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Mapping the World of Nutrition: Citation Analysis Helps Digest the Menu of Current Research

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The basic task of nutritional science is "to formulate a diet over the lifetime of an individual that will optimize health, well-being, and longevity. This calls for providing the necessary chemical components in the right proportion and avoiding or minimizing toxic substances," according to Harold J. Morowitz, professor of molecular biophysics and biochemistry, Yale University, New Haven, Connecticut.[1]

From this broad definition, it is clear that the science of nutrition draws on a variety of research areas, including biochemistry, physiology, and psychology. In past essays, we have discussed topics related to nutrition, such as food additives,[2] fasting,[3] and anorexia.[4]

To organize and trace the literature of the diverse research areas pertaining to nutrition, as well as to pinpoint "hot" nutritional research, we use the research-front files we have created from the *Science Citation Index® (SCI®)* and the *Social Sciences Citation Index® (SSCI®)*.

Research Fronts

Research fronts, or subspecialty groups sometimes called invisible colleges, develop as authors cite relevant papers in their fields. Using co-citation analysis, we identify those papers most frequently cited together, or co-cited. Core papers associated in this way may share key theories, results, methods, or discussion. Table 1 is a selected list of research fronts related to nutrition, covering such areas as diet and cancer, minerals, vitamins, and proteins. Research-front names are derived algorithmically using key words or phrases in the citing literature. Keep in mind that some fronts may represent complex combinations of topics, so these labels are by necessity extremely abbreviated.

Just as we are able to cluster smaller groups of core papers, we can also create hierarchies of research fronts by determining whether citation links exist between these critical "smaller" clusters—clusters that are, by definition, more specialized areas. We do this in five hierarchical levels. The highest level, the C5 "global" map of science, shows the interconnections between very broad areas of knowledge. At the next lower level of clustering, the identified partitions are more recognizable as traditional "disciplines" or specialties.

Figure 1 illustrates a C4 map for 1986, showing the major research areas in the social and natural sciences. Nutrition research topics are found in the areas designated as "Heart disease" (#86-0131), "Metabolism" (#86-0144), and "Physiology" (#86-0096), to name a few. The proximity of points connected by lines on this map is a result of co-citation patterns existing between specialties and can be interpreted as a measure of the degree of field relatedness. Distances between connected points are inversely proportional to their co-citation strengths.

Any one of the points on the C4 map can be explored further by examining its lower member clusters on a more specific level. By zooming in on "Genetics and immunology" in Figure 1, you can create the C3 map found in Figure 2. Here, "Molecular biology" (#86-0073) is "central," although the literature on immunology is larger. Radiating from the central point are various clusters concerning both basic and applied nutrition research, including "Proteins and amino acids" (#86-0353), "Protein synthesis" (#86-0888), and "Amino acid sequences" (#86-1091).

Peripheral areas often concern subject matter that is less theoretical. For instance, "Nutrition in health and disease" (#86-0104), "Carbohydrate biochemistry" (#86-0802), and "Dietary fats and cancer" (#86-0455) are located on the periphery of Figure 2. This means that the literature in these clusters is less co-cited with the literature in other identified areas. This could change in the future. Quite often these areas are in a transitional state until they move in closer or even disappear from subsequent annual maps.

Major Nutrients

Some of the topics in Figure 3 deal with lipids. These compounds, along with carbohydrates and proteins, fall into the class called energy nutrients because the energy they contain may be used by the body for such functions as heating, building and repairing cell structures, and motility. In addition, the energy may be stored in body fat and other compounds for later use.[5] (p. 25)

Lipids, generally called fats, are naturally occurring substances that cannot be dissolved in water. Members of the lipid family include the triglycerides, phospholipids, and sterols. In addition to being a major energy reserve, lipids provide nourishment and structural support for many tissues.[6] (p. 105)

In an earlier essay we discussed the important role of cholesterol in the body when we described the achievements of Nobel laureates Michael S. Brown and Joseph L. Goldstein, University of Texas Health Science Center, Dallas.[7] (Other Nobel Prizes awarded for work concerning cholesterol include the 1928 chemistry prize, to Adolf Otto Reinhold Windaus; the 1964 prize in physiology or medicine, to Konrad Bloch and Feodor Lynen; and the 1975 chemistry prize, to Sir John Warcup Cornforth and Vladimir Prelog.) Recently, a new drug, called lovastatin, made headlines in the popular press as an effective remedy to reduce high cholesterol levels in the blood, which can subsequently reduce the risk of heart disease.[8] Note that in Figure 3, two prominent fronts deal with cholesterol research—"Low-density lipoprotein cholesterol" (#86-2071) and "Coronary heart disease and lipid research" (#86-3615).

Usually most of the body's energy is derived from carbohydrates, those compounds composed of carbon, hydrogen, and oxygen. Carbohydrates are broken down in the body into glucose or other sugars before further metabolism. Glucose is absorbed into the bloodstream and travels to specific organs, such as the brain, where it is broken down to provide energy. To store energy for future use, glucose may also be converted to glycogen or fat.[6] (p. 141) However, the amount of glycogen is small compared to the body's main stores of energy: fat, in the form of triglycerides.[9]

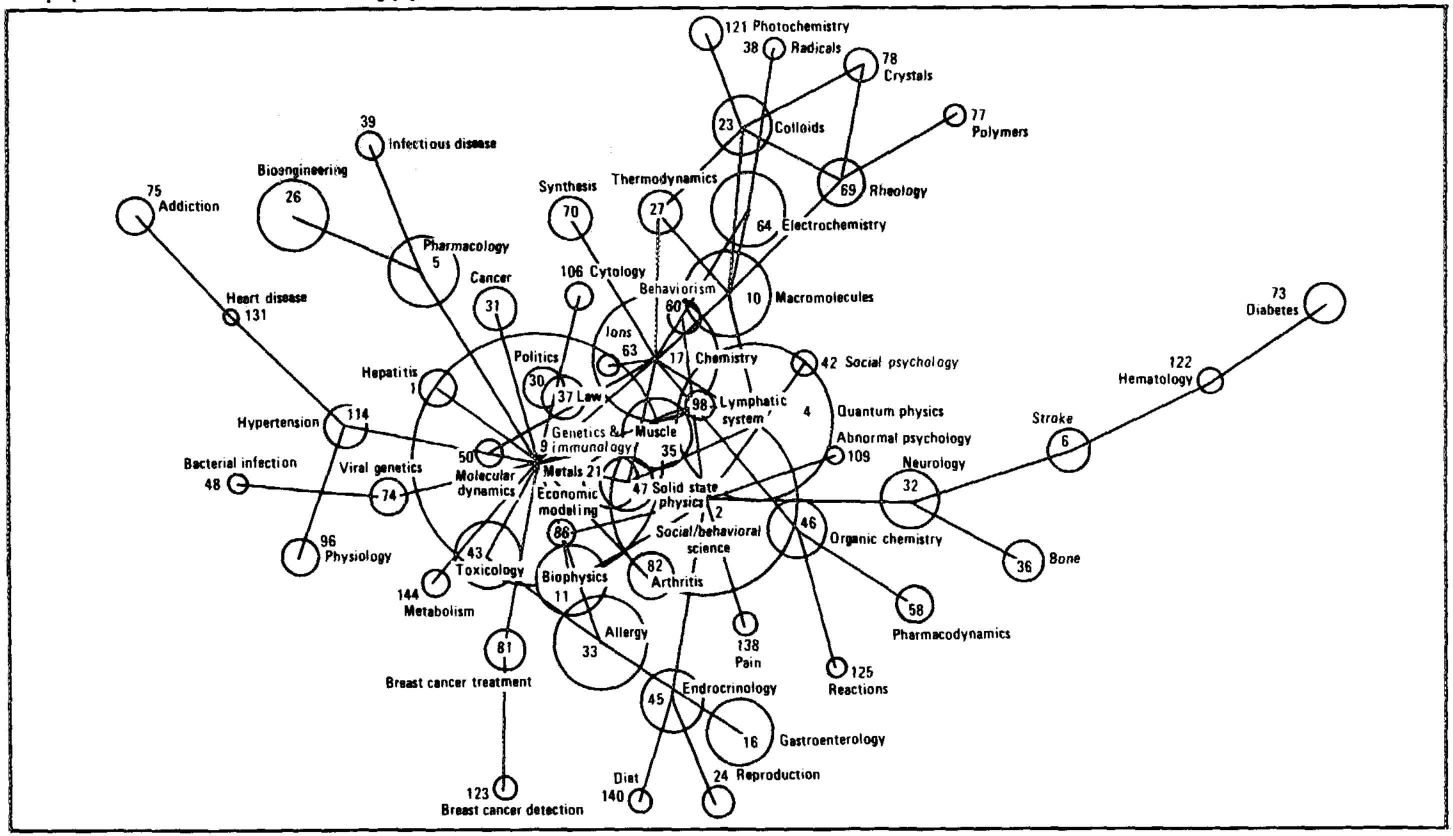
In the body, dietary protein is first broken down to amino acids, which contain carbon, hydrogen, oxygen, and nitrogen. These amino acids are then resynthesized into the necessary proteins, which have a variety of functions in the body. Some proteins are enzymes that facilitate certain chemical reactions. Other proteins are used by the body to replace parts of worn-out cells, build new tissues, act as antibodies, and maintain the water, salt, and acid balances of the body's fluids. The organic part of excess amino acids is changed to glucose or fat; the nitrogen is excreted as urea.[5] (p. 138)

Essential Nutrients

Although the body can make new nutrients from carbohydrates, lipids, and proteins, there are certain compounds that cannot be synthesized by the body in amounts necessary for maintaining health. In fact, several of the amino acids are essential, as are two of the fatty acids. These essential nutrients must be supplied by food.

During the first part of this century, identification and characterization of essential

Figure 1: Map of C4 cluster #86-0001, showing major research areas in the social and natural sciences. Lines connecting nodes represent co-citation strengths. The circle around each node is proportional in area to the number of citing papers. Names refer to 1986 C3-level *SCI*® /*SSCI*® research fronts. Each of these, in turn, has its own group of research fronts.



nutrients dominated nutritional research. Now the focus is on understanding interrelationships among nutrients and nutrient interactions with physiological systems and disease processes. Scientists have established that the macrominerals (such as calcium, magnesium, phosphate, potassium, and sodium) and trace minerals (including iron, zinc, and copper) are required by the body in specific concentrations for good health.

Mineral research often focuses on the dietary intake of specific population groups, the availability of minerals from food, and on metabolism. For example, the dietary requirements for zinc intake for pregnant women are different than those for elderly women. In the front on "Iron and zinc nutritional status" (#86-1446), listed in Table 1, a paper by G.F. Kirsten and colleagues, Department of Pediatrics and Child Health, University of Cape Town and Institute of Child Health, Red Cross War Memorial Children's Hospital, South Africa, discusses the serum zinc and copper levels found in healthy pregnant women from middle and upper socioeconomic classes.[10] Maternal serum zinc and copper levels during pregnancy and the months immediately following birth show a specific trend with low zinc and high copper levels at term. These patterns appear to be caused by normal hormonal changes typical in pregnancy.[11] Normal nonpregnant adult levels are usually attained 8 to 12 weeks after delivery.[10]

Vitamin intake and metabolism are also important research areas. If specific vitamin concentrations in the body are above or below the optimum level, adverse effects may occur that can lead to death. The front from Table 1 on "Vitamin-A toxicity and chronic hypervitaminosis-A" (#86-5186) has 54 published papers citing 4 core documents. In one of the core papers in this front, Frank R. Smith and DeWitt S. Goodman, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, note the well-known fact that excessive vitamin-A intake can result in skeletal pain, dermatitis, and hepatic inflammation. They studied the mechanism of vitamin-A transport in the body and the effects of excessive dosage.[12]

The Recommended Dietary Allowances (RDA) have been established by the Food and Nutrition Board (FNB) of the National Academy of Sciences/National Research Council (NAS/NRC). Dietary standards have also been developed for use in many other countries as goals for good nutrition. In the UK, for instance, such standards are known as Recommended Daily Allowances. In a recent article in *Chemistry & Industry*, nutritionist Ann F. Walker, University of Reading, UK, notes that "techniques for measuring human nutritional requirements have improved and nutritional scientists have now more confidence in defining minimum physiological intakes of nutrients than ever before."[13] Accordingly, reassessments of recommended nutrient intakes are currently occurring throughout the world. Table 2 is a selected list of organizations providing information on nutrition research.

Recently, the report of the committee preparing the 10th edition of the RDA in the US was rejected by the NAS/NRC. The disagreement concerns the fundamental basis for establishing dietary allowances, according to Kay B. Franz, Department of Food Sciences and Nutrition, Brigham Young University, Provo, Utah.[11] Originally, recommended allowances of nutrients were established at minimum levels necessary to prevent starvation.[14] Now recommendations are intended to maintain health and are calculated based on available dietary sources and the needs of various population groups, to name just two of the many factors in the equation.[11] A new factor—the possible interaction between nutrient intake and disease—may have been introduced by the FNB's rejection of the RDA committee's recommendations. The committee had suggested that the RDAs for vitamins A and D be lowered, but the FNB objected, believing that these nutrients may be beneficial in cancer prevention.[13]

Deficiency Diseases

The importance of certain nutrients in the diet became obvious centuries ago from the

Figure 2: Map of C3 cluster #86-0009, "Biochemistry and genetics," showing links between C2 research fronts.

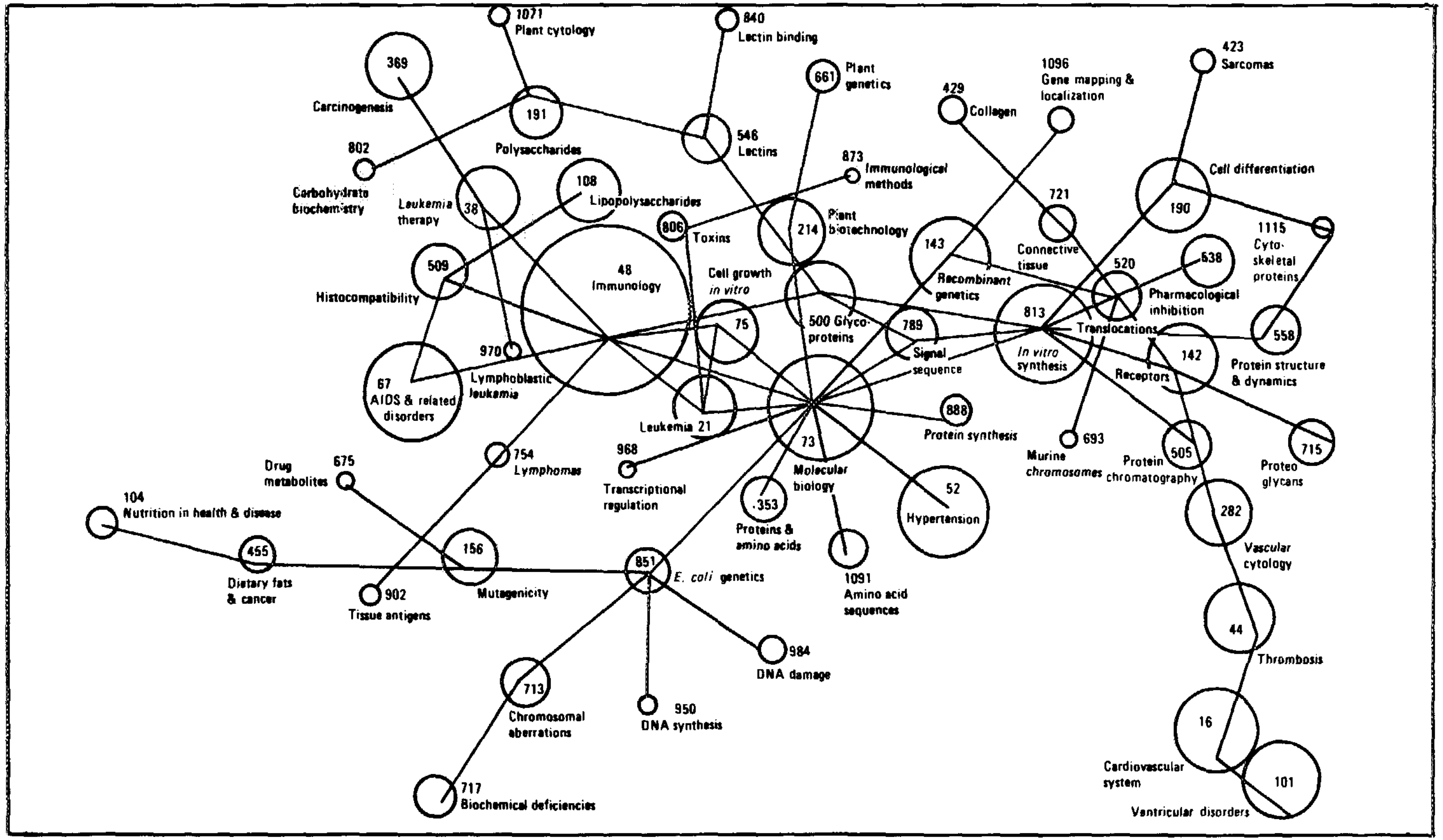
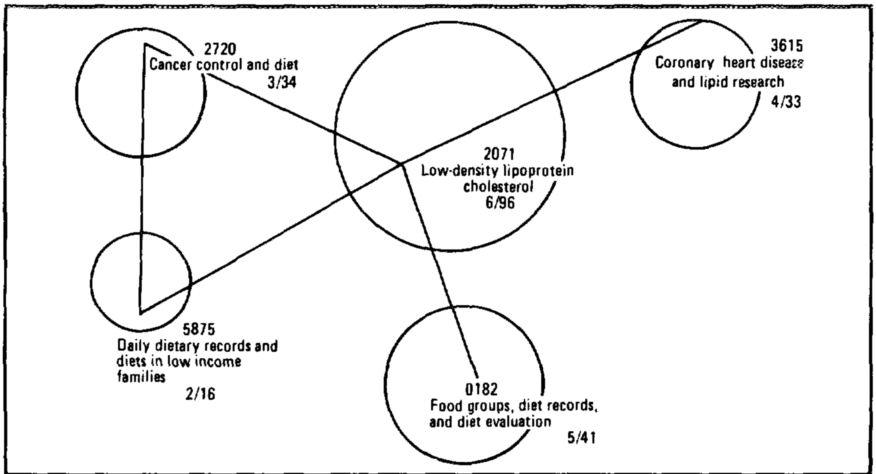


Figure 3: Map of C2 cluster #86-0104, "Nutrition in health and disease," showing some major areas of research for 1986. Numbers of core/citing papers for each C1 front are shown after the research-front name.



number of diseases that developed as a result of poor diet. For example, with the advances in navigation and cartography in the late fifteenth century, prolonged sea voyages became possible. Sailors were forced to subsist for extended periods on biscuits, salted meat, cheese, and dried legumes. Scurvy became a feared disease for seafarers. Jacques Cartier, a French navigator and explorer, described the symptoms of the disease affecting his crew: "Some did lose all their strength and could not stand on their feet. Their legs became swollen, the sinews contracted and turned black as coal.... Others had their skin spotted with spots of blood of a purple color.... Their mouths became stinking, their gums so rotten that all the flesh did fall off, even to the root of the teeth."[15]

In 1747 British physician James Lind conducted the first experiment to find the best treatment for scurvy. He found that citrus fruits promoted a speedy recovery from the disease. However, it wasn't until the 1920s that it was firmly established that scurvy was caused by a vitamin-C deficiency.[15] Today, research on vitamin C (ascorbic acid) includes studies to determine the most beneficial levels of this vitamin in the body. Table 1 includes a front on "Ascorbic acid levels" (#86-4955), which contains 32 citing papers.

In 1937 Sir Walter N. Haworth, Birmingham University, UK, was awarded the Nobel Prize in chemistry for his investigations on carbohydrates and vitamin C. And of course, Nobelist Linus C. Pauling has long been a proponent of the curative potential of vitamin C, including the presumed prevention of cancer.

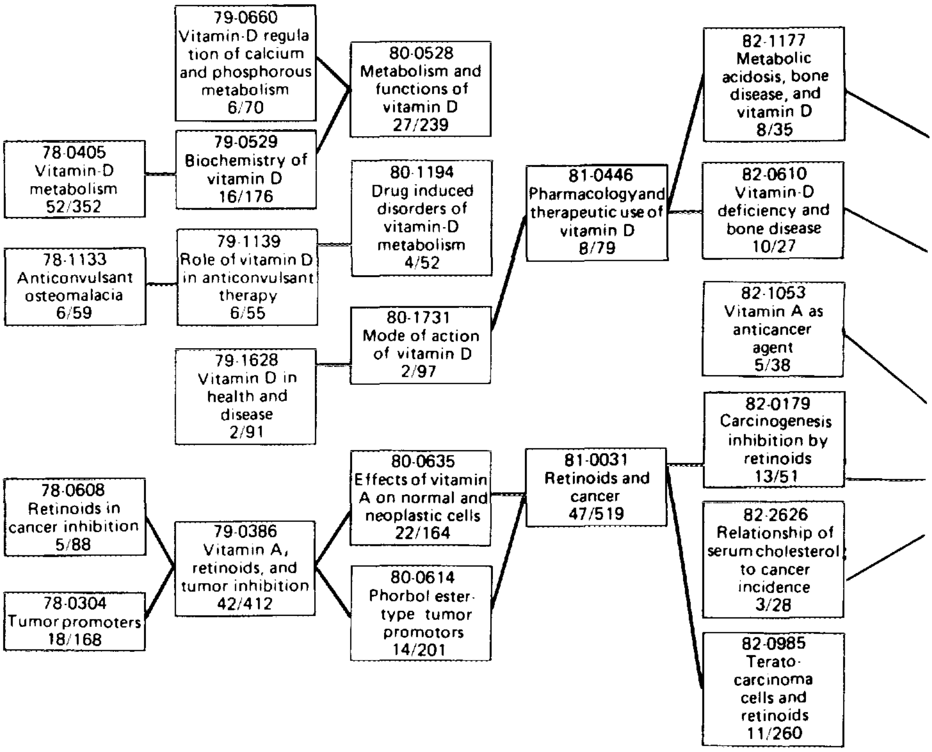
Hippocrates prescribed ox liver, a rich source of vitamin A, for the cure of night blindness, a sign of vitamin-A deficiency.[11] The importance of vitamin A was indirectly rediscovered in 1909 by German physician Wilhelm Stepp, who found that egg-yolk extracts contained a fat-soluble material that is necessary for good health.[16] Vitamin A was called a "fat-soluble accessory" in 1915 by Elmer V. McCollum and Marguerite Davis, University of Wisconsin, Madison, to differentiate it from other health factors that were water soluble.[11,17] In addition to liver and egg yolk, foods that include vitamin A include butterfat, fish-liver oil, and yellow-orange fruits and vegetables like carrots, sweet potatoes, cantaloupes, and peaches.[18]

Vitamin A plays two roles in keeping the eye healthy. In the retina, vitamin A is required for normal functioning of the visual pigment; a deficiency results in night blindness. Vitamin A is also needed by the cornea; a deficiency causes the cornea to grad-

Table 1: Selected list of 1986 *SCI®/SSCI®* research fronts dealing with various aspects of human nutrition. A = number of core papers. B = number of citing papers.

Number	Name	A	B
	CANCER AND NUTRITION		
86-1128	Nutrition and diet in the etiology of cancer	7	128
86-3671	Nutritional antioxidants and cancer prevention through nutrition	4	38
86-7528	Vitamin A in cancer; cellular retinol binding protein	3	152
	FIBER		
86-3526	Dietary fiber and fecal bulking	12	123
86-5281	Dietary fiber and wheat bran supplements	2	16
86-8504	Nutrition in cancer and dietary fiber in breast cancer etiology	2	45
	MALNUTRITION		
86-0240	Nutrition in Kenya	8	51
86-1065	Malnutrition in hospitalized patients and metabolic management of critically ill surgical patients	20	201
	MINERALS		
86-0548	Low dietary zinc intake	6	60
86-1446	Iron and zinc nutritional status	19	155
86-3260	Indexes of mineral metabolism	2	38
86-3429	Zinc supplementation in anorexia nervosa and functional consequences of zinc deficiency	2	16
86-5366	Clinical zinc deficiency and zinc metabolism during total parenteral nutrition	4	40
86-5473	Copper and zinc deficiencies	6	46
86-7003	Trace elements in nutrition; excesses and deficiences of copper and zinc	2	19
	PROTEINS AND AMINO ACIDS		
86-1630	Leucine metabolism and plasma amino acids	6	59
86-1862	Benefits of a low protein, essential amino acid, keto acid diet	6	69
86-2757	Oral aspartame, plasma amino acid ratios, and various protein concentrations	30	362
86-2911	Nutritional quality of available lysine and other free amino acids	5	41
86-3619	Plasma amino acid metabolism	4	98
86-4096	Effect of leucine and amino acid transport	10	112
86-5218	Methionine metabolism and S-adenosyl amino acids	3	34
86-5501	Plasma arginine, brain tryptophan, and branched-chain amino acids	8	77
86-6772	Protein markers and nutritional assessment	3	31
	SALTS		
86-1119	Dietary calcium intake and calcium's role in hypertension	59	629
86-4562	Sodium chloride-dependent hypertension and high salt diets	6	50
	VITAMINS		
86-1979	Biosynthesis of vitamin B12	7	41
86-2527	Serum retinol and vitamin E in an alcoholic population	4	54
86-3671	Vitamin-C radicals and nutritional antioxidants	4	38
86-3907	Metabolism of vitamin B6	13	76
86-4238	Vitamin-D supplementation in pregnancy	2	16
86-4643	Vitamin-B12 deficiency and folate in depression	2	15
86-4955	Ascorbic acid levels	2	32
86-5186	Vitamin-A toxicity and chronic hypervitaminosis-A	4	54
86-5344	Vitamin-B6 deficiency and its effect on lung elastin crosslinking	2	33
86-5577	Vitamin-A stability and nutrient supplements	3	25
86-5948	Riboflavin status and pediatric multiple-vitamin preparations	2	14
86-6364	Vitamin-K deficiency	5	32
86-7879	Ascorbic acid copper-ion system	3	28
86-8147	Serum vitamin-D metabolites and bone metabolism	2	35

Figure 4: Historiograph tracing progression of selected research fronts on vitamin A and vitamin D for the years 1978-1986. Numbers at the bottom of each box refer to the number of core/citing papers for that year. (All examples are meant to be illustrative and are not necessarily comprehensive.)

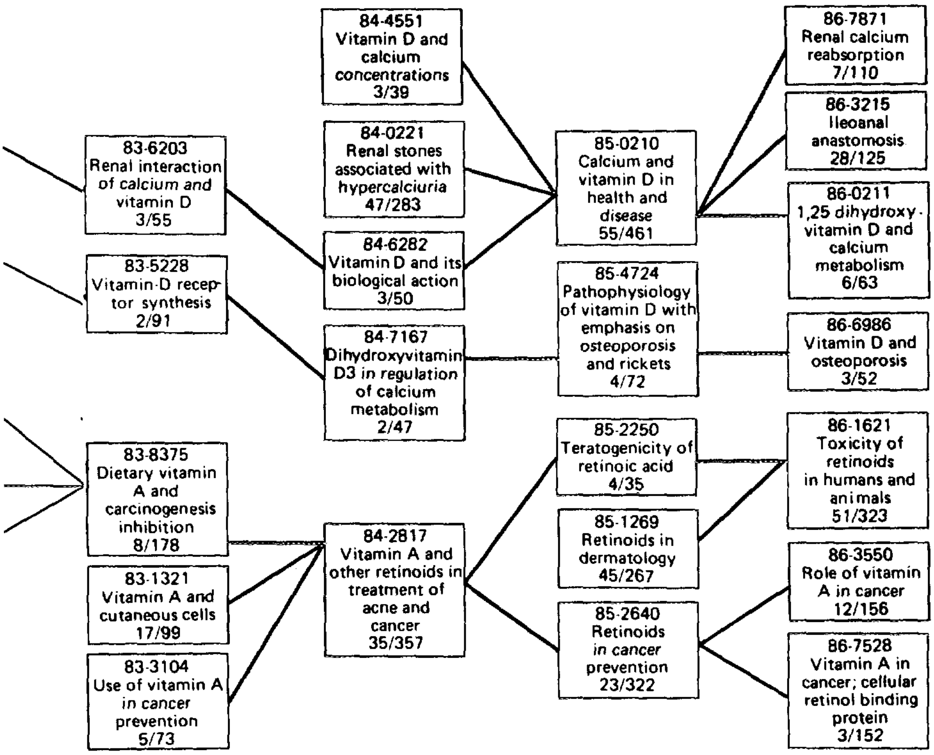


ually deteriorate, a major cause of blindness in children in many countries.[11] In 1967 George Wald, Harvard University, received the Nobel Prize for elucidating the role of vitamin A in vision. Goodman cites estimates that about 500,000 new cases of vitamin-A deficiency with active corneal involvement occur annually in India, Bangladesh, Indonesia, and the Philippines. This figure does not include other areas where the disease is known to occur, such as Africa, Central and South America, or the Middle East.[19]

Neville R. Belton, Department of Child Life and Health, University of Edinburgh, Scotland, notes that another worldwide problem is a bone disorder that is called rickets when it affects infants and children; it is known as osteomalacia when it occurs in adults.[20] The condition is caused by a deficiency of vitamin D, which regulates the intestinal absorption of calcium and phosphorus by the bones and teeth in the body. In rickets, a lack of vitamin D causes calcium to be poorly absorbed from the diet, which in turn prevents normal bone formation; bones weaken and become deformed. In osteomalacia, although the protein matrix supporting the bone is properly formed, it is not properly calcified, making the bones soft and pliable. The result is bone pain and microfractures.[11,21]

Vitamin D is unique in that it can be obtained by the body without the help of food. The vitamin is formed when ultraviolet rays of the sun strike 7-dehydrocholesterol, a fatty substance just under the skin.[20] Belton's paper is included in the research front on "Vitamin-D supplementation in pregnancy" (#86-4238), found in Table 1.

The precise role of vitamins A and D in the body is still being investigated. To document the progress of this research, we have developed a historiograph on the effects of



vitamins A and D in health and disease (see Figure 4). Each box includes the name of the research front, as well as the number of core articles and citing (published) papers. The fronts that are included are determined by the continuity of the core literature from year to year. If the same core documents are cited at the required thresholds in two adjacent years, then a "string" is established. By continuing this procedure, a historiograph is developed.

Not all deficiency diseases arise from a lack of vitamins; they may instead result from mineral deficiencies. For instance, although iron is one of the most abundant minerals on earth, iron deficiency may be the most prevalent nutritional problem in the United States. Iron is an important part of the hemoglobin molecule, which is necessary to transport oxygen from the lungs to the tissues. While iron deficiency causes physical problems, Betsy Lozoff and Gary M. Brittenham, Case Western Reserve University, Cleveland, Ohio, cite evidence that a lack of iron may adversely affect behavior by causing diminished attention span, intelligence, and learning ability; apathy; irritability; and tension. These problems can have enduring consequences for infants and children by interfering with proper development.[22] Lozoff and Brittenham's paper is part of the current literature that cites into front #86-1446, "Iron and zinc nutritional status" (mentioned earlier).

Diet and Cancer

A favorite theme in the popular press is the newly discovered cancer-fighting or cancer-promoting foods, ranging from bacon, bran, and broccoli to calcium, carrots, and coffee. These claims may lead the reader to believe that cancer prevention is only a matter of eating the correct foods, whereas the problem is actually more complicated. Other

Table 2: Selected list of organizations supporting research and disseminating information on nutrition.

American Board of Nutrition
6212-B Old Keene Mill Court
Springfield, VA 22152

American College of Nutrition
P.O. Box 831
White Plains, NY 10602

American Dietetic Association
430 North Michigan Avenue
Chicago, IL 60611

American Institute of Nutrition
9650 Rockville Pike
Bethesda, MD 20814

American Society for Parenteral and Enteral Nutrition
8605 Cameron Street, Suite 500
Silver Spring, MD 20910

Commonwealth Bureau of Nutrition
Rowett Research Institute
Bucksburn, Aberdeen AB2 9SB
United Kingdom

Food and Nutrition Board
National Research Council
2101 Constitution Avenue, NW
Washington, DC 20418

Institute of Nutrition of Central America and Panama
Carretera Roosevelt—Zona 11
Aptdo Postal 11-88
Guatemala, Guatemala

International Life Sciences Institute—Nutrition Foundation
1126 16th Street, NW
Washington, DC 20036

International Union of Nutritional Sciences
Institute of Biology
41 Queen's Gate
London SW7 5HU
United Kingdom

Joint FAO/WHO/OAU Regional Food and Nutrition Commission for Africa
FAO Regional Office for Africa
P.O. Box 1628
Accra, Ghana

Society for Nutrition Education
1700 Broadway, Suite 300
Oakland, CA 94612

factors in addition to diet play a role in cancer, such as familial risk of cancer, exercise regimen, and contact with environmental hazards.

Although there is no simple explanation about the role that diet may play in cancer prevention, many scientists have found a tentative link between certain types of food and some forms of cancer. For instance, Bruce Armstrong and Richard Doll, Radcliffe Infirmary, Oxford, UK, note that there is a strong correlation in developed countries between fat consumption and cancer deaths.[23] David J.A. Jenkins and colleagues, Department of Nutritional Sciences, University of Toronto, Canada, state that a number of hypotheses have been developed to explain the mechanism for the promotional effect of fat in cancer. One current theory suggests that increased intake of fat may result in the increased loss of bile acids to the colon, which may damage the colonic mucosal cells and result in cancer of the colon.[24]

Other evidence suggests, however, that it is not fat intake that contributes to cancer and heart disease but, instead, excessive caloric intake and obesity.[11] A study by Jaakko Tuomilehto, Department of Epidemiology, National Public Health Institute, Helsinki, and colleagues at the institute and the Department of Community Health, University of Kuopio, Finland, found that men with a high body mass were significantly more likely to have heart attacks than their normal peers.[25] Other studies have found that diets that were high in total calories—regardless of their percentages of fat, protein, and carbohydrates—were associated with a higher risk of various forms of cancer in both rats[26] and humans.[27]

While increased fat or calorie intake may promote cancer, fiber intake may prevent some types of cancer. However, the exact mechanism of fiber in cancer prevention has not yet been defined. Dietary fiber is actually a general term for various complex plant substances that are partially or completely indigestible. These include water-soluble fibers found in plant stems, seeds, and fruit, and water-insoluble fibers found in cereal grains and vegetable skins.[5] (p. 76) Table 1 contains three fronts concerning fiber research.

A landmark in stimulating interest in this research area was a 1971 article by Denis

P. Burkitt, Unit of Geographical Pathology, St. Thomas Hospital, London, UK, who observed that some African tribes eating a diet high in unprocessed, fiber-rich foods had lower rates of certain cancers than did Western populations.[28] According to David Kritchevsky, Wistar Institute, Philadelphia,[9] Burkitt's interest in this area was stimulated by a 1956 paper by T.L. Cleave, surgeon captain, Royal Navy, UK, in which Cleave suggested that many modern ills are due to the ingestion of refined sugar and flour.[29] Cleave's paper has been cited 43 times—9 of them by Burkitt—according to the *SCI*.

One theory regarding the mechanism of fiber in cancer prevention was proposed by Burkitt in a 1981 *Citation Classic®*. He wrote that "any carcinogens concentrated in a small faecal volume and retained a long period in the gut might be more dangerous than those diluted in a large faecal volume, moved along more quickly, and excreted more often" as a result of fiber intake.[30]

The research front on "Nutrition in cancer and dietary fiber in breast cancer etiology" (#86-8504), found in Table 1, contains a review paper by Kritchevsky on the role of fiber. He notes that there are problems in finding strong evidence that fiber can help prevent cancer. One problem stems from the differences in methodology and sources of dietary data. In addition, the average person generally eats fiber-rich foods, not specific fibers alone. The other components included in fiber-rich foods may act as additional variables in the methodology.[31]

Vitamin A is a recent arrival to the cancer prevention scene. K.A. Madani and Mohamed B. Elmongy, Department of Nutrition, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, note that in a cancerous disease malignancies occur when the process of cellular differentiation is lost. Retinoids, which are analogues of vitamin A, are known to be involved in the enhancement of cell differentiation. Madani and Elmongy review several possibilities for the mechanism of action of retinoids in cancer prevention.[32] This paper is included in the front on "Vitamin A in cancer; cellular retinol binding protein" (#86-7528), found in Table 1.

Other papers suggest that the dietary intake of a precursor of vitamin A, called beta-carotene, is more closely linked with a lowered risk of developing cancer than is the ingestion of vitamin A itself.[33,34] Carotenoids are found in carrots, green leafy vegetables, and some yellow and red fruits and vegetables; retinoids and vitamin A occur chiefly in foods of animal origin, such as milk, cheese, butter, egg yolk, and liver.[34]

Conclusion

We have touched upon just some of the issues that dominate nutrition research today. A future essay will discuss nutrition journals. Judging by the C4 map in Figure 1, nutrition research is so diverse that it is impossible to assign it any single major point of reference. It will be interesting to study the impact of journals devoted solely to nutrition and to observe how they interact with journals in other disciplines, such as biochemistry.

However, the multidisciplinary character of this field increases the difficulties in altering the attitudes of researchers and clinicians. Until now, nutritional science has not been given the priority it needs in medical training. As this essay went to press, I learned about a new program at The Rockefeller University, New York, sponsored by the Pew Memorial Trust. Medical students completing their first year of study will spend one year in the Rockefeller laboratories, learning the methods of basic, fundamental science as applied to problems in human nutrition. Jules Hirsch, professor and senior physician, who is in charge of the program, has told me that it is the aim of these fellowships to interest medical students in careers as physician-scientists investigating the important issues of human nutrition.[35]

* * * * *

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