiveness from symbols printed in black.

Dahlberg, R. E. 1967. Toward the improvement of the dot map. International Yearbook of Cartography 7:157–166. This article provides a conceptual and methodological review of the dot method. Fifty references are cited.

Davis, J. C., and M. J. McCullagh, eds. 1975. Display and Analysis of Spatial Data. John Wiley & Sons, New York. 378 pp. This book provides a very extensive technical examination of computer-assisted cartography.

Dickinson, C. C. 1973. Statistical Mapping and the Presentation of Statistics, 2d ed. Edward Arnold, London. This illustrated British textbook discusses techniques for effective presentation of numerical relationships on maps and diagrams.

Guelke, L. 1976. Cartographic communication and geographic understanding. Can. Cartog. 13(2):107–122. The author stresses that information on maps must be placed in appropriate contexts to maximize the user's understanding of reality.

International Yearbook of Cartography. Annual, from 1961. Distributed by Rand McNally & Co., Chicago. This publication contains numerous articles on cartographic subjects.

Jenks, G. F. 1963. Generalization in statistical mapping. Ann. Assoc. Am. Geogr. 53(1):15–26. The author offers advice on a major problem in statistical cartography.

Keates, J. S. 1973. Cartographic Design and Production. Halstead Press, John Wiley & Sons, New York. 240 pp. This well-produced book includes chapters on vision and perception, cartographic symbols, map design, special-purpose and special-subject maps, the technical basis of cartography, and map production.

Meyer, M. A., F. R. Broome, and R. H. Schweitzer, Jr. 1975. Color statistical mapping by the U.S. Bureau of the Census. Am. Cartog. 2(2):101–117. This article, illustrated with maps in multiple colors, describes the Census Bureau's choropleth maps, including the two-variable "cross" maps, on which the distributions are mixed to represent category combinations. The use of computer output on microfilm to produce maps in color is discussed.

Monkhouse, F. J., and H. R. Wilkinson. 1971. Maps and Diagrams: Their Compilation and Construction, 3d ed. Methuen & Co., London; Barnes & Noble, New York. 522 pp. This revision of a comprehensive British text is fully illustrated and includes material on computer graphics and other new developments in cartography.

Muehrcke, P. 1974. Thematic cartography. Resource paper No. 19. Commission on College Geography, Association of American Geographers, Washington, D.C. 66 pp. This discussion of data collection, mapping, and image processing suggests ways to gather and map data more speedily and efficiently.

Muller, J. C. 1976. Objective and subjective comparison in choroplethic mapping. Cartog. J. 13(2):156–166. Statistical analysis can be supplemented by visual comparison of choroplethic maps to determine spatial correspondence of geographical distributions. The author identifies elements of visual recognition that map users can employ to associate or differentiate distributions.

Peucker, T. K. 1973. Computer cartography. Resource paper No. 17. Commission on College Geography, Association of American Geographers, Washington, D.C. 75 pp. The author presents numerous examples and brief explanations of diagrams drawn by plotter and line printer output. A discussion of SYMAP is included.

Raisz, E. 1962. Principles of Cartography. McGraw-Hill Book Co., New York. A clear and well-illustrated textbook by a noted cartographer.

Rhind, D., ed. 1977. Contemporary cartography. Institute of British Geographers, Transactions New Series 2(1):1–124. Subjects examined by various authors include computer-aided cartography, selection of class intervals, perception and maps, nonautomated cartographic techniques, orthophotomaps, and cartography 1950–2000.

Ristow, W. W. 1974. Cartographic information services of the Library of Congress. Am. Cartog. 1(2):125–130. This article summarizes the activities and facilities of the Geography and Map Division, Library of Congress.

Robinson, A. H. 1962. Mapping the correspondence of isarithmic maps. Ann. Assoc. Am. Geogr. 52(4):414–425. This article examines methods of studying the degree to which two statistical surfaces portrayed on isarithmic maps are positively or negatively related.

Robinson, A. H., R. D. Sale, and J. Morrison. 1978. Elements of Cartography, 4th ed. John Wiley & Sons, New York. This standard university textbook provides a comprehensive introduction to cartographic work. It is well illustrated, and contains a very full bibliography.

The American Cartographer. Semiannual journal of the American Congress on Surveying and Mapping. From 1974. This is a varied journal with articles on many facets of cartographic work.

The Canadian Cartographer. Semiannual journal, from 1964.

The Cartographic Journal. Semiannual journal of the British Cartographic Society. From 1964. It carries numerous illustrated articles on many phases of cartographic work.


## POTENTIAL OF REMOTE SENSING FOR INVENTORYING SURFACE FEATURES ON EARTH

(John B. Peterson)

Ever since the development of aerial photography to map the earth's surface during World War I and the rapid advances in this technique since then, man's capacity to sense remotely the radiation from earth's surface has greatly increased. Improvements in technology led through such steps as color photography, color infrared photography, and thermal infrared sensing to the multispectral sensing of radiation from 0.3 $\mu$m to 15 $\mu$m with electronic sensing devices. These devices can be carried on aircraft or satellites. Aircraft can also carry radar equipment that will sense microwaves of even longer wavelengths than those representing the thermal infrared.

The development of multispectral scanners that could scan the radiation coming from the earth rapidly enough to provide an almost continuous flow of data, which keep up with the forward flight of aircraft and even satellites, has made possible very rapid surveillance of the earth scene. Paralleling these improvements, advances in computer-based technology, using pattern-recognition techniques, have made it possible for scientists to analyze the enormous volume of data coming from such sources rapidly enough to make the data useful in interpretation and application. The resolving power of such electronic surveillance makes it possible, with meteorological satellites, to identify and easily delineate scenes of contrasting radiance from areas as small as 2 hectares coming from the earth's surface. Even smaller areas can be identified with greater effort and expense. When the LANDSAT 1 satellite (previously known as ERTS, for Earth Resources Technology Satellite) was launched in 1972, the resolution was reduced to a diameter of 80 m.

The multispectral scanners now in use provide quantitative, replicable data that can be digitized and used through proper computerized techniques to make gray-scale printouts that can be converted to color maps through special techniques, either in true color, color infrared, or false color, whichever may be most appropriate for identifying and delineating special portions of the scene. Such data may also be treated statistically to show such things as the percentage of land in corn or the percentage of land under water in a flood. They also can be used in other ways, for example, to make automatic boundary decisions concerning the separability of different land features.

The LANDSAT 1 multispectral scanner data are received from the satellite by the National Aeronautical and Space Administration (NASA) and recorded on computer-compatible tape and in a photographic form as they are processed for delivery to users. The computer-tape form of the data does not have geometric corrections applied to it. The Laboratory of Applications to Remote Sensing (LARS) of Purdue University has developed a technique to correct geometric distortions, including earth rotation effects. These images are also rescaled so that the horizontal and vertical scales are the same.

At LARS, geometric corrections using ground-control points are applied to images that have first been corrected for scale, rotation, and skew by the uncontrolled transform. When the recorrected data are overlayed on a standard USGS 7½-minute quadrangle map, no error can be observed visually, and the estimated error is about 48 m, using a quadratic polynomial. This is a promising approach for accurately correcting LANDSAT-type data to map coordinates.

Geographers now have the capacity, through computer techniques, to overlay data on base maps and to smooth the data between reference points. LARS has this same capacity, in addition to its current capability to secure data on a temporal basis from the earth's surface with every cloud-free pass of the satellite. The capacity of LARS to rectify computer gray-scale printouts of LANDSAT data to accuracies approaching those of a geodetic survey and to convert these to current maps as a basis for overlaying data make the technology now available useful in studies of the distribution of geochemical features of the earth's surface. Statistics relating the geographic distribution of the geochemical features of the earth's surface may now be approached. The possibilities of further success in rectifying maps made from satellite data, and in the overlaying of statistics on such a geographic basis, are promising enough that further research in this area can be expected to produce significant refinements. If such improvements in the technique are found necessary for the purpose of relating disease conditions to geochemical characteristics, particularly those associated with such parameters as certain soils, geological features, and communities of native plants, they are readily within reach.

A recent (1976–1977) cooperative program between Soil Conservation Service (SCS) personnel in Missouri and LARS scientists shows that a combination of digitalized LANDSAT multispectral scanner (MSS) data and ancillary data effectively identified and delineated 14 soil subgroups, 7 soil families, and 18 soil series classes. This is a definite demonstration of great potential benefit from using MSS satellite data in soil mapping and in inventorying other land-surface features. A successful study, conducted by LARS, with the cooperation of the SCS, of the land use in 85,000,000 acres of watershed in the United States draining into the Great Lakes demonstrates the capability of using satellite data to update land-use conditions rapidly and efficiently. Category levels I and II are being used in this project.

| Level I | Level II |
|---|---|
| Agriculture | Row crops |
| | Close-grown crops |
| | Pastures |
| | Orchards |
| Urban | Commercial–industrial |
| | Residential |
| Forest | Forest |
| No Major Use | Water |
| | Wetland |

Using LANDSAT data, LARS has the capability to resolve every data point that would provide detail to about 1½ acres for the above categories. However, because of the need to do this work as economically as possible, the land is only being differentially classified down to about 6 acres per unit. These 85,000,000 acres were classified and mapped in only a few months for approximately $200,000. This represents a great saving compared with the cost of a similar survey by conventional on-the-ground methods.

LARS is also heavily involved in the NASA-sponsored Large-Area Crop Inventory Experiment (LACIE), in which a major attempt is being made to determine whether there is a capability to estimate, during the growing season, the production of wheat on a worldwide basis. This involves estimates of both area and yield.

The sensitivity of the electronic sensing devices is so great that slight differences in shades of color of bare soils can be picked up on a quantitative basis, at least as closely as they can be distinguished by the human eye. This makes possible the sorting out of major soil associations and major soil zones in the United States that appear to be closely correlated with the areas of high or low incidence of diseases, such as cancer, hypertension and other cardiovascular disease, and urolithiasis, being studied by this Workshop.

## THE PRESENTATION OF MEDICAL DATA IN MAP FORM

(Vincent P. Barabba and Richard H. Schweitzer)

The presentation of data in map form makes the data easier to use. By displaying the tables in a spatial setting the user gains further insight into the practical aspects of the data. In this manner, spatial interrelations of small-area characteristics can be seen that might be lost in a table.

This function can best be illustrated by the use of a map to summarize the complex interrelation of an aspect of population growth and a current topical problem of sociologists and demographers—the increasing proportion of the elderly in certain parts of the nation.

During the twentieth century the nation has experienced a general shift of the population toward the western and southern states. There has been an even more dramatic shift of the population from the heartland to the coastal and Great Lakes regions of the nation. In a similar manner, it has been noted that the nation's heartland (outside of metropolitan areas) contains a disproportionately high percentage of elderly population in comparison with the rest of the nation. Using a relatively new technique of automated cartography developed by the Bureau of the Census, these two data items can be shown for the nation's 3141 counties (or county equivalents) in a two-variable map. This map (Plate I) shows that large areas of the nation have a relatively large proportion of the elderly. One of these areas is the central plains; another is the retirement areas of Florida and the Southwest. The map also highlights those areas of the nation that have steadily been losing population; over 150 counties have had a declining population for at least the last 70 years. The counties with the most rapid rates of growth have tended to be within 100 miles of the nation's coastlines or the Great Lakes. In summary, the map graphically shows that there are many areas in the Middle West that have both a high proportion of elderly and also have had a steadily declining population over the last 60–70 years.

The map highlights (with yellow and light orange) counties that have concurrently a high proportion of elderly and an overall long-term population decline. These counties are centered on the rural, farming areas of the central plains in Kansas, Iowa, and Missouri. The major urban centers of St. Louis, Davenport, Rock Island, Moline, Des Moines, Omaha, and Kansas City encircle this area. The purple color signifies that these urban counties are growing and have a noticeably younger population than the nearby rural areas. Likewise, many of the rural counties along the Ohio River and in Alabama, Virginia, and Illinois suggest that other prime agricultural areas of the nation are losing their young, childbearing families and are experiencing a general out-migration with resulting demographic and economic imbalances.

The areas that have experienced a decline of the mining industries in Montana, Nevada, California, and Colorado (and also the decline of the whaling industry in Maine and on Nantucket Island) are clearly highlighted in orange. An extreme example of this can be found in the three counties in Colorado that are shaded red. These counties were the heart of the silver-mining region in the late 1800's and proudly boasted Leadville as the region's major city. Today, this region is one of the nation's finest skiing areas with Vail, Aspen, and Snowmass located there to attract a younger population. Hence the red color on the map.

The counties shaded dark green are the growth areas with a high proportion of elderly persons—the retirement areas of Florida, New Mexico, and Lake County, California. The predominance of purple, dark blue, and dark green in the coastal states and near the Great Lakes confirms that these areas are continuing to grow. The predominance of the lighter tones in the central interior regions signifies that these areas have either a stable or declining population-growth pattern.

Using computer output and microfilm plotting devices, the Census Bureau can produce these types of map quickly and inexpensively. The low cost and short preparation time of these new techniques now make it possible for the research analyst to prepare many graphic displays to test the validity of various data relations or more clearly to identify particular geographic areas. There is, however, a basic trade-off involved in these endeavors. First, the cost of graphic presentations is generally greater than that of tables. Second, the cost of a graphic display generally necessitates presenting only a portion of the available data. To some extent, the researcher who elects to use a graphical display, rather than the traditional tabular display, must be aware of the balance between two important characteristics of statistical presentation, accuracy and completeness, and ease of use.

The researcher must also decide what the map should show or in some instances create a rank-ordered set of priorities. Once the major theme of the map has been selected, the form and design of the map(s) should be developed with the assistance of a trained cartographer. The reason for this admonition is that often in the early stages of research the statistical map may be used as a source of ideas; later, in the final report, the same map or a modified version may be used to represent ideas. The latter map must clearly focus on the desired aspect of the statistics that are to be presented without including other extraneous data. Even the simplest set of data can usually be looked at from more than one point of view; a poorly designed map can add to the confusion.

One basic problem for any researcher who uses graphical displays is to decide how the data should be divided or grouped for presentation. Nominal or ordinal data sets often have logical "classes" implied in the structure of the data. This was the case for the data for the portion of Plate I referring to the year of maximum population. The distribution of the data for the other variable, percent elderly population, could have been transformed in many different ways to present a particularly desired emphasis. For instance, the data could have been displayed in quartiles, or in arithmetic deviations from a mean value, or in standard deviations, or in some mathematical (i.e., geometric or logarithmic) intervals, or in a normalized data structure. Any one of these approaches will display the data for a given map in a unique manner that emphasizes a particular aspect of the data. The statistical basis for each of these data-grouping techniques is covered in any general statistics text.

One approach that helps the user to restructure the data for a graphical display is a concept known as Social Area Analysis (SAA) (Shevky and Bell, 1955). The basic building blocks of SAA used in the example described in this paper are drawn from the Census Bureau's tract books. The same techniques can be applied to other data for larger geographic units such as counties or state economic areas.

The use of census or National Center for Health Statistics (NCHS) data in its published forms may present problems, depending on the purpose for which it is intended. Census information is presented in a variety of ways that include maps, congressional-district data books, published results of the decennial and economic censuses, electronic tapes, and punchcards. Another problem is that the varied forms of data are more than matched by their volume. The researcher's dilemma is often that he possesses too much, rather than too little, information. One need only to thumb through the published results of a census of housing and population to realize how difficult it is to translate that mass of data into a usable area-information profile for a research analysis.

To accomplish the basic goal of easily and accurately describing a particular phenomenon, the researcher must determine the fewest specific variables that will describe the data without sacrificing accuracy. SAA, as used in this paper for fictitious Center City, organizes a large number of potential variables (Table 36) into three ordered sets of characteristics that summarize the economic, family, or ethnic composition of an area. To absorb even this or-

TABLE 36 Important Variables Used in Social Area Analysis

| |
|---|
| *Unordered Variables* |
| Total population |
| Race |
| Sex |
| Nativity |
| Married couples |
| Families or unrelated individuals |
| Number of dwelling units |
| Owner- or renter-occupied dwelling units |
| Type of structure |
| Condition and plumbing facilities |
| Year structure was built |
| Number of all occupied dwelling units |
| Number of persons in dwelling unit |
| Number of households |
| Population per household |
| Population in households |
| Institutional population |
| Years of school completed |
| Residence in 1955 |
| Income |
| Age |
| Marital status |
| Employment status |
| Major occupation group |
| Women in the labor force |
| Persons per room |
| Type of heating fuel |
| Refrigeration equipment |
| Television |
| Monthly contract rent |
| Value of one-dwelling-unit structures |
| Spanish surnames (certain areas) |
| |
| *Ordered Variables* |
| Economic characteristics |
| Condition and plumbing facilities |
| Persons per room |
| Years of school completed |
| Income |
| Employment status |
| Major occupation group |
| Type of heating fuel |
| Refrigeration equipment |
| Monthly contract rent |
| Value of one-dwelling-unit structures |
| Family characteristics |
| Sex |
| Married couples |
| Families or unrelated individuals |
| Owner- or renter-occupied dwelling units |
| Type of structure |
| Age |
| Marital status |
| Women in the labor force |
| Institutional population |
| Ethnic characteristics |
| Race |
| Nativity |
| Spanish surnames |

dered information can prove difficult; therefore the number of variables is further reduced under the three basic indices by eliminating redundant data items (Table 37).

*Economic Status*

The index of economic status is made up of two factors, selected because they accurately reflect many other factors. The two elements that have been found best to describe economic status are education and occupation. Income, for example, is not used, because although income and education are generally related, a college professor may earn less money than a truck driver. Therefore, economic status is not measured simply by the amount of money people earn. For our purposes, economic status is a cross between the type of work and the attainable goals or status that a good education implies.

As we shall soon discover, the accuracy of the descriptions decreases as we reduce the number of variables included. Although it is much easier to use only two characteristics, the description is really not so complete as if we had used all those characteristics available. We have created a definition of economic status based on those subjective judgments. If you accept as adequate this definition of economic status, established by the person's job and education, then we are further along the accuracy scale than if you argue that income is just as important as occupation or education. Both the provider of information and the user should be aware of this trade-off, as they attempt to synthesize reams of data into easy-to-use formats.

In this example of the use of SAA, information concerning education is secured by determining the ratio or proportion of the census-tract residents over 25 years of age who have less than an eighth-grade education. The greater the portion of residents over 25 years of age with less than an eighth-grade education, the lower the education score for the census tract.

Occupation information is secured by determining the ratio or proportion of residents of a census tract who are classified as laborers, operatives, or craftsmen, as opposed to secretarial, sales, or professional personnel. "Operatives" is a general classification of workers, somewhere below craftsman in level of skill, who operate machinery (excluding those engaged in transport operations). That is to say, we develop a blue-collar:white-collar ratio. Therefore, the greater the proportion of residents who are classified as laborers, operatives, or craftsmen, the lower the occupation score for the census tract.

TABLE 37 Major Indices and Variables Used for Measuring Them

| |
|---|
| Index of economic status |
| Education |
| Occupation |
| Index of familization |
| Fertility ratio |
| Women not in labor force |
| Owner-occupied dwelling units |
| Index of ethnic status |
| Race |
| Nativity |
| Spanish surnames (when available) |

*Familization Status*

The term "familization" represents three ratios: fertility, women not in the labor force, and single-family dwelling units. These selected variables are intended to indicate changes in the structure or function of elements within society at a level higher than the immediate family. Fertility is intended to reflect differences in the relation of the population to the socioeconomic system. Measures of housing type and of women not in the labor force should show differences in the function and structure of the family.

Obviously, one characteristic of familization is children. Consequently, we use a fertility ratio—the number of children under 5 years of age in relation to the number of women 14–44 years of age, the childbearing age span. Therefore, the greater the proportion of children under 5 years of age in relation to women 14–44 years of age, the higher the familization score for that census tract.

The second characteristic of familization is the mother's role. We assume that the family situation of a working mother is different from that of a nonworking mother. Therefore, we use the measurement of women not in the labor force. The greater the proportion of women not in the labor force, the higher the familization score for that census tract.

The third characteristic of familization involves housing information. Family situations differ according to the types of housing units occupied, and, historically, where persons owned their home, the structure itself was that of a single-family dwelling unit. And, naturally enough, living in single-family units differs, to some extent, from multiple-unit living areas in terms of life style and social attitudes.

By combining these three factors, many different family situations can be quickly and easily described. For example, a high score of familization would describe a neighborhood primarily made up of families having several children (fertility ratio), living in single-family housing units (single-family dwelling ratio), and with wives who generally remain at home (women not in the labor force).

A possible index of ethnic status could be derived from three factors: race, nativity (country of origin of first- and second-generation Americans), and Spanish surnames. (In the censuses of 1960 and 1970, there was a special section developed for Spanish surnames in the southwestern states, which is only available for that section of the country.) In the interest of brevity, we shall not go into the ethnic index in depth, although the same principles of graphic presentation would apply to it.

*Developing Indices*

SAA information may be arranged for reading from computer printouts in the following manner. We shall use tracts 1 and 16 as our examples.

Table 38 consists of the occupation and education factors discussed earlier. The occupation–ratio column indicates that in tracts 1 and 16, for every 1000 employed people, 642.7791 and 166.5804 persons, respectively, are classified as laborers, operatives, and craftsmen. Under the education–ratio column, for every 1000 persons over 25 years of age, tract 1 has 434.2468 persons who have not gone past the eighth grade, and tract 16 contains 115.9570 who have not.

The columns titled "standard score" involve a concept that permits us to place a great many variables on a comparable scale by setting each geographic unit's ratio for a specific variable, on a scale of 0–100. The formula for determining the standard score is detailed in Shevky and Bell (1955). Thus, the standard score allows us to view the relation, not only of the variables within each geographic unit but also of the variables in different units. This scale is not merely a rank order; rather, the computation places a given geographic unit's ratio for a given factor in rela-

TABLE 38 SAA Economic Index

| | Occupation | | Education | | | |
|---|---|---|---|---|---|---|
| Census Tract | Ratio/1000 | Standard Score | Ratio/1000 | Standard Score | Economic Index | Designation |
| 1 | 642.7791 | 5.9324 | 434.2468 | 28.6723 | 17.302 | 1 |
| 2 | 584.2244 | 17.4993 | 354.4380 | 46.5572 | 32.028 | 2 |
| 3 | 658.7029 | 2.7869 | 495.2849 | 14.9938 | 8.890 | 1 |
| 4 | 663.4189 | 1.8553 | 536.9531 | 5.6561 | 3.756 | 1 |
| 5 | 576.6870 | 18.9882 | 562.1926 | 0.0000 | 9.494 | 1 |
| 6 | 624.9143 | 9.4614 | 497.8335 | 14.4227 | 11.942 | 1 |
| 7 | 556.2031 | 23.0345 | 468.5586 | 20.9831 | 22.009 | 1 |
| 8 | 366.8831 | 60.4325 | 418.6240 | 32.1733 | 46.303 | 2 |
| 9 | 608.3105 | 12.7413 | 477.4692 | 18.9863 | 15.864 | 1 |
| 10 | 463.2239 | 41.4015 | 291.4524 | 60.6720 | 51.037 | 3 |
| 11 | 613.5962 | 11.6972 | 384.9197 | 39.7263 | 25.712 | 2 |
| 12 | 574.9316 | 19.3349 | 493.2986 | 15.4390 | 17.387 | 1 |
| 13 | 500.0000 | 34.1368 | 432.9158 | 28.9706 | 31.554 | 2 |
| 14 | 507.3169 | 32.6915 | 438.1443 | 27.7989 | 30.245 | 2 |
| 15 | 406.1392 | 52.6779 | 309.5544 | 56.6154 | 54.647 | 3 |
| 16 | 166.5804 | 100.0000 | 115.9570 | 100.0000 | 100.009 | 4 |
| 17 | 580.9480 | 18.1465 | 316.5193 | 55.0546 | 36.601 | 2 |
| 18 | 611.9690 | 12.0186 | 400.1794 | 36.3067 | 24.163 | 1 |
| 19 | 535.9609 | 27.0331 | 396.4377 | 37.1452 | 32.089 | 2 |
| 20 | 496.1191 | 34.9034 | 428.5713 | 29.9441 | 32.424 | 2 |
| 21 | 390.9312 | 55.6821 | 333.1924 | 51.3183 | 53.500 | 3 |
| 22 | 289.7031 | 75.6785 | 223.9245 | 75.8048 | 75.742 | 4 |
| 23 | 476.5457 | 38.7700 | 370.0786 | 43.0522 | 40.911 | 2 |
| 24 | 281.0515 | 77.3876 | 284.4827 | 62.2339 | 69.811 | 3 |
| 25 | 458.3333 | 42.3676 | 350.7642 | 47.3805 | 44.874 | 2 |
| 26 | 486.7161 | 36.7609 | 500.0000 | 13.9372 | 25.349 | 2 |
| 27 | 380.6060 | 57.7217 | 301.8582 | 58.3401 | 58.031 | 3 |
| 28 | 437.5962 | 46.4640 | 471.6636 | 20.2073 | 33.376 | 2 |
| 29 | 395.9390 | 54.6929 | 364.4443 | 44.3148 | 49.504 | 2 |
| 30 | 460.3499 | 41.9693 | 374.3147 | 42.1029 | 42.036 | 2 |
| 31 | 557.8181 | 22.7155 | 455.8674 | 23.8272 | 23.271 | 1 |
| 32 | 600.2764 | 14.3284 | 420.6763 | 31.7134 | 23.021 | 1 |
| 33 | 597.0605 | 14.9636 | 447.7122 | 25.6547 | 20.309 | 1 |
| 34 | 528.6755 | 28.4723 | 325.5303 | 53.0353 | 40.754 | 2 |
| 35 | 476.1511 | 38.8479 | 273.2798 | 64.7445 | 51.796 | 3 |
| 36 | 345.6631 | 64.6243 | 269.3333 | 65.6289 | 65.127 | 3 |
| 37 | 339.5249 | 65.8368 | 225.6201 | 75.4249 | 70.631 | 3 |
| 38 | 305.5554 | 72.5471 | 199.4060 | 81.2994 | 76.923 | 4 |
| 39 | 404.9114 | 52.9205 | 247.3282 | 70.5601 | 61.740 | 3 |
| 40 | 445.1997 | 44.9620 | 196.8162 | 81.8797 | 63.421 | 3 |
| 41 | 402.1274 | 53.4704 | 298.3674 | 59.1224 | 56.296 | 3 |

tion to all other geographic units in the Center City area under study.

By adding together a given tract's standard scores and dividing by the number of factors involved, we derive the composite economic index score. After each economic index score appears the number 1, 2, 3, or 4, representing the division of the index into four parts. The lowest portion, 0–24, is designated 1; 25–49 is 2; 50–74 is 3; and the highest, 75–100, is 4. We could also have divided the scale on the basis of the percentage of tracts that fell into various categories, e.g., top 25 percent or lowest 25 percent of all tracts.

When the occupation and education factors for tracts 1 and 16 are converted to standard scores, we find that tract 1, with an occupation ratio of 642.7791, receives a standard score of 5.9324, whereas 16, with a ratio of 166.5804, receives a standard score of 100. A score of 100 means that tract 16 has the fewest number of residents classified as laborers, operatives, or craftsmen of any census tract on the sheet, with the scoring arranged to reflect the value judgment that the fewer the number of laborers, operatives, and craftsmen in a tract, the higher the economic status of that unit.

The education standard score of 100 designates tract 16 as the one with the lowest proportion of residents with less than an eighth-grade education, whereas tract 1 receives 28.6723.

When we combine the education and occupation standard scores for tract 1 and divide by two, the number of factors, we derive an economic index score of 17.302, which is rather low, and the tract receives a number 1 designation. By comparison, tract 16's combined and divided score receives an economic index score of 100 and a number 4 designation.

Table 39, the familization index, shows that under "fertility ratio" for every 1000 women between the ages of 14 and 44 in census tract 1 there are 887.9446 children under 5 years of age, whereas in tract 16 for every 1000 designated women there are 306.0747 children under 5 years. In the case of children, the more there are, the more the tract is said to be familized, so the higher the standard score. Thus tract 1 receives a designation of 95.2145, whereas tract 16 is a 0.0000.

In relation to working women (Table 39), there are 314.4822 women in the labor force for every 1000 women over 14 years of age in census tract 1, and 327.1570 in tract 16. Tract 1 receives a standard score of 61.9785 and tract 16 a score of 52.2127.

The last factor is single-family dwelling units, with tract 1 having a ratio of 780.2900 and receiving a standard score of 80.0612, and 16 having a ratio of 926.1016 and a score of 100.

As in the case of the economic index, we add together a given tract's standard scores and divide by the number of factors (in this instance, three) to obtain the designation for the index of family status. Again, the 0–100 index is divided into parts identical to the economic index, but the designations are now alphabetic with 0–24, the lowest portion, labeled D, and the highest portion, 75–100, labeled A.

Thus, for the purposes of family status, tract 1 is an A tract, tract 16 is a B.

If, at this point, this technique appears complicated, imagine the complexity of having to use 19 variables instead of the 5 we employed in the economic and familization indexes.

We have described four levels of economic status—No. 1 being low and No. 4 being high—on the basis of occupation and education. Next, we have described four levels of familization—D being low and A being high—on the basis of number of children, women in the labor force, and single-family dwelling units.

We can further reduce the data by combining these levels of status into one easy-to-read table entitled social area key (Table 40). Such a table enables us to see at a glance the overall socioeconomic profile of each census tract. For example, in tract 1 we have an economic index designation of 17.302, or a 1, and an index of family status of 79.0847, or A. Therefore, the SAA score of census tract 1 is 1-A. Census tract 16 has an economic index of 100, or 4, and an index of family status of 52.4042, or B. Thus tract 16 has an SAA score of 4-B.

If we were to describe the economic and familization differences between tracts 1 and 16 based on the social area key, we could say that residents in tract 1 tend to be laborers, operatives, and craftsmen, with less than an eighth-grade education, whereas residents of tract 16 tend to work in capacities other than those prevalent in tract 1, such as secretarial, sales, and professional jobs, and tend to be educated beyond the eighth-grade level.

As regards familization differences, we know that for family rank, on the social area key, tract 1 scores a 79.0847, placing it in the highest category with an A designation, whereas tract 16 scores only 52.4042, making it a B. In reviewing familization scores of the two tracts, we discover that the standard scores for women in the labor force and owner-occupied dwellings are not significantly different. In terms of familization, the only significant difference is the number of children under 5 years of age in relation to women between the ages of 14 and 44 years. When the three standard scores are combined and divided, naturally census tract 1 receives a higher index of family status because of its higher fertility-standard score.

Therefore, if we were describing the familization differences between the two census tracts, we would say that residents in census tract 1 tend to have many young children in their families, the women tend not to hold jobs, and families usually reside in single-family housing units. Residents of tract 16 almost always reside in single-family units, the women tend not to hold jobs, and there are usually no children under 5 years of age in households in that tract.

From our description of the two tracts, it is possible to assume that the resident's needs and concerns may differ

TABLE 39 SAA Familization Index

| Census Tract | Fertility Ratio/1000 | Fertility Standard Score | Women in Labor Force Ratio/1000 | Women in Labor Force Standard Score | Single-Family Dwelling Ratio/1000 | Single-Family Dwelling Standard Score | Family Status Index | Desig-nation |
|---|---|---|---|---|---|---|---|---|
| 1 | 887.9446 | 95.2145 | 314.4822 | 61.9785 | 780.2900 | 80.0612 | 79.0847 | A |
| 2 | 775.5662 | 76.8254 | 340.1772 | 52.3170 | 800.4326 | 82.8156 | 70.6527 | B |
| 3 | 796.7083 | 80.2851 | 336.7275 | 53.6141 | 592.2163 | 54.3434 | 62.7475 | B |
| 4 | 667.5256 | 59.1462 | 302.4739 | 66.4936 | 521.7390 | 44.7060 | 56.7819 | B |
| 5 | 725.6279 | 68.6538 | 377.7239 | 38.1993 | 530.1606 | 45.8577 | 50.9036 | B |
| 6 | 825.8601 | 85.0553 | 345.3872 | 50.3580 | 273.1543 | 10.7137 | 48.7090 | C |
| 7 | 917.1892 | 100.0000 | 375.0000 | 39.2235 | 246.3884 | 7.0537 | 48.7591 | C |
| 8 | 502.3696 | 32.1208 | 477.1321 | 0.8215 | 194.8051 | 0.0000 | 10.9808 | D |
| 9 | 762.5730 | 74.6993 | 421.8750 | 21.5984 | 570.1243 | 51.3224 | 49.2067 | C |
| 10 | 687.1333 | 62.3547 | 395.6184 | 31.4709 | 819.2295 | 85.3859 | 59.7372 | B |
| 11 | 868.2205 | 91.9870 | 336.5442 | 53.6831 | 797.7161 | 82.4441 | 76.0380 | A |
| 12 | 639.9490 | 54.6337 | 346.6577 | 49.8803 | 604.3955 | 56.0088 | 53.5076 | B |
| 13 | 569.2598 | 43.0664 | 339.5889 | 52.5383 | 603.2195 | 55.8480 | 50.4842 | B |
| 14 | 620.3472 | 51.4261 | 348.0391 | 49.3609 | 458.7412 | 36.0915 | 45.6262 | C |
| 15 | 495.4441 | 30.9875 | 414.0127 | 24.5546 | 427.4753 | 31.8161 | 29.1194 | C |
| 16 | 306.0747 | 0.0000 | 327.1570 | 57.2127 | 926.1016 | 100.0000 | 52.4042 | B |
| 17 | 760.7449 | 74.4001 | 356.1965 | 46.2937 | 803.2520 | 83.2011 | 67.9650 | B |
| 18 | 525.7729 | 35.9504 | 379.4253 | 37.5596 | 736.6816 | 74.0980 | 49.2027 | C |
| 19 | 528.6819 | 36.4264 | 366.6956 | 42.3460 | 815.6565 | 84.8973 | 54.5566 | B |
| 20 | 524.1633 | 35.6870 | 345.7249 | 50.2311 | 702.5920 | 69.4365 | 51.7849 | B |
| 21 | 446.4788 | 22.9751 | 392.9246 | 32.4838 | 693.9810 | 68.2590 | 41.2393 | C |
| 22 | 504.8354 | 32.5243 | 370.1187 | 41.0589 | 710.4722 | 70.5141 | 48.0324 | C |
| 23 | 539.3257 | 38.1681 | 367.7417 | 41.9527 | 599.5422 | 55.3451 | 45.1553 | C |
| 24 | 548.1926 | 39.6191 | 365.4773 | 42.8041 | 589.4519 | 53.9653 | 45.4628 | C |
| 25 | 578.8335 | 44.6330 | 405.7141 | 27.6749 | 509.5237 | 43.0357 | 38.4479 | C |
| 26 | 670.4543 | 59.6254 | 312.1147 | 62.8686 | 393.3401 | 27.1483 | 49.8808 | C |
| 27 | 440.6777 | 22.0258 | 479.3159 | 0.0000 | 523.1479 | 44.8987 | 22.3082 | D |
| 28 | 496.1240 | 31.0988 | 355.1401 | 46.6909 | 224.8366 | 4.1066 | 27.2988 | C |
| 29 | 472.4263 | 27.2210 | 403.5242 | 28.4983 | 253.6585 | 8.0478 | 21.2557 | D |
| 30 | 560.8108 | 41.6838 | 334.0908 | 54.6055 | 562.3440 | 50.2585 | 48.8493 | C |
| 31 | 560.4551 | 41.6256 | 298.8762 | 67.8464 | 479.0286 | 38.8657 | 49.4459 | C |
| 32 | 594.4517 | 47.1887 | 338.1294 | 53.0870 | 769.6077 | 78.6004 | 59.6254 | B |
| 33 | 615.9272 | 50.7029 | 318.5408 | 60.4524 | 527.7410 | 45.5268 | 52.2273 | B |
| 34 | 600.5933 | 48.1937 | 328.4534 | 56.7252 | 844.8740 | 88.8926 | 64.6038 | B |
| 35 | 622.5264 | 51.7827 | 314.6943 | 61.8987 | 888.7202 | 94.8883 | 69.5232 | B |
| 36 | 443.4468 | 22.4789 | 367.1304 | 42.1825 | 888.8887 | 94.9113 | 53.1909 | B |
| 37 | 563.6018 | 42.1405 | 363.8496 | 43.4161 | 910.7791 | 97.9047 | 61.1538 | B |
| 38 | 509.6582 | 33.3135 | 288.9316 | 71.5856 | 903.9546 | 96.9715 | 67.2902 | B |
| 39 | 518.8582 | 34.8189 | 325.6519 | 57.7786 | 919.5906 | 99.1096 | 63.9024 | B |
| 40 | 830.6218 | 85.8345 | 302.1226 | 66.6257 | 919.1313 | 99.0468 | 83.8357 | A |
| 41 | 516.8809 | 34.4953 | 379.0847 | 37.6877 | 716.9810 | 71.4041 | 47.8624 | C |

considerably, and a recognition of this difference and of the factors that cause it can be of crucial importance for effectively dealing with each tract's problems.

### *Construction of a Two-Variable Matrix*

A method of illustrating the relations between economic and familization status and highlighting the differences between census tracts is to construct a two-variable matrix.

In Figure 43, the economic index key, there are four boxes. From left to right, each box represents a range of the 0–100 economic standard scores: box 1, 0–25; box 2, 25–50; box 3, 50–75; and box 4, 75–100.

By contrast, in Figure 44, the familization index key, the boxes A, B, C, and D represent the range of the familization standard scores. (From bottom to top: box D, 0–25; box C, 25–50; box B, 50–75; and box A, 75–100.)

When the two indices are combined into the social area typology (Figure 45), 16 different types of census tracts based on economic and familization status can be seen.

TABLE 40 Social Area Key

| Census Tract | Economic Index | Economic Rank | Family Rank | Family Index |
|---|---|---|---|---|
| 1 | 17.302 | 1 | A | 79.0847 |
| 2 | 32.028 | 2 | B | 70.6527 |
| 3 | 8.890 | 1 | B | 62.7475 |
| 4 | 3.756 | 1 | B | 56.7819 |
| 5 | 9.494 | 1 | B | 50.9036 |
| 6 | 11.942 | 1 | C | 48.7090 |
| 7 | 22.009 | 1 | C | 48.7591 |
| 8 | 46.303 | 2 | D | 10.9808 |
| 9 | 15.864 | 1 | C | 49.2067 |
| 10 | 51.037 | 3 | B | 59.7372 |
| 11 | 25.712 | 2 | A | 76.0380 |
| 12 | 17.387 | 1 | B | 53.5076 |
| 13 | 31.554 | 2 | B | 50.4842 |
| 14 | 30.245 | 2 | C | 45.6262 |
| 15 | 54.647 | 3 | C | 29.1194 |
| 16 | 100.000 | 4 | B | 52.4042 |
| 17 | 36.601 | 2 | B | 67.9650 |
| 18 | 24.163 | 1 | C | 49.2027 |
| 19 | 32.089 | 2 | B | 54.5566 |
| 20 | 32.424 | 2 | B | 51.7849 |
| 21 | 53.500 | 3 | C | 41.2393 |
| 22 | 75.742 | 4 | C | 48.0324 |
| 23 | 40.911 | 2 | C | 45.1553 |
| 24 | 69.811 | 3 | C | 45.4628 |
| 25 | 44.874 | 2 | C | 38.4479 |
| 26 | 25.349 | 2 | C | 49.8808 |
| 27 | 58.031 | 3 | D | 22.3082 |
| 28 | 33.376 | 2 | C | 27.2988 |
| 29 | 49.504 | 2 | D | 21.2557 |
| 30 | 42.036 | 2 | C | 48.8493 |
| 31 | 23.271 | 1 | C | 49.4459 |
| 32 | 23.021 | 1 | B | 59.6254 |
| 33 | 20.309 | 1 | B | 52.2273 |
| 34 | 40.754 | 2 | B | 64.6038 |
| 35 | 51.796 | 3 | B | 69.5232 |
| 36 | 65.127 | 3 | B | 53.1909 |
| 37 | 70.631 | 3 | B | 61.1538 |
| 38 | 76.923 | 4 | B | 67.2902 |
| 39 | 61.740 | 3 | B | 63.9024 |
| 40 | 63.421 | 3 | A | 83.8357 |
| 41 | 56.296 | 3 | C | 47.8624 |

Figure 46 shows the manner of relating the 41 census tracts of Center City to the social area typology.

We have placed the 100-point economic index on a horizontal scale. The economic score of census tract 16 is 100; so we move to 100 on the economic index (horizontal scale). Tract 16 scores 52.4 on the familization index (vertical axis), so we move up to 52 and place the number 16 at that point. We also know that 100 equals 4 in economic status, and 52.4 equals B in familization status, therefore census tract 16 is a 4-B census tract.

At this point, we have taken the census-tract book of Center City and reduced it to one typology, based on five characteristics, which relates the economic and familization status of all the census tracts in Center City. To review briefly the exact extent to which we have condensed the original tract data, we first took our census-tract book with its 32 detailed characteristics of each of the 41 census tracts, amounting to 1312 data items. We made some subjective judgments and decided to use only certain variables that social scientists have used in previous studies. We therefore had two key categories of data, economic and familization status—three categories if ethnicity is included. We were then working with 10 economic variables and 9 familization variables in each of our 41 census tracts—in all, 779 data items.

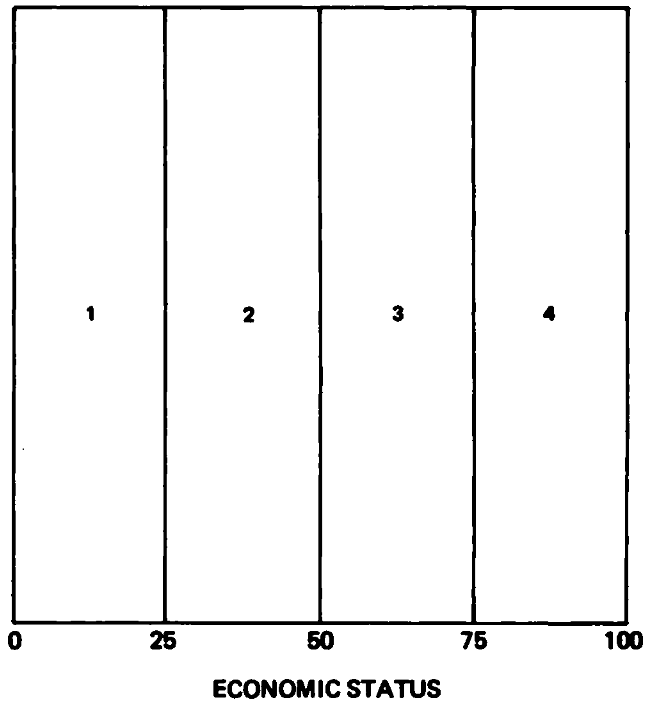


FIGURE 43 Economic index key.

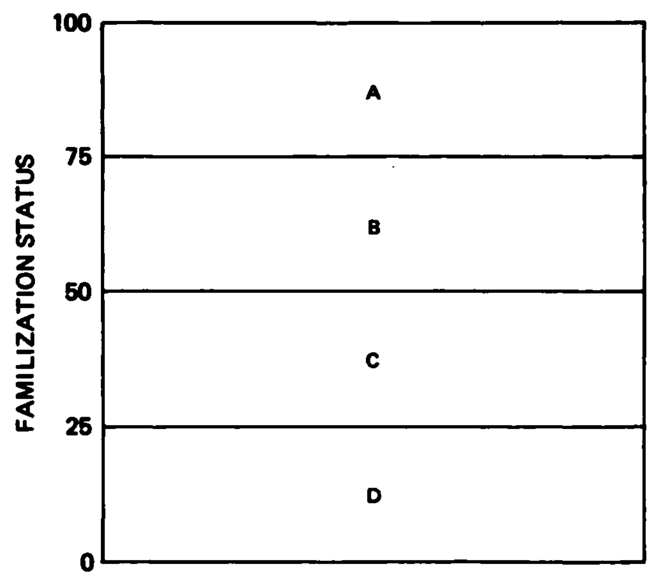


FIGURE 44 Familization index key.

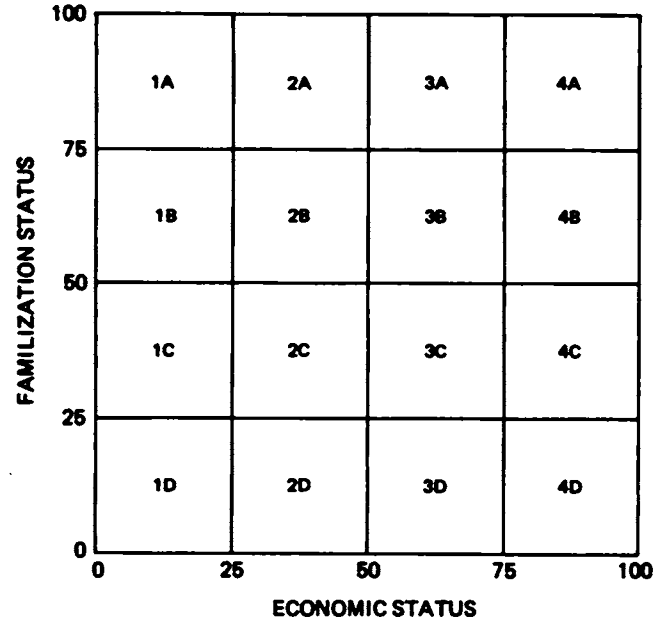


FIGURE 45 Social area typology.

| | | |
|---|---|---|
| 10 economic variables | × 41 census tracts | = 410 data items |
| 9 familization variables | × 41 census tracts | = 369 data items |
| 19 variables | × 41 census tracts | = 779 data items |

We systematically determined which variables most efficiently described each of our concepts. We found that economic status could be described by education and occupation characteristics and that familization status could be described by fertility, working women, and housing-

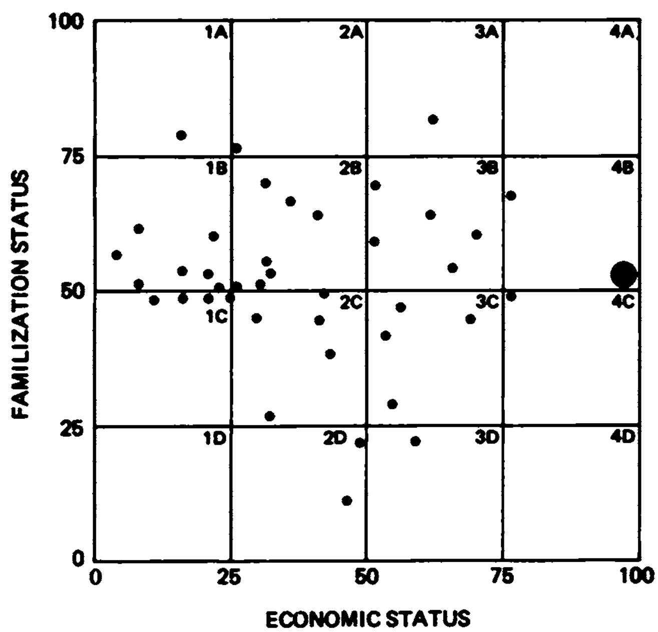


FIGURE 46 Social area index of Center City.

unit occupancy characteristics. By this further reduction, we were now dealing with two economic variables and three familization variables in each of our 41 census tracts—in all 205 data items.

| | | |
|---|---|---|
| 2 economic variables | × 41 census tracts | = 82 data items |
| 3 familization variables | × 41 census tracts | = 123 data items |
| 5 variables | × 41 census tracts | = 205 data items |

We normalized these variables within each concept by placing them on a standard score scale of from 0 to 100. From this procedure we derived one index score for each of our two concepts in each of our 41 census tracts—in all, 82 data items.

| | | |
|---|---|---|
| 1 economic index | × 41 census tracts | = 41 data items |
| 1 familization index | × 41 census tracts | = 41 data items |
| 2 indices | × 41 census tracts | = 82 data items |

Finally, by collapsing the 100-point indices into four categories and assigning alphabetical and numerical designations, we combined the four categories for each concept and created 16 possible positions within a matrix, allowing us to place each of our 41 census tracts in a social context with descriptive economic and familization relations.

In developing this easy-to-use typology, have we, in fact, traded off accuracy? Yes and no. Let us look first at the economic status index of census tract 16 in Table 38. We see that census tract 16 ranks highest in economic status with a score of 100. This implies, if we have not lost any accuracy, that census tract 16 should rank among the highest tracts in all of our economic variables. We know already, in the case of our two most efficient variables, occupation and education, that it ranks highest. But what about the other variables? Does our economic status index really reflect them accurately? The census-tract data book contains the information necessary to verify our theory. Plotting all the relevant economic characteristics of tract 16 would have yielded the following results:

| Variable | Rank |
|---|---|
| Income | 1st |
| Persons per room | 1st |
| Type of heating fuel | 2nd |
| Contract monthly rent | No renters |
| Value of owner-occupied dwellings | 1st |
| Condition and plumbing facilities | 2nd |

In fact, for census tract 16 we have developed an index that is easy to use and one in which we have lost very little accuracy while eliminating unnecessary and cluttering detail. In other words, the economic index is an excellent index of economic status in Center City.

Let us look now at familization status. The index is 52.4—almost the median point (23 tracts below and 17 tracts above). However, a review of the standard scores of the elements that contributed to the index number 52.4

reveals that census tract 16 is not at all in the middle relative to its familization variables. In this instance, census tract 16 has the lowest fertility ratio and the highest single-family dwelling-unit ratio and is in the highest third of all tracts relative to women not gainfully employed.

Yet, when we look only to the index, we are left with the impression that census tract 16 is about at the midpoint of familization status. In this case, we have obviously lost accuracy in our attempt to simplify our index.

| Variable | Standard Score | Rank |
|---|---|---|
| Fertility | 0.0 | Lowest |
| Women not in labor force | 57.2 | Third highest |
| Single-family dwelling units | 100.0 | Highest |
| | 157.2 ÷ 3 = 52.4 | |

To summarize the main objective of this illustration, it is important to note that there are sufficient details in the presentation of Table 39 to reflect that deficiency in the index. This example highlights the responsibility of the researcher to present sufficient detailed information and methodological explanation to enable the reader to determine how much confidence he can place in the data.

### *Displaying the Data on a Map*

To display these two indices on one map we shall use the three primary colors, red, blue, and yellow, to relate the two concepts of economic and familization status. To help us appreciate what happens in cross-mapping, let us first illustrate how these primary colors relate to the color spectrum.

If we take two vertical bars, one yellow and the other red, and blend them with two horizontal bars of yellow and blue we will produce the four squares, one each of purple, orange, green, and yellow (Plate IIa).

Using the same colors, but, this time separating the vertical red bar into three shades of red and the horizontal blue bar into three shades of blue, we blend the vertical and horizontal bars in the same way, creating a 4 × 4 matrix of 16 squares of different colors and shades. In the corners of our matrix we find the same purple, orange, green, and yellow colors that were generated when we blended the two vertical and horizontal bars of primary colors. The basic difference between the 4-color matrix and the 16-color matrix is in the tones that are created when the colors are shaded (Plate IIb).

To relate this color-coding technique to a map of Center City, let us return to Figures 43 and 44 in which we developed the economic index key and the familization index key by dividing their respective indices into quadrants. In Plate IIc we use the same index keys but we color code them.

In Plate IId we take the lowest economic status (1) and color it yellow. The second lowest (2) is color coded light red, the second highest (3) is color coded medium red, and the highest economic status (4) is color coded dark red. In Plate IIe, we take the lowest familization (D) and color code it yellow. The second lowest (C) is color coded light blue, the second highest (B) is color coded medium blue, and the highest familization status (A) is color coded dark blue. These two maps show us where the different types of persons, as identified by their economic and familization status, are located in Center City. As far as economic status is concerned, the higher economic census tracts are located north of the river and clustered together. As far as familization status is concerned, the lowest familization is located in the center of the city, and drawing concentric circles further from Center City, familization status gets higher.

Now we have two maps that provide an excellent overview of Center City. If we wish, we can blend the two maps together, creating Plate IIf, which provides an even better overview for use in understanding the interrelation of the two indexes.

The Census Bureau's Geography Division staff has recently developed the ability to produce full-color, cross-classification maps using computerized mapping techniques and COM (Computer Output on Microfilm) units (Schweitzer, 1975). Because of the reduction in costs and time, this new mapmaking ability opens up a variety of analytic uses not before feasible. For instance, the relatively low cost of this approach now makes it possible for the researcher to develop alternate maps of the same data by varying the class intervals or by using various data-classing techniques described earlier. The map or maps that present the desired emphasis could then be chosen for the final report.

The concepts we have discussed are illustrative of what is possible through the graphical presentation of statistics and with a particular approach to data analysis. Up to now, we have not mentioned the psychological aspects of presenting graphics, the study of which is still in its fledgling stages. At this point, we have little knowledge of how often readers misinterpret graphic displays or how often such presentations are rejected out of hand. Accurate, relevant, timely, complete, and easily comprehensible data are, of course, essential; we hope that this discussion affords a useful overview of the unique possibilities offered by graphically displaying data in the form of maps.

## RECOMMENDATIONS

- Relevant maps and cartographic procedures should be standardized to fit the needs of geomedical research. Comparison of spatial distributions shown on maps may yield important clues to possible cause-and-effect relationships between geochemical phenomena and human pathology, but such efforts are hindered by the existing variety of map projections, map scales, methods of data classification, and methods of cartographic representation.

- Files of relevant maps and remote-sensing imagery should be assembled and made available for use in geomedical research. The enormous number and diffuse character of such aids are at present serious obstacles to their effective utilization.
- A cartographic data bank should be created and continuously updated so that relevant maps and remote-sensing imagery may be easily referenced.
- Files should be maintained of consultants who would be available to advise geomedical researchers concerning technical aspects of cartography and remote sensing.
- The mapping of food crops should be intensified, with a view to finding relationships among spatial patterns of crops, geochemical phenomena, and human pathological conditions.
- A thorough exploration should be made of the possibilities for capitalizing on the rapidly developing applications of using satellite data to map landscapes, soils, geological formations, and other features with geometric correctness and with a resolution of 1.1 acres or better.
- Researchers seeking an effective format for presentation of their data or those seeking ways to apply multivariate considerations to geographic distributions should familiarize themselves with the wide range of cartographic innovations available.

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# X

# *Data and Information Systems*

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## GENERAL CONSIDERATIONS

(Wellington B. Stewart)

Relating disease to trace elements obviously requires the manipulation of large quantities of data. Digital computers seem well suited to this purpose because they have the ability to calculate rapidly and to store, access, manipulate, and display data and the results of computations.

A computer sytem is in reality a complex of machines, programs, and people. The hardware is complicated and requires human intervention to keep it running properly or to repair it when it fails. Most computers also require systems software to make them most useful. This software consists of a large number of interrelated programs that perform many difficult, tiresome, and repetitive functions, such as input/output to many devices, scheduling of tasks, and allocation of hardware and software resources. These are complex programs created by humans and requiring human intervention to correct and maintain them.

Any large application system, such as would be needed to assist in mapping diseases and trace elements, also requires many people, much thought and planning, and a major effort in data collection. Before data are collected, the primary objectives of their use must be clearly known, and an explicitly stated hypothesis should exist. Decisions must be made about validity and form of the data, the processing and storage techniques to use, and the best methods to display output. Moreover, existing experiments of nature must be explored by identifying existing data on such experiments, gaps in these data, and means, including mapping, for browsing through the data in ways that facilitate recognition of meaningful relations. A properly synthesized geographic information system can often provide important and even critical support in this area. Although over 60 systems concerned with some aspects of the problem exist, very few combine a capability for graphic and geographic mapping of data with the on-line statistical manipulation required for such purposes as on-line creation and browsing through maps of residual variance.

The generation of maps by computer has been done successfully in several instances, particularly by the Bureau of the Census (Peucker, 1972). The mapping of some specific diseases by mortality has also been accomplished. Relating the mortality or morbidity figures to the human exposure to trace metals, however, requires not only maps, and perhaps different displays, but also analyses of statistical significance and some type of controlled biological experimentation.

The potential usefulness of mapping diseases and geographical information has been demonstrated for at least one disease (Lindberg *et al.*, 1973). By using certain characteristics of terrain and flora, they were able to predict with good reliability the expected occurrence of Rocky Mountain spotted fever. Such an approach to testing certain hypotheses regarding the association of trace elements and disease might well be useful.

Cancer mortality has also been mapped, by county, throughout the United States, and such data can be related to environmental factors by overlapping maps. Although maps of data coded according to different schemes may be overlain, this procedure is less satisfactory in practice than in theory. Problems arise because of fragmentation of coded areas and the averaging and interpolations required to superimpose data coded in different manners. Experience with geographic information systems in other contexts suggests that new data should be coded in a standardized manner, perhaps according to census tracts (all systems have advantages and disadvantages—the census-tract system is fairly stable and often provides resolution desired for such situations as divided water supplies).

Finding adequate data for the necessary analyses seems at the moment to be difficult. Large quantities of geologic data now exist, but their amount, quality, and definition are difficult to assess. It seems obvious that a central registry should be created. For each data set, the registry should include estimates of its reliability and resolution, the nature of its geocoding, and the custodian of the data. A logical place for these data could well be the Environmental Information System Office of the Oak Ridge National Laboratory (see Appendix B). This office already has much information of this nature and has the capability to store and retrieve more.

The problem of finding good data on the distribution of diseases is perhaps even more difficult. The most easily available data for disease in the United States at the county level are death certificates; every death in the United States must be reported to the county, state, and federal governments. Abstracts of these certificates are available, and maps of causes of death can and have been made. Morbidity data are also needed, but with the exception of some communicable diseases, no uniform nationwide system of collecting morbidity reports exists. However, recent legislation establishing Professional Standards Review Organizations (PSRO) offers some hope that morbidity data will ultimately be collected with a geographic reference (see Appendix C). Such data might prove more useful than death certificates in identifying the actual distribution of disease. The PSRO data, moreover, may have a finer geographical definition than do death certificates. Generally, however, considerations of privacy make it difficult to get exact addresses, and we can predict that much disease data will probably be available only at the county level or at best by census tract or zip code.

Before undertaking a large and expensive data-collection effort, the desirability of standardized geocoding must also be considered. Current data are coded geographically according to different schemes, including area-boundary coding, network coding (as with streams), and point systems (as with wells or sources of pollutant emission).

The costs of data collection are usually several times those of the computer system required to store, retrieve, and analyze the data. For this reason, it is important to design hypotheses testing these experiments of nature so that the greatest value can be obtained from existing data and new data needs can be qualitatively and quantitatively specified. It may be possible to collect the new data during a program primarily carried out in another related context. It is also important to describe and catalog sources of existing data and the structure, geocoding, reliability, geographic resolution, and coverage, as well as the accessibility of computer networks containing existing data bases.

Therefore, the following questions need to be answered in the design of a supporting geographic information system:

- What is the hypothesis, defined as explicitly as possible?
- What data are needed to test the hypothesis or, perhaps, subsequently developed hypotheses?
- If adequate data exist, where are they, what is their structure?
- How can data be obtained, and what geographic or other conversion must be performed?
- What new data are needed from which geographic areas coded in what systems? Who will collect them, and what is the cost?
- What is the size of the data base?
- What models are to be run with the data?
- What is the relative importance of batch and interactive exploratory processing?
- What is the anticipated longevity of the study?

Interactive geographic information systems with access to appropriate data bases can be powerful tools to explore associations of data of different types.

## CHANGING PERSPECTIVES IN THE MANAGEMENT OF LARGE DATA BASES

(Ben T. Williams and Peter A. Alsberg)

Several assumptions appear reasonable when mapping techniques are used to study the geographic and environmental correlates of disease:

- The data desired for study or browsing may not at present be specified or specifiable.
- Much of the needed data may never have been collected. Much of the data that have been collected may not be in machine-readable form.
- If the data are in a machine data base, they are probably accessed through several different systems. These systems have different operating systems, data-base organization, and geographic reference systems.
- The value of such a study is not yet clear, making it unlikely that society will subsidize the development of a dedicated, centralized system.

For these reasons, the problem of using diverse and dispersed data bases must be confronted. The following requirements are necessary to use such data bases:

- Knowledge that the data base exists.
- Access to the data base. (Unless the data base is to be

physically transported to the user or a central site, remote access to the data base is implied.)

- Knowledge of the organization and content of the data base.
- Knowledge concerning the completeness and quality of the data.

Furthermore, the indispensable capability of browsing through data to discover relations requires the following:

- Interactive graphic displays with multidimensional characteristics.
- A data-base organization that permits rapid retrieval, correlation, and possible graphic superposition of variables on maps.
- A means of storing subsets of data, selected while browsing through the data bases of interest, for subsequent study.
- Appropriate analysis packages to support statistical studies.
- Possibly a teleconferencing capability to support collaboration with other researchers.

At least some of the time, the data of interest will be in scattered sites. Therefore, a provision must be made for linking into a network to permit the greatest flexibility. Some data bases may be initially excluded from consideration because of problems with data quality or the lack of adequate or known completeness. The adequacy or desirability of other data bases can only be tested by trial. The only alternative to the transfer of each data base to a central site, cumbersome for widely scattered users, is linkage in a network. Such a linkage implies standard network protocols and interfaces, as in networks like the ARPANET (a nationwide network of major academic computer centers sponsored by the Advanced Research Projects Agency of the U.S. Department of Defense).

Some remarks on the storage of very large data banks have already been made in the previous section. For the purposes of browsing through subsets of several data banks, new devices are appearing that may have appeal at the user's node of a network. An example is the video-disk storage device. It can provide subset storage at the local node for manipulation by a local front-end processor or an advanced intelligent terminal (a terminal having built-in processing and possible storage capabilities). Though present versions of this device are designed for sequential access, random-access devices are under development and may cut local storage costs significantly.

Network protocols can standardize some aspects of the computer communications; however, other problems of standardization are encountered. The user must know the organization and structure of each of the data bases, as well as the unit in which each data item is expressed. Much as interface processors can handle network access protocols, other processor functions can provide translation to common data structures. Indeed, these kinds of processor capabilities may be found in the advanced capability intelligent terminals under development at several sites. These generally incorporate the intelligence-systems notions of Pask (1975), Donald Lindberg (University of Missouri, Columbia, personal communication, 1975), and others.

In developing predictive models of disease occurrence from multiple environmental variables, problems of combinatorial explosion can occur. These can rapidly exceed the capabilities of even the largest parallel machines. Even before machine capacity is exceeded, the limits of human comprehension of complex relations are encountered. This is why real-time browsing by the user through the relations of data is important. Aids such as multidimensional graphing are sought to facilitate this browsing. A real-time browsing capability implies that machine capacity cannot be exceeded and that sufficient processing power exists to support real-time interaction.

It is in this real-time interaction that the human creative talent can be used to develop insights into potentially interesting relations. One must beware of the costs involved when examining multiple variables in large data bases. In addition to monetary costs, the use of processing time may grow so exorbitant that it may prohibit real-time interaction. Appropriate processing strategies must be used in constructing the interaction to prevent exorbitant resource consumption.

Recently there have been substantial advances in efficient processing strategies at several sites. For example, at the Center for Advanced Computation of the University of Illinois, considerable effort has been devoted to the "query-tuning" approach. One or two orders-of-magnitude reduction in the size of the processing job can be achieved in two or three different areas (Alsberg *et al.*, 1975; Alsberg, 1975). This results in significant improvements in the management of complex data-base problems. Through judicious use of such techniques it is feasible to provide some freedom in browsing through large data bases characterized by multiple variables and located at several sites with different access parameters.

In mounting an effort devoted to problems of geochemistry in health and disease it may be important to employ some resources in the design of the required front-end processors and the associated relational, translational, and interface software. Such a development would have significance also to other multivariable problems in biology, social sciences, and perhaps mainly in the complex problems of clinical research and clinical medicine.

## PROBLEMS ASSOCIATED WITH MANAGING LARGE DATA BASES

(Larry J. Peck and Gerald U. Ulrikson)

The management of large computerized data bases is complex and expensive, requiring sophisticated computer hardware and software, as well as highly skilled personnel. Principal problem areas include operational management, data structures, storage devices, hardware and software transition, data integrity, and input/output.

The operational management problem makes efficient utilization of resources a necessity, which normally dictates the consolidation of several products into one data file. A coordination effort is required that includes establishing standard data-element definitions and file structures, managing the assignment of new data elements, performing data-base documentation, and managing access by users. This coordination effort extends to the computer operations level where data-element formats, file structures, and access software must be designed and implemented at data base start-up, and the ongoing operations of file reorganization and recovery, maintenance of data management software, testing of file integrity, activity and makeup, and performance of analytical data base design studies must also be organized and managed (Huffenberger and Wigington, 1975).

Efficient storage and rapid retrieval of large data bases require the use of data-structuring techniques such as indexing or clustering and partitioning. However, these techniques complicate the data-management problem and add an extra data-management burden. Indexes or inverted files, which provide mapping of key values to records containing those values, are commonly used to provide rapid retrieval in large data files. However, inverted files require additional storage beyond that required by the data base, and file updates and corrections typically require that changes be made in the indexes as well as the file, especially in the case of secondary indexes (Belford *et al*., 1975). Indexing is, therefore, expensive because of the additional maintenance and storage required for data-base updates. Clustering and partitioning is another data-structuring technique used for efficient retrieval, which involves structuring the data base so that items that are frequently retrieved together are stored together. Data may be clustered in a variety of ways, but as retrieval needs change the data clusters must also change, which causes an additional maintenance burden on the managing organization.

On-line computer storage also constitutes a major problem area. Disk storage is expensive, and it is not uncommon for large on-line files to encompass several storage devices, which tends to complicate file backup and most file-handling procedures. Use of mass storage devices such as the photostore at Lawrence Livermore Laboratory (LLL) has shown that there never seems to be enough on-line storage; even a trillion bits of capacity is eventually not enough (Fletcher, 1975). Giant storage devices such as the LLL photostore are unsuited for frequent data access, and additional on-line disk space is therefore needed as a working area for manipulation of data. Photostore-like devices present another problem: they use a destructive-write mechanism in which the storage medium is actually destroyed by writing data on it, and the storage medium can be used only once. Mass storage devices thus tend to be unsuitable for data bases requiring frequent updates and corrections. Because there never seems to be enough on-line storage, alternatives such as the window concept of Systems Development Corporation (SDC) are being used (Cuadra, 1975). With the SDC concept, the working day is divided into 3-hour blocks, and during any given block of time only a subset of the total set of data bases is made available to users. Although this approach helps to alleviate the data storage problem somewhat, it complicates the operational problem because data bases are continually being shuffled on- and off-line.

Closely related to the storage problems is the problem of continually changing computer hardware and software. Large data bases, especially bibliographic bases, tend to grow over a period of years, while hardware and software tend to remain in a state of flux. It is not uncommon for a data base to pass through several computers, operating systems, and storage devices over a period of years. Transition may involve software modifications, several database manipulation steps (such as copying and reformatting), and testing of the data base on the new hardware or operating system, all of which are usually performed in the early hours of the morning or during other periods of low usage. During a hardware or software transition, or even in a day-to-day operation, where an extensive data-handling operation is involved, integrity becomes a problem because data may be accidentally destroyed or altered by hardware or software error or by personnel error (for example, a dropped disk pack or an incorrectly labeled disk).

In a network environment, the integrity of a large data base becomes an even greater problem. Multiple copies of the data base may exist at various nodes in the network, or the data base may be partitioned across the network. Backup and recovery operations become more complicated, costly, and error prone. Also, in a shared data-base environment the possibility exists for one user to interfere with another, causing a deadlock situation (Chu and Ohlmacher, 1974).

Additional problems with large data files are keyed input and hard-copy output. Although computers can manipulate large files fairly rapidly, input and output remain a bottleneck. On-site minicomputers with editing and correcting capabilities linked to a master computer are currently the trend for data input (Skolnik and Snyder, 1975); however, most data-input groups are lagging far behind with older-generation input devices, such as the keypunch machine. Hard-copy (readable paper) output continues to be expensive. Although COM (computer output-to-microfiche) devices are available with uppercase and lowercase characters, users are reluctant to accept microfilm and microfiche because special equipment is needed to make them readable.

In summary, large data files present a variety of problems, ranging from operational management of the data base to keyed input and hard-copy output. Software for data compression and automatic restructuring of data bases based on utilization may offer solutions to some of today's data-management problems, and future trends toward computer networking for sharing resources and data bases may help to reduce the expense associated with large data bases in the future.

## STATISTICAL ASPECTS OF THE ANALYSIS OF DATA AND THE CONDUCT OF SURVEYS

(Henry L. Lucas)

At this Workshop, where the Data and Information Systems Work Group considered ways of studying the existing census and survey data to obtain clues about the relations between certain classes of disease and the geochemical environment, we discussed statistical matters and the use of geographic maps. The existing data have been gathered largely for other purposes, and, not surprisingly, many questions and problems have arisen regarding their use. Although new data from specially designed surveys are badly needed, we discussed a few such completed studies of limited scope. There was some debate about the value of those findings, and numerous views were expressed about the types of new data needed. A number of statistical matters relevant both to analyzing data and to conducting surveys did not, however, receive attention; subsequent remarks will deal with some of these.

Certainly, many new data will have to be accumulated and analyzed before the relations between human disease and geochemical factors are clarified. Just what the new data should be is debatable, but, obviously, effort should not be expended to gather information already available. To ensure against redundancy, and to design future surveys otherwise efficiently, calls for a thorough analysis of existing data. Such analysis would also yield clues to pursue in other ways, such as in basic nutritional, biochemical, and physiological research and in clinical studies with humans. In terms of general strategy, searching out, collating, and carefully analyzing the relevant existing census and survey data should receive high priority.

### *Some Basic Statistical Matters*

The analysis of data of any sort should be based on an appropriate mathematical model that takes into account all knowledge and insight about phenomena of interest and, equally critically, about the character of the data. The particular arithmetic done should then be determined by applying the statistical principles of estimation and testing hypotheses in the context of that model. The information extractable is, of course, limited by the information inherent in the data, but explicit formulation of adequate models brings into focus what can and cannot be learned, thus providing insurance against misinterpretation.

For most practical purposes, the principles of estimation and testing hypotheses can be translated to generalized least-squares or, equivalently, to generalized regression approaches. The most powerful algorithms handle many "response" (dependent) variates (e.g., data on many diseases) as well as many "explanatory" (independent) variates (e.g., data on geophysicochemical factors), variates that are categorical (e.g., soil type, ethnic background) as well as quantitative (continuous) in character (e.g., mineral contents, time), and data in which the error (unexplainable variability) takes unusual or unknown patterns. These general algorithms are not included in many packages of computer programs, but they are becoming more widely available. Given these approaches, the relevancy and the adequacy of an analysis mainly rests on how well the underlying model reflects what is known, what is hypothesized, and what is unknown about the phenomena of interest, and what is known and unknown about the ways the data to be analyzed were taken. Thus, problems of data analysis distill largely into formulating appropriate underlying models.

In designing surveys, as in analyzing data, all knowledge and insight about the phenomena of interest should be taken into account. Again, formulation of an appropriate mathematical model is basic; the model brings into focus specifically what new data are needed to complement data already available. The statistical principles involved are those of stratification and randomization applied in the context of the model, with joint consideration of practical matters, such as measurement problems and costs of alternative sampling schemes.

### *Some Substantive Matters*

A number of phenomenological matters pointed out at the Workshop show that appropriate models for expressing the relations between disease and the geochemical environment cannot be simplistic. Basic research reported shows that numerous geochemical moieties (e.g., a variety of trace elements) might be involved in interactive ways. Human exposure can occur through oral consumption, inhalation, skin contact, and radiation, and some of the pathways from the ultimate sources are indirect and many-faceted. Foods and beverages consumed in a given locale can come from many geographical sources, and their character is conditioned by industrial processing and home preparation. Water is of ground, surface, or mixed origin. It is sometimes transported long distances, and its character is conditioned by municipal and home treatment and by type of conduit. Exposure by means of inhalation, skin contact, and radiation is affected by many factors. Further confounding is added by genetic, dietary, and other ethnic and socioeconomic items, by migration, and by time trends in geographical sources of food and water, in water pollution and treatment, in air pollution, and in food production (including soil amendments and irrigation), processing, and preparation practices. In addition, plants and animals that are food sources may serve as buffers against extremes of soil and water character for some mineral elements and as concentrators for others, and the effects might derive from shifts in organic moieties and metallo-organic complexes. These matters must be encompassed as best as possible in formulating models for statistical analysis and in designing surveys.

The exact quantity and character of relevant data that exist are not clear, but potentially useful data appear to be available on a number of subjects, among them the following:

- Disease incidence and prevalence; mortality and morbidity.
- Soil types, geologic formations, surface water and groundwater bodies, climatic factors.
- Chemical and physical character of soils and waters.
- Fertilizer and irrigation practices; water-treatment practices.
- Composition of plants, animals, and consumed foods and waters.
- Food production, transport, and consumption.
- Air pollutants, occupational exposures.
- Population density and movements, ethnic background, type of employment, and other socioeconomic items.

Remote sensing (e.g., by satellite) is developing rapidly and presumably will provide increasing amounts of information that might be useful.

In the Workshop, it was emphasized that data of the foregoing types vary greatly in completeness and quality. The basic sampling or observational units employed, the geographical coverage and degree of resolution realized, and the time period over which measurements have been obtained vary, in some cases markedly, among different factors, and from place to place and time to time on individual factors. For disease incidence and prevalence, geographic coverage is fairly complete in the United States and some other countries over a number of decades, but the precision varies markedly among observational units (e.g., counties) because of variations in population size. Many mineral elements and compounds have been widely measured in soils, rocks, water, plants, animals, and food, as well as many organic moieties in plants, animals, and food, but data on most trace elements, for example, are sparse or spotty. In particular, data on trace elements are scanty for the food and the water (including beverages) actually consumed. Similarly, data are spotty on environmental exposure by means of inhalation, skin contact, and some kinds of radiation. The existing data are also beset with variations in measurement methods. Sample handling and chemical methodology differ from place to place and from time to time. Similarly, diagnostic and autopsical criteria for human diseases may vary. These matters clearly must be taken into account in analyzing the existing data.

Despite the number and the complexity of the exposure paths and the numerous geochemical moieties that might be involved, there are striking geographic patterns in disease occurrence, suggesting that certain local geochemical conditions play a dominant role. There have, however, been noticeable time trends in the patterns of diseases. These might be associated with factors such as changes in crop-production practices, the increasing transport and processing of food and resulting modifications of foods consumed, changes in air-pollution levels, changes in source and treatment of water, changes in occupational conditions, and movements of the populace. It is thus advisable to take time trends into account in studying the relations of interest.

*Model Formulation*

It is not possible to consider here how to take all the foregoing substantive matters into account, but an attempt will be made to provide some general methods that can be employed. A model consists of mathematical statements describing how a set of response variates are known or postulated to be related to a set of explanatory variates. Because some explanatory variates may be unrecognized, because knowledge about the nature (mathematical form) of the relations is almost always imperfect, and because there are always measurement inaccuracies, the model must include error terms. Crudely, a mathematical model can be represented by (response variates) = (function of explanatory variates) + (error terms). Many people are familiar with multiple linear regression involving one response variate. Thus, it is convenient to discuss several points in that context and then to make comments about more general formulations.

The basic linear model (regression equation, without interactions) can be written as

$$y_i = w_i\mu + z_{1i}\theta_1 + z_{2i}\theta_2 + \ldots + z_{qi}\theta_q + x_{1i}\beta_1 + x_{2i}\beta_2 + \ldots + x_{pi}\beta_p + \epsilon_i.$$

The symbols are defined as follows: $y_i$ is the value of the response variate for the $i$th observational unit; $w$ takes the value unity for all observational units so that $\mu$ represents the general mean for $y$; the $z$'s index categorical variates for the unit and take values ranging from zero to unity so that the $\theta$'s are their "effects" (the $z$'s are often called "dummy" variates); the $x$'s are quantitative variates so that the $\beta$'s express the changes in $y$ per unit change of the $x$'s; $\epsilon_i$ is the error term for the $i$th unit.

A response variate of interest would, of course, be the value of disease occurrence (say, cases/100,000) for an observational unit, e.g., a county. The $x$'s would be average values of quantitative explanatory variates (e.g., mineral contents of soil and water, of vegetation, or of food and water consumed) for that county. The $z$'s would index explanatory factors, such as the proportions of the county area covered by soils of different categories, proportions of food from local and from major outside producing counties, proportions of the county populace that fall in different ethnic, occupational, and socioeconomic groups. Also, $z$'s can be employed to index by which of two or more methods a quantitative explanatory variate was measured.

The use of indexing variates is illustrated by Table 41. Only the columns headed by $w$ and the $z$'s would be employed as explanatory variates; the other columns are simply used to compute $z_4$, $z_5$, and $z_6$. Data such as the proportions of food from local and outside sources likely could only be approximated for many counties; hence, the combined soil indices would be approximate, but such figures are better than neglecting food source.

The table, for illustrative purposes, is simplistic. There are more than two major outside food-producing areas, more than three relevant soil categories, and there could

TABLE 41 Illustration of Indexing Variates

| County | Mean Coefficient | Proportions of Food From Outside Counties[a] County per se | C | F | Proportions of Soil in Different Categories: Local $S_1$ | Local $S_2$ | Local $S_3$ | County C $S_1$ | County C $S_2$ | County C $S_3$ | County F $S_1$ | County F $S_2$ | County F $S_3$ | Combined Soil Indices $S_1$ | $S_2$ | $S_3$ | Method for Fe in $H_2O$ 1 | 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ($w$) | | | | ($z_1$) | ($z_2$) | ($z_3$) | | | | | | | ($z_4$) | ($z_5$) | ($z_6$) | ($z_7$) | ($z_8$) |
| A | 1.0 | 0.2 | 0.4 | 0.3 | 1.0 | 0.0 | 0.0 | 0.0 | 1.0 | 0.0 | 0.2 | 0.3 | 0.5 | 0.26[b] | 0.49[c] | 0.15[d] | 1.0 | 0.0 |
| B | 1.0 | 0.5 | 0.4 | 0.0 | 0.2 | 0.7 | 0.1 | 0.0 | 1.0 | 0.0 | 0.2 | 0.3 | 0.5 | 0.10 | 0.75 | 0.05 | 1.0 | 0.0 |
| C | 1.0 | 0.6 | —[e] | 0.2 | 0.0 | 1.0 | 0.0 | — | — | — | 0.2 | 0.3 | 0.5 | 0.04 | 0.66 | 0.10 | 1.0 | 0.0 |
| D | 1.0 | 0.7 | 0.1 | 0.0 | 0.0 | 0.8 | 0.2 | 0.0 | 1.0 | 0.0 | 0.2 | 0.3 | 0.5 | 0.00 | 0.66 | 0.14 | 0.0 | 1.0 |
| E | 1.0 | 0.1 | 0.8 | 0.0 | 0.0 | 1.0 | 0.0 | 0.0 | 1.0 | 0.0 | 0.2 | 0.3 | 0.5 | 0.00 | 0.90 | 0.00 | 0.0 | 1.0 |
| F | 1.0 | 0.5 | 0.4 | —[e] | 0.2 | 0.3 | 0.5 | 0.0 | 1.0 | 0.0 | — | — | — | 0.10 | 0.55 | 0.25 | 1.0 | 0.0 |
| G | 1.0 | 0.4 | 0.0 | 0.4 | 0.0 | 0.0 | 1.0 | 0.0 | 1.0 | 0.0 | 0.2 | 0.3 | 0.5 | 0.08 | 0.12 | 0.60 | 0.2[f] | 0.8[f] |

[a]Proportions do not necessarily sum to 1.0 because all food sources probably cannot be identified.
[b]0.26 = 0.2(1.0) + 0.4(0.0) + 0.3(0.2).
[c]0.49 = 0.2(0.0) + 0.4(1.0) + 0.3(0.3).
[d]0.15 = 0.2(0.0) + 0.4(0.0) + 0.3(0.5).
[e]County *per se* corresponds to the omitted outside county.
[f]Some determinations made by one method and some by a second in county G.

be more than two chemical methods used for determining a mineral content. In addition, there would have to be constructed a considerable number of additional $z$'s defined in appropriate ways to handle the variety of categorical variates noted earlier. The $w$ and $z$'s formed would be entered along with the quantitative measures ($x$'s) into the regression equation on which analysis is based.

The possibilities with which indexing variates can be used to handle complications of various sorts are obviously manifold. What is adequate and feasible with respect to the definition of categorical variates and the fineness of categories would have to be worked out with substantive experts considering the data available, and care has to be taken to avoid redundancy both within and between the indexing and the quantitative variates. The number of categorical variates and the number of categories for each can be very large when analyzing large masses of data. Nevertheless, the complexity must be kept within bounds. For example, soil type would have to be grouped into a relatively few major categories. In fact, the grouping would perhaps best be two or more dimensional; one dimension, for example, characterizing mineral makeup (in turn associated with geologic source and other factors), a second dimension characterizing drainage features, and other organic features.

### *Problems in Analysis*

By employing both indexing and quantitative variates in the model, great power and flexibility can be realized. After formulating a satisfactory model, it would be found, no doubt, that for many observational units, data are not available on some of the quantitative variates ($x$'s) or to form some of the indexing variates ($z$'s) that are included in the model. Surely, however, there are 1000 or so counties, from among the over 3000 in the United States, for which reasonably good data on most of the geophysicochemical and conditioning factors (perhaps even most trace elements) are directly available or for which good approximations can be derived by various interpolational devices. From among these, 500 counties or so could be selected for analysis. Those chosen should well cover extremes as well as intermediate values for all quantitative explanatory variates in all combinations, and the full range of categorical variates should also be well covered. Geographic maps of individual variates and combinations would be useful in identifying and selecting the counties to be used.

Actually the observational units do not all have to be individual counties. If the population is sizable and the desired data are complete for a county, it should, however, be a unit. Other observational units could consist of several counties combined. Such would be desirable where the populations are small in size, but the counties combined should be similar with respect to geophysicochemical and conditioning factors. Usually, counties combined would be contiguous, but they do not have to be. Again maps would be particularly useful in identifying individual counties to use as units and counties to combine.

For this kind of work, it is ordinarily best to employ models that are linear in the parameters to be estimated (i.e., $\mu$, the $\theta$'s, the $\beta$'s), but it is not always reasonable to assume that the relations between the response and the explanatory variates are linear. In fact, evidence cited at the Workshop indicates that the relations between disease and trace-element levels are not linear; also the elements can interact. These matters can be handled by introducing squares, cross products, or other functions of the $x$'s and by using such factors as logs or square roots of disease occurrence.

In this kind of data, one must be concerned about heterogeneity of error. For one thing, the precision with which disease occurrence is assessed in an observational unit (i.e., a county or group of counties) varies depending on population size. Other factors can also result in error heterogeneity. To handle this problem, weighted versions of regression analysis need to be used (Andrews, 1974).

In general, the analysis of data like those of concern here is an iterative process. One starts by fitting a reasonable model. The pattern of deviations, or "residuals," from fit (i.e., observed less predicted) should then be carefully studied for clues regarding better forms in which to use the explanatory variates. Study of the residuals also yields insight into additional variates on which data may be needed to account for sizable residuals not associable with the explanatory variates used. Residual patterns can be examined, not only for the set of observational units employed to fit the model but also for additional units on which appropriate data are available. Various graphical procedures, including geographic maps of the residuals, can be invaluable aids.

Evidence cited at the Workshop indicates that the rates of occurrence for different diseases are positively or negatively correlated with each other. This suggests some communality of underlying causes. Hence, it is desirable to study simultaneously the relations of several or many diseases both to each other and to environmental factors. Extensions of linear regression to encompass several response variates (known collectively as multivariate analysis) are fairly generally available.

The time trends in disease occurrence probably contain additional information on the relations of interest; hence, they should also be studied. One can proceed by first relating each disease and each explanatory variate to time in each observational unit. For this, an expression of the form $u = \alpha_0 + \alpha_1 p_1 + \alpha_2 p_2$ is useful. In the expression, $u$ represents any variate, $p_1$ and $p_2$ are the linear and quadratic orthogonal polynomials for time, $\alpha_0$ is the mean level, $\alpha_1$ measures the linear trend, and $\alpha_2$ measures the curvature. Once the $\alpha$'s are obtained for each variate for each unit, then those for the disease can be jointly related to those for the explanatory variates by employing multivariate algorithms.

### *Survey Design*

The kinds of surveys needed to provide better clues about the causal relations between disease and the geochemical environment are not of the general type in which the sampling design ensures representativeness of a universe (e.g., the United States). Instead, the surveys should be of the analytic type. Here, representativeness of the universe is not a criterion. Instead, the goal is to distribute the sampling units measured over the universe in such a way that all combinations of extreme and intermediate levels of recognized potentially explanatory quantitative variates and of all categories of the potentially important categorical variates are represented by as equal a number of units as is feasible.

All sampling units of similar character with respect to the combination of levels of explanatory variates form a stratum, and the very large number of strata so formed correspond to the treatments in a large multifactor (factorial) experiment. From among the sampling units in each stratum, the ones measured should be selected at random—two units in 30 or so strata to estimate sampling errors and one unit in each of the remaining strata. As was noted previously, the taking of new data redundant to those existing should be avoided. Thus, in future surveys, the exact stratification scheme, the strata sampled, and the variates measured in some or all sampled strata should be such that the new data complement the old in forming the large factorial pattern, and the new and the old data can be analyzed jointly. As we have already pointed out, this procedure dictates a rather exhaustive analysis of existing data prior to any extensive new survey work.

## RECOMMENDATION

An enthusiastic and interested group (e.g., those interested in geochemistry and health at the University of Missouri) should implement a project to seek out, collate, and adequately analyze the existing data relevant to the relations between disease and the geochemical environment. Such an ambitious and arduous project would require considerable funds and sufficient personnel appropriate to retrieve and analyze the data. However, there have been and still are in existence several equally ambitious and heavily funded projects of similar nature in ecology, certain areas of environmental pollution, and certain health areas; hence, such large projects are feasible. These projects all heavily exploit high-speed computing, but, in general, they have not made use of the powerful statistical methodology that is available. In some instances, the analytical approaches are very simplistic and there is great risk that results will be relatively uninformative, if not misleading. A project to study the relations of disease to the geochemical environment could and should be planned and conducted to take full advantage of sophisticated statistical concepts and algorithms.

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# *Appendixes*

# Appendix A

## *Atlas of Cancer Mortality for U.S. Counties: 1950–1969*

As an adjunct to the Keynote Address: Cancer, Geography, and Geology—A Problem for Interdisciplinary Cross-Fertilization, by Schneiderman *et al.* (Chapter I, this volume), several pages describing National Cancer Institute procedures and results have been extracted from the work by T. J. Mason, F. W. McKay, R. Hoover, W. J. Blot, and J. F. Fraumeni, Jr., 1975, *Atlas of Cancer Mortality for U.S. Counties, 1950–1969* [U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, Md., DHEW Publication No. (NIH) 75-780], as follows.

Geographic patterns of cancer are useful in developing and testing etiologic hypotheses. The rates for many cancers vary strikingly from one part of the world to another, providing critical leads to environmental and genetic determinants. Less well known is the geographic variation for cancer within countries. In the United States, cancer mortality statistics have been analyzed for geographic divisions and states, and an earlier publication by the Epidemiology Branch of the National Cancer Institute[1] included maps showing the state-by-state distribution of age-adjusted rates for the 18-year period, 1950–1967.

As a geographic unit for study, the county has advantages over larger areas, with respect to the greater homogeneity of demographic and environmental characteristics. The Epidemiology Branch[2] recently compiled for each county of the continental United States the total number of cancer deaths and age-adjusted death rates according to sex and race (whites and nonwhites) for the 20-year period, 1950–1969. The populations of some counties were too small to yield reliable mortality rates for certain cancer sites, but for most counties sufficient numbers were available to calculate meaningful values. The Epidemiology Branch is using the mortality data in the volume for various epidemiologic investigations, including correlation studies with demographic and environmental variables collected on a county level by governmental and other agencies.

This atlas supplements the county tabulations of cancer mortality[2] and is designed to help visualize geographic variation at the county level. The maps should serve to identify counties, or clusters of counties, with elevated cancer rates, which in turn may provide etiologic clues. Correlation studies may help to link the patterns of mortality with suspected risk factors (e.g., occupational or ethnic composition of the counties). Perhaps the greatest value of the maps will be to designate high-risk communities where analytical-epidemiologic studies may detect specific carcinogenic hazards. In high-risk communities, control programs for early detection and prevention of cancer may also yield special dividends.

The geographic patterns illustrated in this atlas are limited to the U.S. white population. For nonwhites, the cancer mortality and populations at risk on the county level were too small to provide the data needed for a parallel set of maps. The geographic analysis of cancer in nonwhites has required special methods and will be part of a detailed investigation of racial differences. The county resource will also be the basis for a report on the

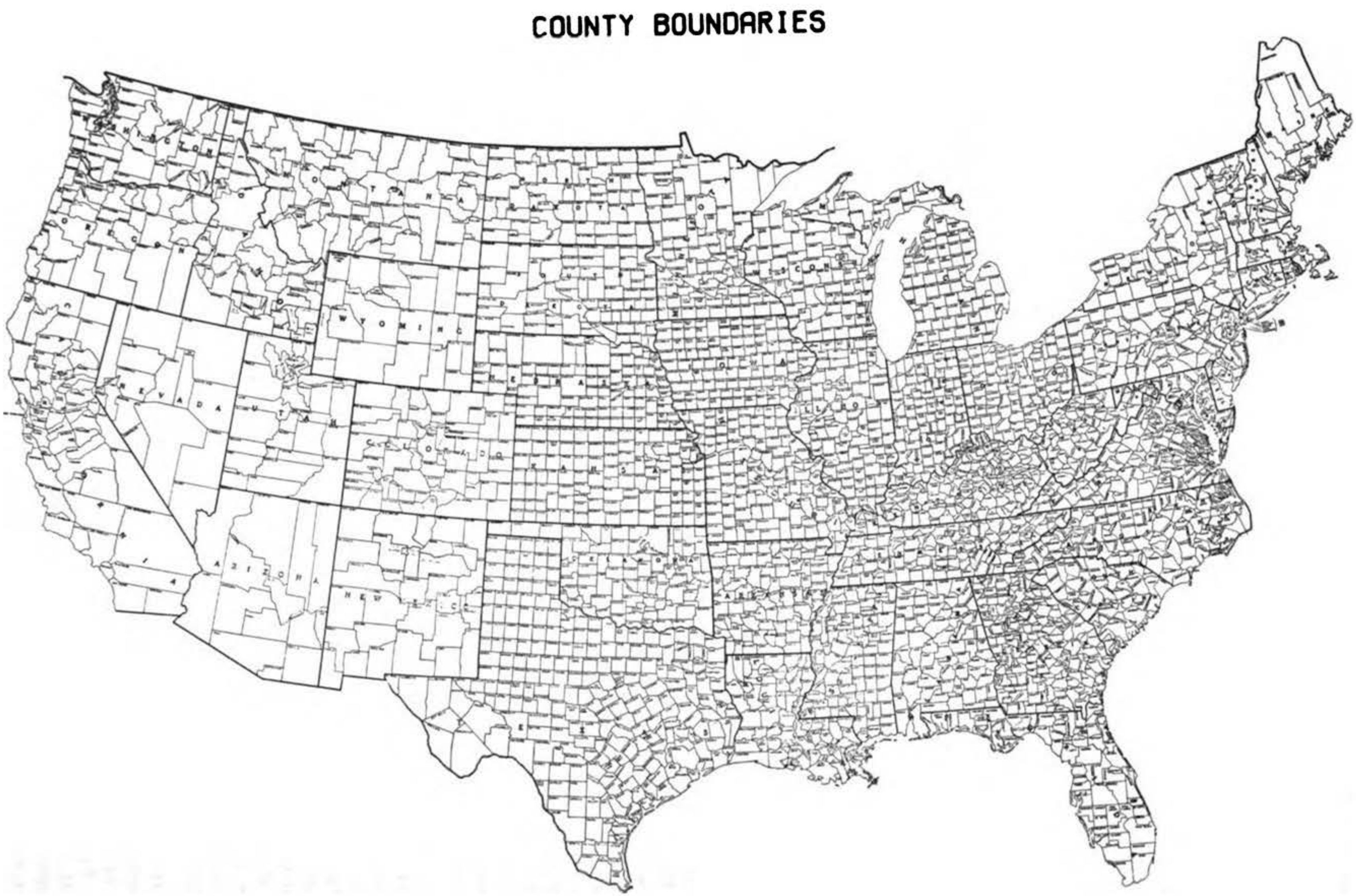



FIGURE A.1 County boundaries.

effect of urbanization, socioeconomic status, and latitude on cancer mortality.

## METHODS

The source of data for this report consists of all death certificates from the 48 contiguous states, 1950–1969,[a] listing cancer as the cause of death. We ascribed each death to the county of usual residence given on the certificates. Average annual age-adjusted mortality rates (per 100,000) were calculated for white males and females by individual county or state economic area (SEA) for the 20-year period. The direct method was used for these calculations, with the total U.S. population for 1960 as the standard. White-county populations were taken from the 1950, 1960, and 1970 censuses,[3–5] and intercensal estimates were derived by linear interpolation. Cancer sites were classified according to the Sixth Revision of the International Classification of Diseases (ICD).[6]

The mortality rates for individual counties or SEA's were compared with rates for the total United States, including Alaska and Hawaii. The national rates are virtually the same as those of the contiguous United States. Confidence intervals for all age-adjusted rates were calculated using the standard error estimated by the method of Chiang.[7] Statistically significant differences resulted when the 95 percent confidence intervals for the local and national rates did not overlap. When no mortality was reported for a given site in a county or SEA, statistical significance was assessed by calculating the probability of no mortality assuming that the number of deaths in a given age group follows a Poisson distribution. If the calculated probability was less than 0.025, the zero rate for the county or SEA was classified as significantly lower than the U.S. rate. Otherwise, the zero rate was considered to be not significantly different.

All maps in this atlas were produced by an automated cartography system which we developed for the IBM 360/370 computers at the National Institutes of Health (NIH). The approach taken is similar to that of Schweitzer[8] and Broome.[9] Our system interfaces with an integrated graphics software package available for use with COM (Computer Output on Microfilm) equipment at NIH. This software provides a means of controlling the intensity and movement of an electron stream directed at the face of a cathode-ray tube (CRT) in much the same manner that a stylus is controlled to produce lines on a conventional flatbed plotter. The image produced on the CRT was photographed, and the negative was used to prepare printing plates.

The input requirements for the system are a file of *x-y* coordinates for the boundaries of individual counties and states, and a file to indicate how the counties are to be shaded. The *x-y* coordinates were developed from a magnetic tape provided by the Geography Division, Bureau of the Census.

The maps are presented in two sections. For the common sites of cancer, we maintained the identity of the 3056 counties[a] of the contiguous United States. For the remaining sites, we used SEA's, which are single counties or groups of counties with similar economic and social characteristics.[10] In the establishment of SEA's the Bureau of the Census has taken into account demographic, climatic, physiographic, and cultural factors, as well as industrial and commercial activities. Thus, SEA's are relatively homogeneous units intermediate in size between states and counties. We have included maps which present the boundaries for counties (Figure A.1) and SEA's (Figure A.2) to facilitate the evaluation of elevated mortality in contiguous units.

Site-specific cancer mortality is illustrated with a county map when the total deaths among whites in 1950–1969 exceeded 75,000 and the number of male and female deaths were each greater than 25,000. Exceptions to this rule were made for leukemia and lymphosarcoma–reticulosarcoma, since SEA maps for these categories revealed more informative patterns. All maps using SEA's as the geographic unit are presented [in the original document] after the county maps.

Following the maps [in the original document], a summary table is presented for each cancer site. Each table includes the distribution, in deciles, of both the age-adjusted rates and the number of deaths. These distributions are distinct. For example, Table A.1 shows that ten percent of the counties in the United States have mortality rates for all malignant neoplasms among white males which are less than or equal to 120.68. This does not imply that all rates less than or equal to 120.68 are based upon 68 or fewer deaths (the 10th percentile for the number of cancer deaths among white males by county). From the tables one can assess the relative magnitude of site-specific cancer mortality for any county in the United States as a function of the rate or the number of deaths. The percentile distribution of the age-adjusted rates also provides information concerning the relationship between urbanization and malignancy. For anatomic sites with high mortality in rural areas the median rate approximates that for the total United States. For those sites with high mortality in urban areas the national rate exceeds the median.

The tables also show the age-specific rates (per 100,000) for each cancer site in the contiguous United States for the period, 1950–1969. This presentation facilitates the comparison of site-specific mortality among populations of interest with that of the United States and permits calculation of standardized mortality ratios (SMR's) for any county or group of counties. The graphical presentation of the age-specific rates was limited to consecutive age groups with nonzero rates. For example, stomach cancer mortality (Table A.2) among white females is presented graphically for age groups 0–4 and 5–9, and age groups 15–19 through 85+. Also, rectal cancer mortality (Table A.3) under age 5 years does not appear in the figure for males or females since the rate for the next age group was zero. However, the actual rates for each age group are given in the accompanying table.

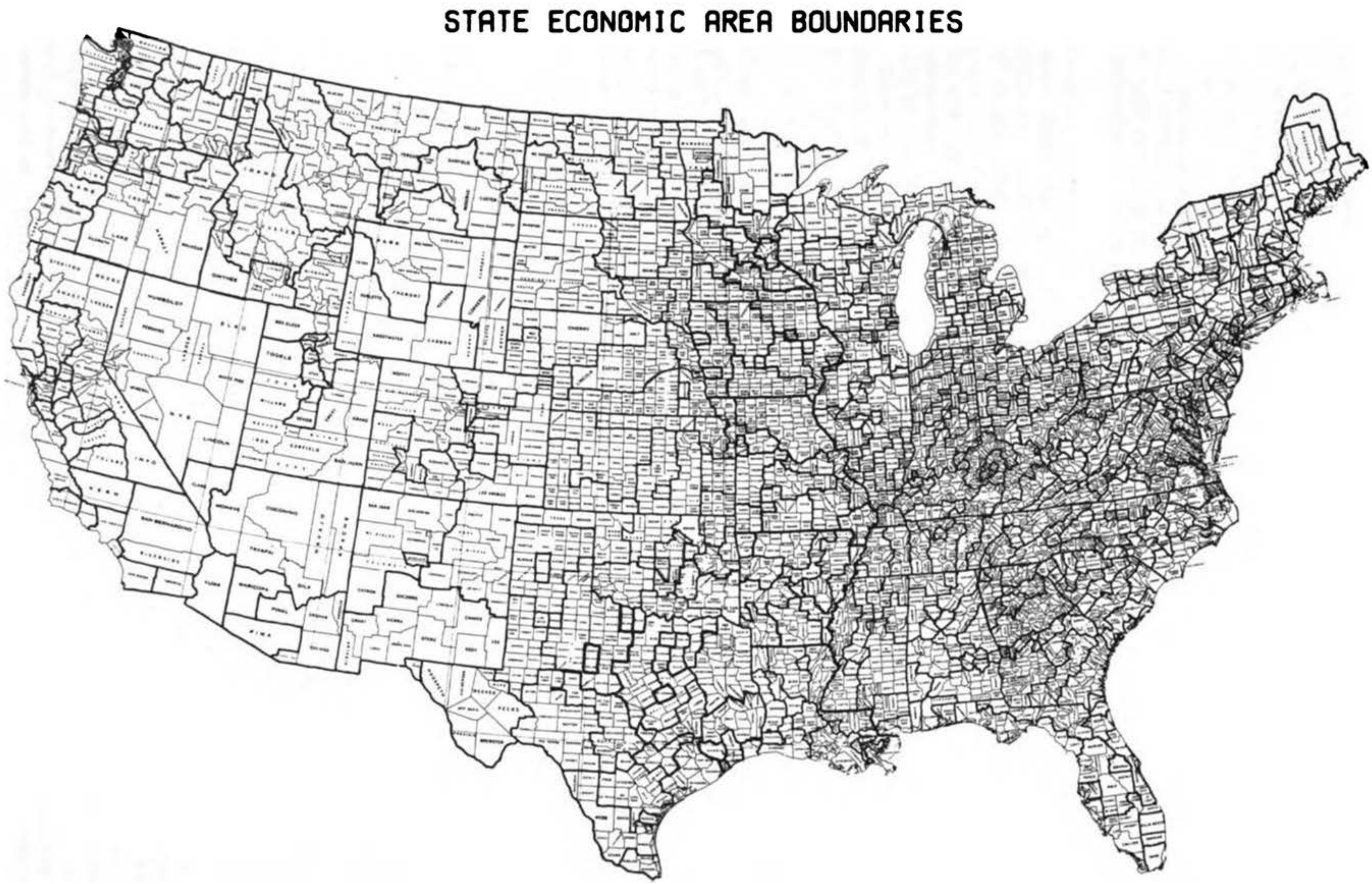



FIGURE A.2 State-economic-area boundaries.

TABLE A.1 Cancer Mortality among Whites, 1950–1969, by County, All Malignant Neoplasms

Percentile ranking of counties according to magnitude of the age-adjusted rates or the number of deaths

| Percentile | Rates Males | Rates Females | No. of Deaths Males | No. of Deaths Females |
|---|---|---|---|---|
| 10th | 120.68 | 95.71 | 68 | 51 |
| 20th | 130.64 | 103.11 | 109 | 84 |
| 30th | 137.17 | 108.06 | 149 | 122 |
| 40th | 142.78 | 112.28 | 196 | 161 |
| 50th | 147.92 | 116.33 | 254 | 210 |
| 60th | 153.07 | 120.15 | 325 | 282 |
| 70th | 158.48 | 124.95 | 436 | 379 |
| 80th | 166.56 | 129.69 | 637 | 564 |
| 90th | 178.06 | 136.32 | 1357 | 1228 |
| Range | 44.58-248.62 | 37.68-373.44 | 2-157396 | 1-139313 |
| Total U.S. | 174.04 | 130.10 | 2572035 | 2253282 |

Number of counties with no deaths: Males 0 Females 0

Number of counties by mapping category

| Category | No. of Counties Males | No. of Counties Females |
|---|---|---|
| Signif. high, in highest decile | 158 | 145 |
| Signif. high, not in highest decile | 0 | 14 |
| In highest decile, not signif. | 148 | 161 |
| Not signif. different from U.S. | 822 | 1444 |
| Signif. lower than U.S. | 1928 | 1292 |

Age-specific rates (per 100,000), U.S. whites

| Age | Males | Females |
|---|---|---|
| 0- 4 | 11.27 | 9.66 |
| 5- 9 | 9.07 | 7.04 |
| 10-14 | 6.75 | 5.35 |
| 15-19 | 9.34 | 6.12 |
| 20-24 | 11.25 | 7.39 |
| 25-29 | 14.52 | 12.75 |
| 30-34 | 20.72 | 25.39 |
| 35-39 | 33.60 | 48.72 |
| 40-44 | 62.09 | 89.30 |
| 45-49 | 116.16 | 144.60 |
| 50-54 | 214.16 | 214.00 |
| 55-59 | 358.95 | 292.52 |
| 60-64 | 559.46 | 387.33 |
| 65-69 | 787.99 | 505.30 |
| 70-74 | 1052.62 | 663.23 |
| 75-84 | 1454.51 | 935.09 |
| 85+ | 1798.98 | 1231.15 |

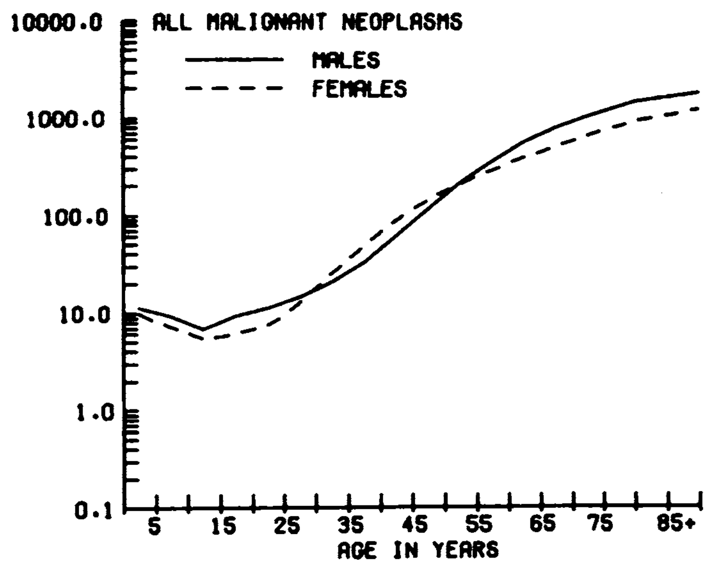


TABLE A.2 Cancer Mortality among Whites, 1950–1969, by County, Stomach

Percentile ranking of counties according to magnitude of the age-adjusted rates or the number of deaths

| Percentile | Rates Males | Rates Females | No. of Deaths Males | No. of Deaths Females |
|---|---|---|---|---|
| 10th | 8.08 | 3.62 | 5 | 3 |
| 20th | 9.59 | 4.73 | 10 | 5 |
| 30th | 10.82 | 5.41 | 14 | 8 |
| 40th | 11.92 | 6.04 | 18 | 10 |
| 50th | 12.93 | 6.64 | 23 | 13 |
| 60th | 14.10 | 7.32 | 30 | 18 |
| 70th | 15.46 | 8.15 | 39 | 24 |
| 80th | 17.06 | 9.21 | 57 | 34 |
| 90th | 19.72 | 10.90 | 114 | 69 |
| Range | 0.00-65.69 | 0.00-98.11 | 0-15832 | 0-10449 |
| Total U.S. | 15.22 | 7.70 | 222524 | 137254 |

Number of counties with no deaths: Males 22 Females 68

Number of counties by mapping category

| Category | No. of Counties Males | No. of Counties Females |
|---|---|---|
| Signif. high, in highest decile | 121 | 87 |
| Signif. high, not in highest decile | 45 | 52 |
| In highest decile, not signif. | 185 | 219 |
| Not signif. different from U.S. | 1840 | 2037 |
| Signif. lower than U.S. | 865 | 661 |

Age-specific rates (per 100,000), U.S. whites

| Age | Males | Females |
|---|---|---|
| 0- 4 | 0.03 | 0.02 |
| 5- 9 | 0.01 | 0.01 |
| 10-14 | 0.01 | 0.00 |
| 15-19 | 0.03 | 0.03 |
| 20-24 | 0.11 | 0.06 |
| 25-29 | 0.28 | 0.27 |
| 30-34 | 0.76 | 0.72 |
| 35-39 | 1.84 | 1.41 |
| 40-44 | 3.84 | 2.65 |
| 45-49 | 7.70 | 4.40 |
| 50-54 | 14.68 | 7.23 |
| 55-59 | 25.79 | 11.98 |
| 60-64 | 44.40 | 19.77 |
| 65-69 | 72.01 | 31.96 |
| 70-74 | 106.12 | 50.94 |
| 75-84 | 159.03 | 86.41 |
| 85+ | 189.37 | 123.56 |

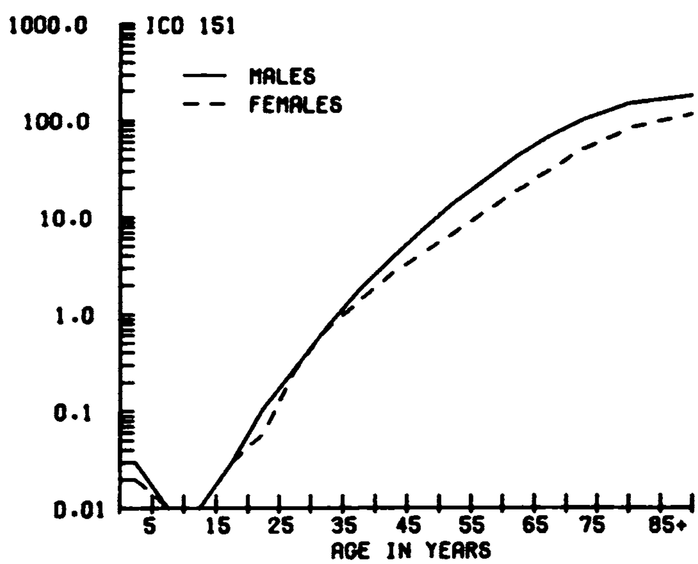


TABLE A.3 Cancer Mortality among Whites, 1950–1969, by County, Rectum

Percentile ranking of counties according to magnitude of the age-adjusted rates or the number of deaths

| | Rates | | No. of Deaths | |
|---|---|---|---|---|
| Percentile | Males | Females | Males | Females |
| 10th | 1.44 | 0.97 | 1 | 1 |
| 20th | 2.52 | 1.85 | 2 | 2 |
| 30th | 3.34 | 2.46 | 4 | 3 |
| 40th | 4.06 | 3.00 | 6 | 4 |
| 50th | 4.71 | 3.44 | 8 | 6 |
| 60th | 5.52 | 3.94 | 11 | 9 |
| 70th | 6.47 | 4.49 | 15 | 13 |
| 80th | 7.40 | 5.18 | 26 | 20 |
| 90th | 8.89 | 6.16 | 58 | 45 |
| Range | 0.00-39.40 | 0.00-36.37 | 0-9446 | 0-6673 |
| Total U.S. | 7.65 | 4.82 | 112232 | 85170 |

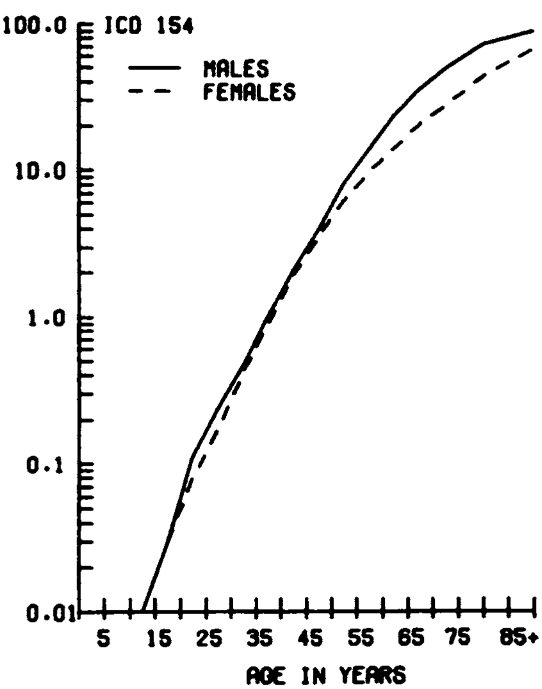
Number of counties with no deaths: Males 184 Females 229

Number of counties by mapping category

| | No. of Counties | |
|---|---|---|
| Category | Males | Females |
| Signif. high, in highest decile | 116 | 78 |
| Signif. high, not in highest decile | 4 | 21 |
| In highest decile, not signif. | 190 | 228 |
| Not signif. different from U.S. | 1440 | 1868 |
| Signif. lower than U.S. | 1306 | 861 |

Age-specific rates (per 100,000), U.S. whites

| Age | Males | Females |
|---|---|---|
| 0- 4 | 0.02 | 0.02 |
| 5- 9 | 0.00 | 0.00 |
| 10-14 | 0.01 | 0.00 |
| 15-19 | 0.03 | 0.03 |
| 20-24 | 0.11 | 0.08 |
| 25-29 | 0.24 | 0.17 |
| 30-34 | 0.47 | 0.42 |
| 35-39 | 1.01 | 0.92 |
| 40-44 | 2.13 | 1.93 |
| 45-49 | 4.04 | 3.57 |
| 50-54 | 8.30 | 6.29 |
| 55-59 | 14.53 | 9.82 |
| 60-64 | 24.35 | 14.49 |
| 65-69 | 36.67 | 20.97 |
| 70-74 | 50.22 | 28.13 |
| 75-84 | 73.31 | 44.67 |
| 85+ | 91.58 | 68.93 |



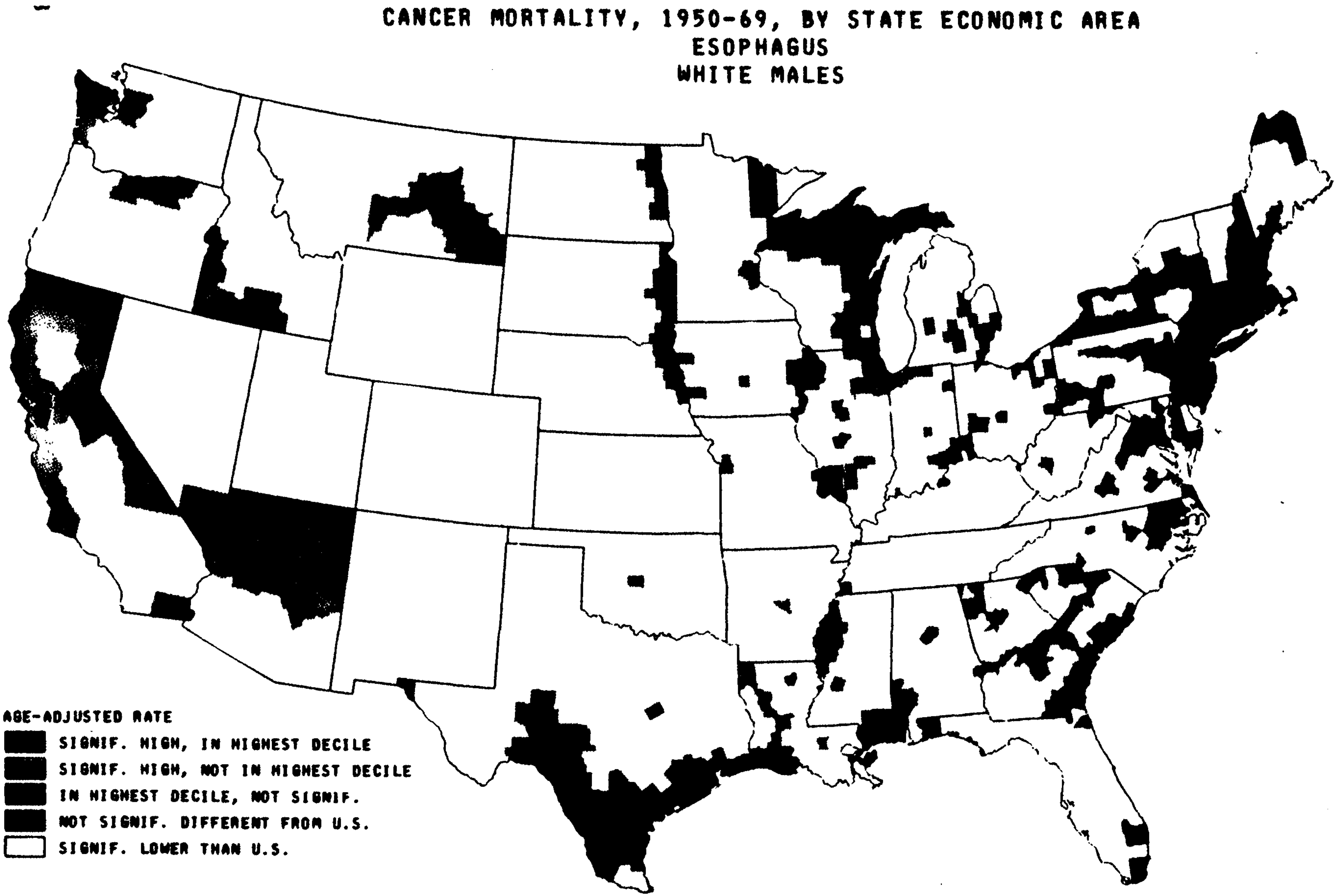



FIGURE A.3 Cancer mortality, 1950–1969, by state economic area, esophagus, white males.

## RESULTS AND DISCUSSION

This section describes some features of the county and state-economic-area maps, and illustrates ways to use this atlas to generate and test hypotheses of cancer etiology.

Inspection of the maps for the various cancer sites reveals striking differences in the geographic patterns of mortality. For a number of cancer sites, however, the patterns are similar and may be grouped into one of five broad categories:

1. A cluster of high rates in the Northeast (New Jersey, southern New York, Connecticut, Rhode Island, Massachusetts) and in urban areas along the Great Lakes (Buffalo, Cleveland, Detroit, Chicago, Milwaukee), but generally low rates for the southern and central parts of the United States
   - other mouth and throat (males)
   - esophagus (males) (Figure A.3)
   - large intestine, except rectum
   - rectum
   - larynx (males)
   - breast
   - bladder (males)
2. High rates in the South and/or Appalachia, but low rates in the Northeast
   - lip (females)
   - other mouth and throat (females)
   - esophagus (females) (Figure A.4)
   - cervix
   - melanoma of skin
   - other skin
   - eye (females)
   - bone (females)
3. High rates in the North Central States (the Dakotas, Minnesota, Wisconsin, upper Michigan)
   - stomach (Figure A.5)
   - kidney
   - prostate
   - lymphosarcoma and reticulosarcoma, etc. (females)
   - multiple myeloma
   - leukemia
4. High rates generally in the rural North, but low rates in the South
   - ovary
   - testis
   - bladder (females) (Figure A.6)
   - other endocrine glands
   - lymphosarcoma and reticulosarcoma, etc. (males)
5. No clearly discernible patterns
   - salivary gland
   - pancreas
   - nose, nasal cavities and sinuses
   - brain and other parts of nervous system
   - connective tissue

Each cancer site could not be classified into one of these categories. For example, lung cancer rates are high in New Jersey and the environs of New York City (as in category number 1), but the predominant aggregation is along the Gulf Coast from Texas to the Florida Panhandle.

The geographic patterns of mortality for selected cancer sites are summarized below.

*Other Mouth and Throat* This group consists of all cancers of the oropharynx, except the salivary glands and nasopharynx. Excess mortality occurs among males in the industrial Northeast and in scattered urban areas across the country. A contrasting picture is seen in females, with high rates throughout the Southeast and relatively low mortality in the Northeast.

*Esophagus* High rates for males are found primarily in urban areas of the Northeast and Midwest. Mortality is significantly low in most of the remainder of the country. County tabulations for esophageal cancer[3] show patches of high rates among males along the Georgia and South Carolina coast. However, this pattern is not detected by the SEA maps. Females do not display the Northeast predominance but show scattered high rates throughout the South.

*Stomach* Both sexes show an extensive cluster of high mortality throughout Minnesota, northern Michigan, Wisconsin, and the Dakotas. Excess mortality is observed in Maine, as well as in parts of New Mexico, Nevada, and southern Colorado.

*Large Intestine, except Rectum* Mortality predominates in the Northeast, particularly in coastal areas, and in areas along the Great Lakes. Patches of exceptionally high rates are found for both sexes in Nebraska.

*Rectum* The patterns are generally similar to those for colon cancer, with consistently elevated mortality in the Northeast and scattered high rates in the Midwest.

*Biliary Passages and Liver* For males, elevated death rates are seen in Texas, extending from the Mexican border along the Gulf Coast into Louisiana. There are patches of high mortality in Appalachia and in the Midwest. For females, elevated rates are also found along the Texas-Mexican border, extending westward into New Mexico, as well as in the rural Midwest and northern Appalachia.

*Lung* For males, consistently high rates are seen along the Gulf Coast from Texas through Florida, with the heaviest concentration in Louisiana. Mortality is also excessive in a belt of counties on the southeast Atlantic Coast, in northern New Jersey, in New York City, and along the Hudson River. The pattern for females is generally similar but less pronounced; however, there is no clustering in Louisiana, and mortality is elevated in Nevada and southern California. For both sexes, mortality is low in the central United States.

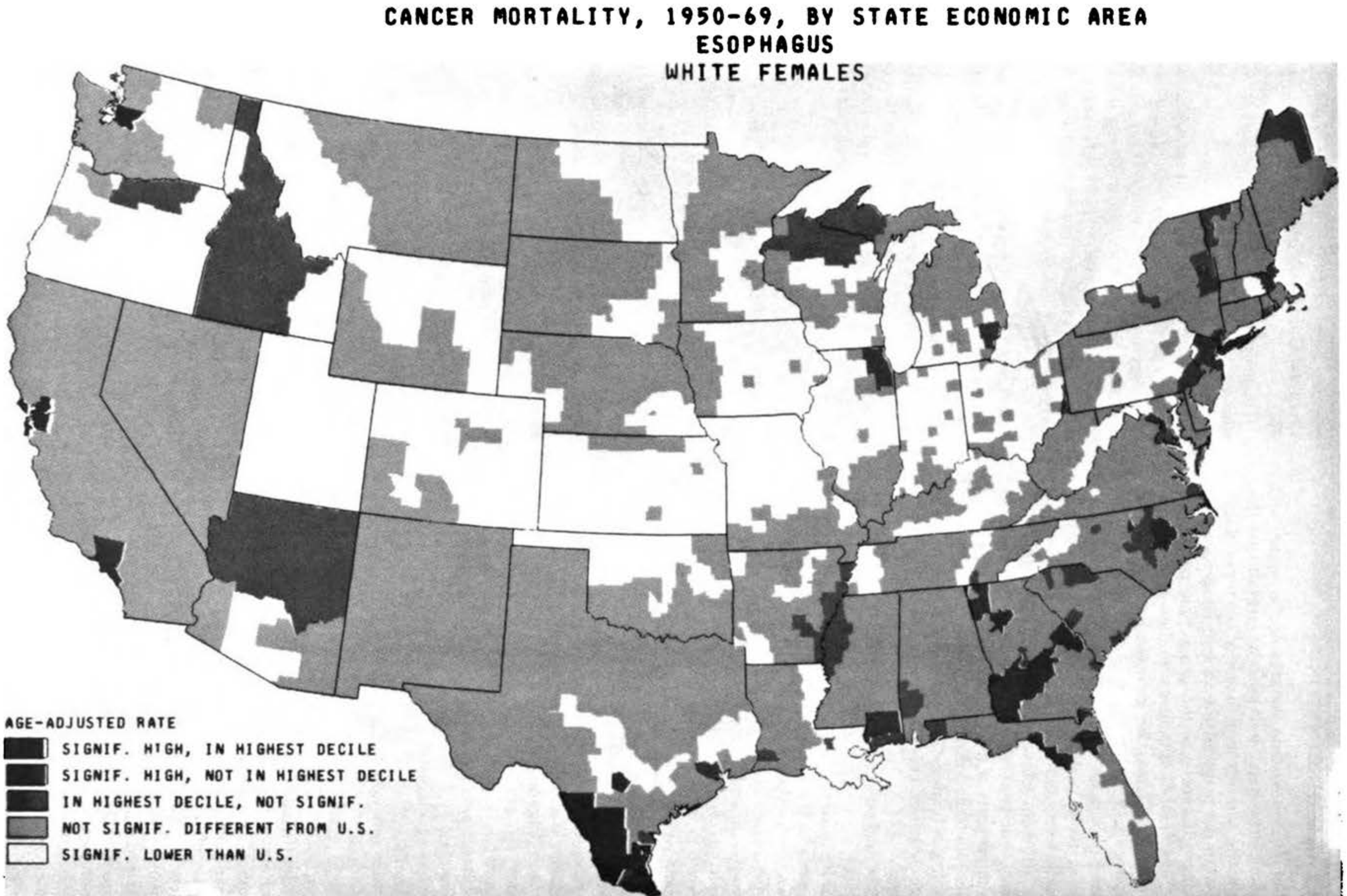



**FIGURE A.4** Cancer mortality, 1950–1969, by state economic area, esophagus, white females.

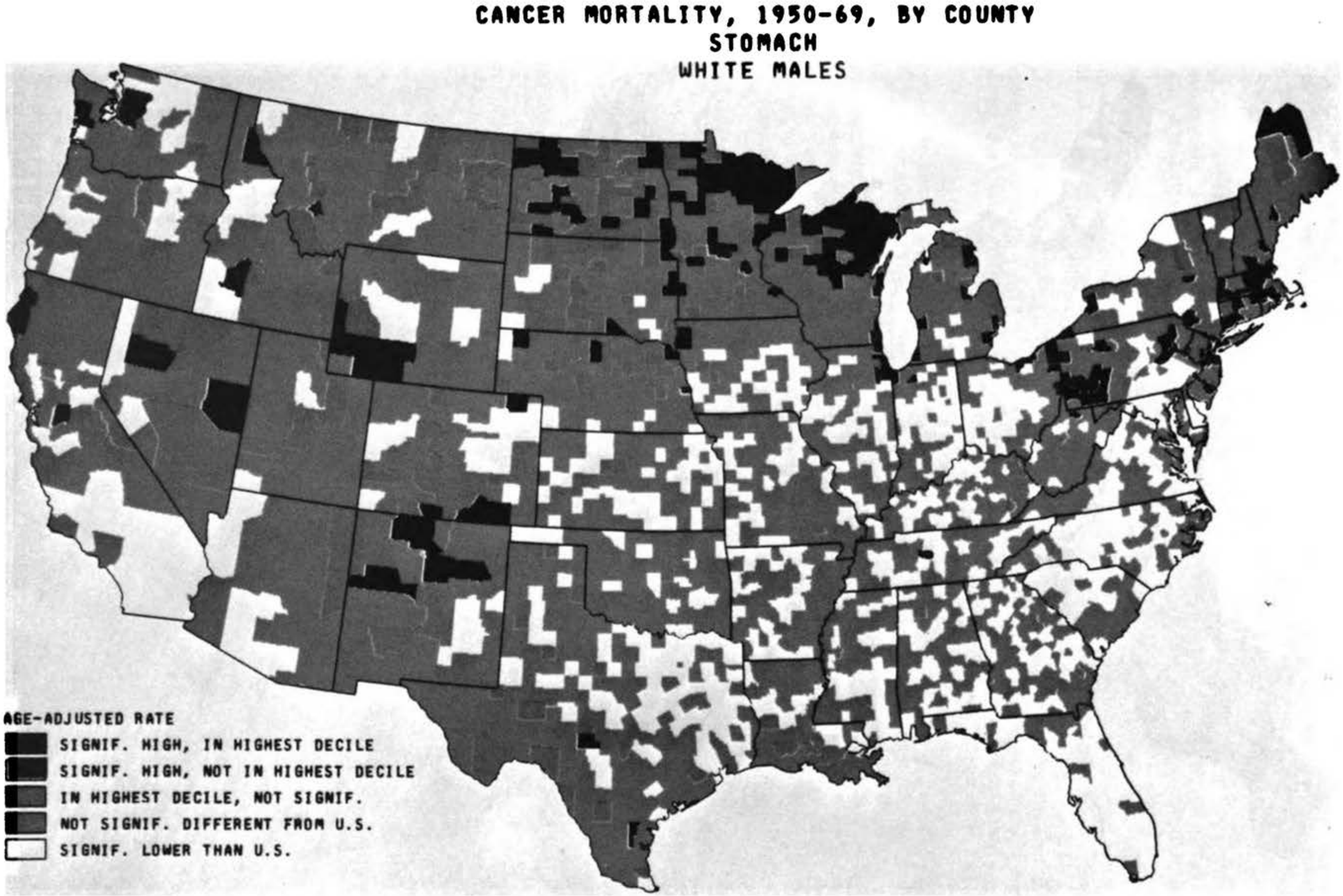



**FIGURE A.5** Cancer mortality, 1950–1969, by county, stomach, white males.

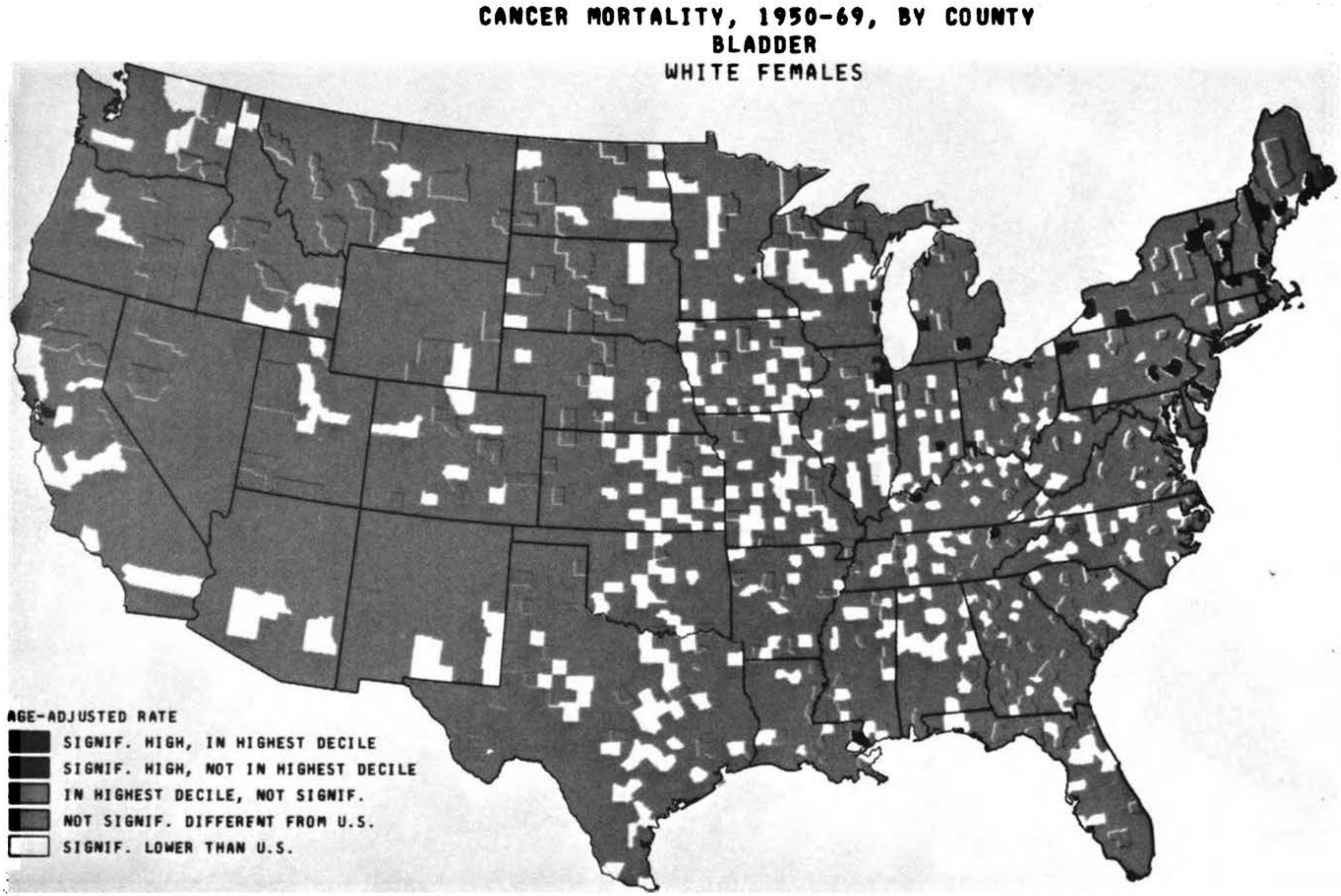



**FIGURE A.6** Cancer mortality, 1950–1969, by county, bladder, white females.

*Female Breast* Mortality is high in northern urban areas, particularly the Northeast. Rates are generally low throughout the South.

*Cervix* High rates are scattered throughout the South, with the heaviest concentration in Appalachia. Except for the upper part of New England, rates in the North are low.

*Ovary* High death rates are scattered in northern counties, many of which are rural. Rates in the South are generally low.

*Prostate* Patches of excessive mortality are found in Iowa, Minnesota, the Dakotas, Utah, and northern New England.

*Testis* Mortality is elevated in northern rural areas. Rates in the South are generally low.

*Kidney* For males, high mortality rates are seen in rural Wisconsin, Minnesota, and the Dakotas. Although significantly higher than the national mortality, the rates in the Northeast are not in the upper decile of all county rates. The pattern for females is similar.

*Bladder* For males, clusters of excessive mortality occur in New Jersey, New York City, and urban areas around the Great Lakes. Rates are elevated also in rural New York and New England, and the Mississippi River Delta in Louisiana. Mortality rates for females are not high in New Jersey but are increased in rural New England.

*Skin (Melanoma and Other)* Both sexes display a striking southern predominance extending from coast to coast.

*Thyroid* In both sexes high mortality rates are seen in the Rocky Mountain and North Central States.

*Bone* For females, a prominent pattern of excess mortality stretches from Oklahoma eastward through the South and into Appalachia. The pattern is less pronounced for males, but scattered high rates occur in Pennsylvania, West Virginia, and certain parts of the South (Louisiana, Mississippi, Kentucky).

*Hodgkin's Disease* There are elevated rates for both sexes in eastern New England. For females, mortality is excessive in the Dakotas and Minnesota. For males, mortality is high in parts of Kansas, Nebraska, and South Dakota.

*Lymphosarcoma and Reticulosarcoma, etc.* For females, high rates are seen in Minnesota and Nebraska. Mortality for both sexes is significantly low in the South.

*Multiple Myeloma* High mortality rates aggregate in Montana, the Dakotas, Minnesota, and Iowa for both sexes.

*Leukemia* For males, scattered high rates are seen in the central part of the country from Texas to Minnesota. The pattern for females is similar.

The geographic patterns of cancer in this atlas may provide leads to the causes of cancer. Similarities in geographic distribution for several cancer sites suggest common etiologic factors. For example, excessive mortality rates for various cancers (mouth and throat, esophagus, colon, rectum, larynx, and bladder) are dominant in the highly industrialized Northeast. Except for colon and rectal cancer, the high rates in this area are limited to males, suggesting occupational determinants. It is nearly certain that industrial exposures have produced the striking geographic clusters of bladder cancer in males. Of the 21 counties in New Jersey, 18 have bladder-cancer rates in the highest decile of male rates for all U.S. counties. Indeed, the rate for Salem County, New Jersey (16.1 per 100,000 population) ranks highest among all American counties with a white population of at least 10,000. In Salem County, approximately one-fourth of the work force is employed in chemical and allied industries,[11] and workers exposed to chemicals such as 2-naphthylamine are known to be at increased risk of bladder cancer.[12]

On the other hand, the Northeast predominance for colon and rectal cancer applies to both sexes. Of the 21 counties in New Jersey, the rates for colon cancer are in the highest decile nationally for 15 counties in males and 16 counties in females. For rectal cancer, the corresponding numbers are 18 and 15. This aggregation suggests etiologic factors, perhaps dietary, common to both sexes.

Since colon cancer is generally more common in populous areas, a cluster of high rates in rural areas would arouse suspicion. Such a cluster occurs for both sexes in some southeastern Nebraska counties. The aggregation may be due to chance, to unusual demographic factors (e.g., socioeconomic, ethnic), or to environmental exposures indigenous to this rural area.

The maps for lung cancer indicate that excessive mortality is not limited to highly populated urban areas where cigarette smoking and air pollution are most prominent. In fact, the rates are highest along the coast of the Gulf of Mexico, particularly in Louisiana. Of Louisiana's 64 counties, 38 have lung cancer rates in the highest decile of male rates for all U.S. counties. Furthermore, of the 31 American counties (top 1 percent) with the highest rates, 13 are in Louisiana. An additional 7 counties in the top 1 percent are found along the Gulf Coast and along the Atlantic Coast from northern Florida to Charleston, South Carolina. Further studies are needed to identify the environmental and demographic factors contributing to the increased risk of lung cancer in these predominantly rural and port areas.

The geographic pattern for stomach cancer seems to be influenced strongly by ethnic factors. The clusters of elevated mortality in both sexes in the North Central States correspond closely with the geographic concentration of persons from Austria, the Soviet Republics, and Scandinavia. These findings are consistent with the increased risk of stomach cancer in the countries of origin.[13]

These examples suggest ways in which this atlas, together with companion tabulations of county-specific mortality,[2] can be used to generate and test hypotheses of cancer causation. It is important to recognize that the associations suggested by the maps are not proof of causation. Even if demographic or environmental characteristics of counties correlate well with the distribution of cancer mortality, the relationships are not necessarily etiologic. For example, the high bladder-cancer rates in New Jersey counties where chemical workers are concentrated suggest occupational determinants, but retrospective or prospective epidemiologic study is needed to establish an industrial hazard. The atlas does not provide definitive answers concerning the etiology of cancer but can suggest risk factors and communities where further epidemiologic and etiologic studies would be rewarding.

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# Appendix B

## *National Environmental Specimen Bank Survey*

ROBERT I. VAN HOOK

A National Environmental Specimen Bank Survey has been completed in a joint effort by the Environmental Protection Agency, the National Science Foundation, and the Oak Ridge National Laboratory (ORNL). The purpose of this survey was to attempt to identify those places in the continental United States that were currently, or had been, storing materials collected in either research or monitoring activities. The objectives of the survey were to identify (1) where collections were located, (2) who maintained the collections, (3) of what the collections consisted, (4) what analyses had been performed on the materials in the collections, (5) how the sample collections had been preserved and stored, and (6) the assessability of the stored materials and associated data to both research and regulatory personnel. The survey was designed to include collections in the following materials: geological, atmospheric, human tissue, animal tissue, plant tissue, and water samples.

Forty-five hundred letters of inquiry were mailed to various individuals around the country who were judged to be potential sources of appropriate information. From these contacts, 650 collections were identified and have been accumulated in a data base at ORNL. The collections included the following types: federal, 143; state, 103; personal, 14; private laboratory, 31; private museum, 13; and university, 345. Over half of the collections identified are taxonomic in nature and have little application to the concept of a National Environmental Specimen Bank, except for their importance in identification of sample material. The appropriateness of the remaining collections are being evaluated by the National Bureau of Standards for a National Environmental Specimen Banking System, whose feasibility is to be examined by a national committee to be set up to develop a proposed five-year plan for such a system, if warranted.

# Appendix C

# *The National Center for Health Statistics*

ARTHUR J. McDOWELL

Within the Office of Health Policy Research and Statistics of the Public Health Service, Department of Health, Education, and Welfare (DHEW), is the National Center for Health Statistics (NCHS). The Center is a research-oriented statistical organization, charged with the primary mission of obtaining, analyzing, reporting, and disseminating reliable, general-purpose, national statistical data related to health. It is also responsible for developing improved methodologies in the entire area of its operation.

NCHS as an organizational entity is less than 20 years old, although some of its functions, notably some of those in the vital statistics field, have been carried out for many decades. In 1975, Public Law 93-353 (1974) established the Center as a statutory agency of the government within DHEW; formerly it was simply a bureau established by administrative order of the Department.

The Center has responsibilities that transcend the PHS and DHEW boundaries. The Office of Statistical Policy of the Office of Management and Budget has designated NCHS as one of the five general-purpose statistical agencies within the federal government, each concerned with a particular field of subject matter. Just as the Bureau of the Census is the agency for population data, for example, and the Bureau of Labor Statistics is the agency for employment and related labor data, the NCHS is designated as the one general-purpose statistical agency in the area of vital and health statistics (Office of Statistical Standards, 1968).

The chart, NCHS Organization and Functions (Figure C.1) shows the organization and functions of the various components of the Center. Within the data-systems grouping, one can identify a number of different kinds of programs using appropriate methodologies to obtain various types of health data. The Division of Vital Statistics, for example, obtains mortality data from the state registration of deaths and analyzes and reports these data by specific cause by age, sex, region, and other variables. The mortality data have an important advantage; they represent complete counts of deaths and so can be subdivided geographically much more finely than can data obtained through sample-survey mechanisms such as are used by most other divisions. These data should prove useful in the study of interrelation with the environment of conditions such as cardiovascular disease and cancer of the stomach. Mortality is, of course, not a relevant indicator for use in connection with studies of genitourinary lithiasis.

Morbidity data are available from several different data systems within NCHS. A survey of hospital discharges from a representative sample of short-stay hospitals provides a basis for estimating magnitude of hospitalized cases, and these data are available separately by specific diagnoses. One can obtain either the total numbers of times a specific diagnosis was listed as a principal cause of the hospitalization or the number of times it was reported as any one of up to five diagnoses tabulated for each hospital discharge.

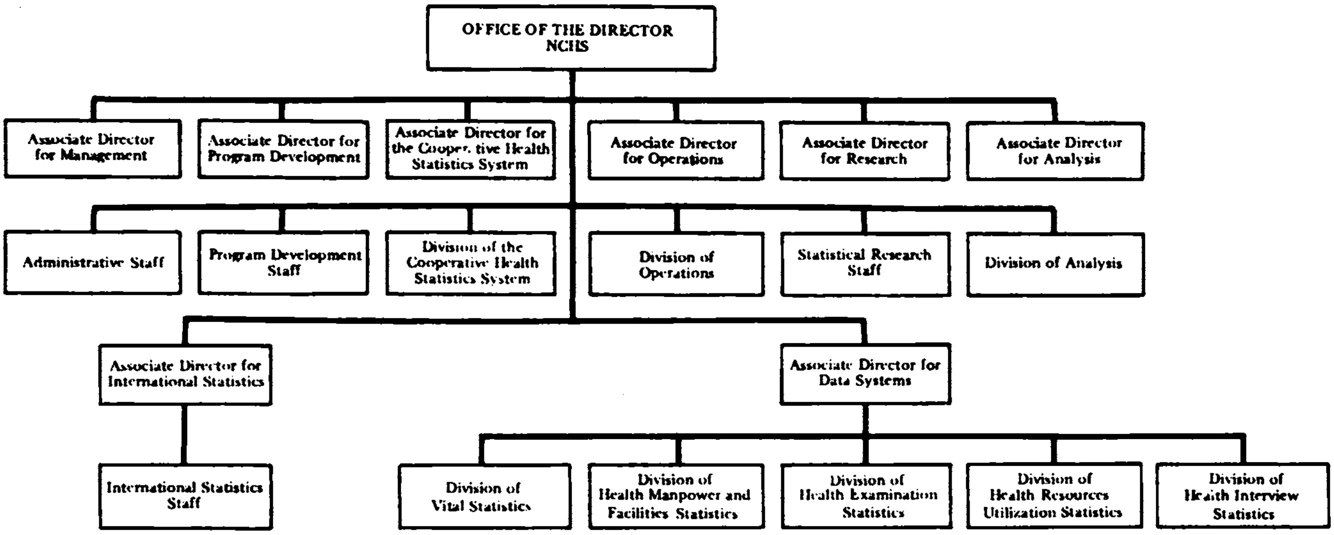


**FIGURE C.1 Organizational chart of the National Center for Health Statistics.**

The Health Interview Survey is another of the data systems in NCHS providing information on morbidity. In this program, the data were obtained by household interview, and they are limited to the information that the informant is able to provide on the nature of the condition being reported. This mechanism provides the best information on the impact of health problems on people's lives—days lost from work or limitation of activity because of illness, for example. For some diagnostic conditions, the information reported may be fairly specific concerning the nature of the medical condition; for others, it will be general.

A recently instituted program within NCHS, the National Ambulatory Medical Care Survey (NAMCS), collects information from a sample of physicians with office-based outpatient practices. It provides information on the physician's diagnosis and on the patient's presenting symptoms, along with other items.

The Division of Health Examination Statistics of the Center provides data obtained from surveys that select representative population samples and perform direct medical examinations, laboratory tests, and procedures on the selected sample persons. Past programs not only provide prevalence data for specific diseases (e.g., coronary heart disease) in the total population but also distributions for the total noninstitutionalized population with respect to various health-related measurement variables such as blood-pressure levels and serum-cholesterol levels. The current program will provide data related to the nutrition status of the U.S. population and will include results of a battery of biochemical tests and some data on certain trace elements analyzed in samples of tap water collected at the household of sample persons. This operation is being carried out with the cooperation of the Environmental Protection Agency and the National Heart, Lung, and Blood Institute.

This describes only some of the programs carried out by the NCHS—those of greatest relevance to the Subcommittee on the Geochemical Environment in Relation to Health and Disease. The Center is also the support agency for this country's National Committee on Vital and Health Statistics, and one of the Technical Consultant Panels (TCP) established by the Committee is concerned with statistics needed to determine the health effects of environmental conditions. This TCP was charged with recommending which statistical data on health effects on the environment should be corrected and the ways in which the recommended data could be corrected and analyzed. The publication *Statistics Needed for Determining the Effects of the Environment on Health* (U.S. Department of Health, Education, and Welfare, 1977a) is the result of the TCP's investigation, and it includes findings and recommendations along with a discussion of types of disease and impairment to which environmental contaminants contribute.

Two other NCHS publications of interest that are available are the *Current Listing and Topical Index to the Vital and Health Statistics Series* (1962–1976 Supplement) (U.S. Department of Health, Education, and Welfare, 1977b), which identifies hundreds of separate NCHS publications and indicates how copies may be obtained, and *Standardized Micro-Data Tape Transcripts* (U.S. Department of Health, Education, and Welfare, 1978). The latter is a catalog of data tapes and describes the NCHS program of making tape transcripts of data available at cost to outside researchers. These publications, which are updated periodically, represent a considerable resource in available data in the area of health statistics. The Center exists to serve many agencies within government and to serve many hundreds of individual research workers in health-related fields.

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# *Index*

The boldface numbers indicate the start of an extensive discussion of the topic.