

THE GEOCHEMISTRY OF DISEASE: A REAWAKENING OF A
MULTIDISCIPLINARY APPROACH TO DISEASE PREVENTION

Rulon W. Rawson
Bonneville Center for Cancer Prevention
520 Wakara Way
Salt Lake City, Utah 84108

During recent years there has been developing among geochemists and among students of physiology and medicine, an increasing interest in trace elements and the roles they play in biological systems. In a recent National Academy of Science publication on "Geochemistry and the Environment", several distinguished scholars addressed themselves to the "Relation of Selected Trace Elements to Health and Disease." In an overview statement, certain pertinent questions were raised: where and under what conditions does the geochemical environment relate to health and disease? How and under what conditions are chemical data on rocks and waters related to soils? Soil data to plants, plant data to subhuman animals, and animal data to human health and disease? (Hopps, 1974)

As a physician with primary interests in the cause and prevention of cancer and other chronic diseases, I am compelled to add to these challenging questions my own question, "Can studies designed to determine levels in the environment, in biological systems, and in body tissues, lead to the use of certain trace elements in the control or primary prevention of certain diseases?"

Current knowledge, some of which has been acquired recently, indicates that a number of trace elements are essential to health. Some of these essential elements in large doses may be toxic to animals and/or man. For

example, fluorine when administered in appropriate doses to children, may protect the teeth against caries, but when administered to children in doses which protect menopausal women against osteoporosis may cause mottling and even unsightly discoloration of the teeth (Hopps, 1974). Another example is that of selenium, a deficiency of which may cause white muscle disease in sheep while an excessive dose may cause fatal liver disease (Muth and Binnas, 1964; Oldfield, 1974).

Of the several trace elements which have been noted to play an important role in normal physiology the record on iodine and its role in the prevention of goiter is probably the best example of an essential element which if deficient in the water or diet may lead to serious but preventable diseases. This record is also an excellent example of the importance of the multidisciplinary approach toward control of a human disease.

In 1894, Emminghaus and Reinholt of the Department of Psychiatry at the University of Freiburg, reported they had observed a shrinkage of goiters in patients they had treated with a thyroid substance. With the Professor of Surgery, Dr. Kraske, who had confirmed their observations, they enlisted the cooperation of the Professor of Physiological Chemistry, Dr. Eugen Baumann. Dr Baumann began studies with the objective of identifying and isolating the active factor in the thyroid. He found that the physiologic activity was not lost when the glands were boiled in acid or heated with alkali. He then found that the active material which was brown in color could be separated from inactive material by boiling with 10 percent sulfuric acid. Later he fused material from the thyroid with sodium hydroxide and then made it acidic with nitric acid. To Baumann's surprise, iodine was liberated. He then demonstrated that normal thyroids were rich in iodine and though he did not demonstrate that iodine is essential to the thyroid's physiological effects, he did label the brown residue from which he recovered the greatest amount of iodine, iodothrin (Kendall, 1964).

Baumann's important observation was the basis upon which many investigators based their interesting studies. The late Dr. E. C. Kendall, after graduating from Columbia University, began a series of studies on the thyroid. On Christmas day of 1914, he isolated

pure crystals from the thyroid gland which he later determined to be thyroxine, the major thyroid hormone (Kendall, 1964). In 1923, Harington, of the University College Hospital Medical School in London, undertook an extension of Kendall's studies and determined the chemical structure to be tetraiodothyronine. His next step then was to synthesize the major thyroid hormone, thyroxine (Pitt-Rivers, 1964). With this basic chemical nature of the thyroid hormone, other investigators using isotopic techniques directed their efforts toward clarification of the biosynthesis of the thyroid hormone, isolation of 3 5 3' triiodothyronine, another thyroid hormone, and toward studies on the actions and their mechanisms of thyroid hormones.

Dr. David Marine, whose training was in pathology, in 1910 began his studies on the pathological anatomy and causes of nontoxic goiter, the hyperthyroidism, and exophthalmus of Graves' Disease and of thyroid neoplasms.

In a series of brilliantly conceived and executed experiments Dr. Marine found that large nontoxic goiters of humans and of dogs were devoid of iodine; that these large iodine deficient goiters in dogs and even normal thyroids had a unique avidity for iodine. He demonstrated with biological tests in tadpoles that though the thyroid trapped iodine rapidly after administering it intravenously, thyroid hormonal activity could not be demonstrated for 30 hours afterwards. He then undertook a series of studies designed to determine the effects of iodine deficient diets on the thyroids of rats and demonstrated the goitrogenic effects of an iodine deficiency which could be prevented with microgram amounts of iodine.

In 1917 Marine and Kimball reported on a successful experiment in goiter prophylaxis they had completed. They had demonstrated that the administration of minute doses of iodine could prevent the development of goiters in school children. In 1924 Marine wrote, "Simple goiter is the easiest and cheapest of all known diseases to prevent and its control may be accomplished as soon as organized society determines to make the effort. The prevention of goiter will mean a great deal more than eliminating of this cervical deformity. It means in addition the control of those forms of physical and mental degeneracy such as cretinism,

mutism and idiocy which are dependent upon thyroid insufficiency" (Marine, 1924).

Soon after Marine's definitive studies were published certain investigators began reporting studies on the epidemiology of nontoxic goiter in which geochemical studies played an important role. In 1923 McClendon and Williams published the results of an important investigation in which they determined the geographic distribution of World War I draftees found to have nontoxic goiters and compared the high intermediate and low goiter incidence with the iodine determinations of drinking water obtained from communities throughout the United States. They stated there was "an inverse ratio between the amount of iodine in surface waters and those of shallow wells or springs and the distribution of goiter." In 1927 McClendon published a review of his extensive studies as well as those of other investigators from various parts of the world on the distribution of iodine with special reference to goiter and concluded that goiter is due to a deficiency of iodine.

In 1933 Von Fellenberg reported on an extensive study he had done on the geographic distribution and per cent incidence of goiter as related to the iodine concentration in the drinking water in Switzerland. Like McClendon he demonstrated that the per cent incidence of goiter was inversely related to the level of iodine in the drinking water.

This relationship of iodine deficiency to the incidence of goiter was widely accepted until certain goitrogenic foods and drugs were demonstrated to interfere with the trapping or utilization of iodine by the thyroid, and certain goiterous families were found to have heritable defects in iodine metabolizing enzymes which resulted in hypothyroidism and compensatory goiters.

Of particular interest to our discussion on geochemistry of disease are observations by Dr. Selwyn Taylor of the Royal Postgraduate Medical School in London. He found a high incidence of goiters in a small community in Ireland and noted the drinking water was exceedingly hard. His analysis of this water revealed a significant level of calcium carbonate (Taylor, 1953). He then studied the effects of calcium carbonate on the thyroids of rats on a low intake of iodine. He found

that 2 percent calcium carbonate in the food enhanced the goitrogenic effects of an iodine deficiency, i.e., thyroid hyperplasia, depletion of colloid, increased thyroid weight and radioiodine uptake. He reported that calcium carbonate did not influence absorption of iodine from the gut. He also found that calcium carbonate goiters could be prevented by larger doses of iodine than needed to prevent iodine deficient goiters (Taylor, 1954).

On comparing maps of goiter distribution in the United States with those provided by a manufacturer of water softeners on the geographic distribution of hard water, we have been impressed by their similarities. It would appear that at least in some communities having hard water, there is an increased incidence of goiter. These observations suggest the need to repeat the elegant studies reported by McClendon but to add to them determinations on the water levels of calcium carbonate and possibly of magnesium carbonate.

In 1974 McKay and Mason of the National Cancer Institute published a most valuable document on "Cancer Mortality for U.S. Counties, 1950 - 1969". This publication is a compilation for a twenty year period, for each county of the continental United States, the total number of cancer deaths by tumor site and age adjusted death rates according to sex and race (whites and non-whites). This volume is proving to be a most valuable resource for various epidemiologic investigations including correlation studies with demographic environmental variables. Correlation of the data provided by this resource with geochemical data has thus far been limited.

However, a very provocative study was reported in 1975 by my former colleagues, Jansson, Seibert and Speer, who prepared from this unique resource the mortality by county for cancers of the stomach, colon, rectum, and breast. Of great interest was the observation that the highest death rates from cancers of the colon, rectum, and breast occurred in counties north of the Ohio River and east of the Mississippi River. As noted earlier, the National Academy of Science published in 1974, the first volume on Geochemistry and the Environment which was devoted to the relation of selected trace elements to health and disease. In this publication we found a map on the distribution of selenium in

plants throughout the United States. Those areas having the lowest concentrations of selenium in the forage were very similar to those having the highest death rates from cancers of the breast, colon and rectum. In 1974 Schrauzer and Ishmael of the University of California at San Diego, reported that the administration of selenite in the drinking water in a concentration of 2 ppm decreased at 15 months, the incidence of spontaneous breast cancer in C3H mice from 82% to 10%. We found then, that Clayton and Bauman and Schamberger had reported inhibiting chemical carcinogenesis of the liver with trace amounts of selenium, and that Shamberger had reported inhibition of carcinogens acting on the skin, liver, and breast by administering trace amounts of selenium (Shamberger, 1970). Subsequently, Jacobs has reported she could inhibit the actions of carcinogens which act on the large bowel of rats by administering selenite in doses of 4 ppm in the drinking water. She has also reported that selenium inhibits the mutagenic effects of potent carcinogens (Jacobs, 1977). Shamberger has also reported finding lower than normal blood selenium levels in most patients with cancer (Shamberger, 1973). Whether this trace metal can inhibit the development of cancer in humans has not yet been investigated.

Examination of other maps on cancer mortality by U.S. counties may open other new areas for investigation (Mason, 1975). The map on the cancer mortality from cancers of the trachea, bronchus, and lung shows the majority of high mortality counties to be on the Atlantic sea coast and along the Gulf. An exception is in North Carolina and the northern half of the South Carolina coast. Is the low mortality in North and South Carolina due to a low consumption of cigarettes, an unlikely explanation, or can it be related to the absence of certain high risk industries? I suggest another question should be investigated. Are there cancer preventing trace elements in the soil or water of the Carolinas?

Another challenging question is excited by examining the map on mortality by county from prostatic cancer (Mason, 1975). Utah, which has a lower incidence rate of prostatic cancer than the national rate, has three counties in which there was for the period of 1950 through 1969, a significantly higher mortality rate from cancer of the prostate. All of these

counties have mining activities. It would be desirable to examine the water soil, and forage in these counties for trace elements. Similarly, the prostatic cancers discovered in these counties should be analyzed for trace elements which might be discovered in the water, soil, or forage.

In studies designed to determine possible causal roles of trace elements in the etiology of any cancer, the investigator should design experiments to determine whether the substance acts as an initiator of the carcinogenic process or as a promoter. Does the element activate an oxidative enzyme activator or a detoxifying enzyme system. Does it promote the action of a carcinogen by interfering with the action of a DNA repair enzyme.

In studies on carcinogen inhibitors it is important to identify the point at which the inhibitor blocks the metabolism - activation or action of the carcinogen or promoter.

There is a need to expand our research on trace elements to identify those which are essential to health of plants of animals and of human health. The localization and metabolism of such elements as well as their actions in various biological systems need to be clarified.

I suggest that epidemiologists committed to the identification of disease causes would find it advantageous to collaborate with geochemists in their studies. Collaboration between geochemists and students of epidemiology and of normal physiology may lead also to exciting frontiers for research on the epidemiology of health.

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