



THE NUTRITION FOUNDATION

NUTRITION AND DRUG INTERRELATIONS



A MONOGRAPH EDITED BY
JOHN N. HATHCOCK AND JULIUS COON

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NUTRITION AND DRUG INTERRELATIONS

THE NUTRITION FOUNDATION

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NUTRITION AND DRUG INTERRELATIONS

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Foreword

The Nutrition Foundation Monograph Series provides systematic coverage of new, important areas of nutritional knowledge. The content of each monograph is planned to consolidate subject material of fundamental importance and broad significance. The texts not only review recent advances, but provide a perspective derived from historical and multidisciplinary viewpoints. The international authors identify areas in which additional useful research should be pursued and address the application of research findings for the benefit of man.

The numerous interrelationships between nutrition and the metabolism and effects of drugs are underscored by the expanding number of therapeutic agents that now are regularly and repeatedly used over long periods of time. Certain of these interrelationships are beneficial; others have potential ill effects. Several established beneficial actions are utilized not only in human medicine, but in animal husbandry and veterinary medicine as well. These aspects are brought together in the present volume.

The Nutrition Foundation is indebted to the authors of this work for their participation in its preparation and to the editors, Dr. John N. Hathcock and Dr. Julius Coon, whose skill has provided the uniformity of coverage desirable for a maximally useful monograph. We are further indebted to the Iowa State University Nutritional Sciences Council, the planning committee of which selected the content and authors of the chapters.

William J. Darby
President
The Nutrition Foundation, Inc.
New York and Washington, D.C.

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Preface

The interrelations between nutrition and drugs have historical and current importance. While some drugs were first discovered in foods, modern increases in diversity and use of drugs have led to numerous interactions with nutrients and diet. These interrelations are important in research, medicine, dietetics, and animal production. The title "Nutrition and Drug Interrelations" was chosen for this monograph and the corresponding symposium because it denotes a wider, more extensive affiliation than the more usual term of "drug-nutrient interactions." The wider scope was intended and, we believe, suitably accomplished.

The chapter titles represent only a fraction of the total subjects which could have been included appropriately under the symposium title. They are organized into four major sections. The section titled Drug Effects on Nutrient Intake, Function, and Requirement gives some important examples of the impacts of drugs on the processes of nutrition. Many of these influences are harmless under optimal nutritional circumstances but may be deleterious when nutritional intake or function is inadequate. The section on Nutritional Effects on Drug Metabolism and Action illustrates several of the numerous influences nutritional condition has on biochemical competence to cope with xenobiotics, including drugs. With ever-increasing use of drugs, food additives, and other substances, increased understanding of the effects of nutrition on their metabolism and elimination is imperative. The section on the Use of Drugs in Animal Feeds gives some examples of the important uses pharmacological agents have in food production, and expresses concern about subsequent effects in the food chain. The last section, Use of Nutrients and Foods as Drugs, demonstrates that the boundary between dietetic and pharmacological treatment is by no means sharp. This overlap is clearly illustrated by the pharmacological (nutritional?) use of vitamin D derivatives to effectively treat certain familial diseases, and by the widespread use of megavitamin treatments of doubtful benefit. These sections represent a functional relationship categorization. It is difficult to imagine a

nutrition and drug interrelation which would not fit aptly into one of these sections. Some chapters are wide enough in coverage to fit possibly into more than one section. Although the perspective and focus of the chapters differ from one section to another and between chapters within sections, we believe the section titles give a subject matter organization that is both informative and useful.

The specific topics and authors were chosen to provide expert information selection and perspective in what we believe are timely subjects in terms of state of knowledge, research activity, and professional interest. Each author was asked to provide the best combination of "state-of-the-art" comprehensive review and "frontiers-of-research" detailed new information in their subject. The ways they interpreted this assignment varies considerably according to their individual viewpoints and the state of knowledge in the particular subject.

The introductory chapter, "The Agile Role of Food: Some Historical Reflections" by James Harvey Young, was included to provide historical and sociological setting and perspective for the extremely variable role of food in human existence and endeavor. In addition to nourishment, the various roles cited include uses of food and drink as drugs or as sources of drugs, as well as fanciful uses for numerous purposes.

No effort was made to cover the diverse field of drugs which occur naturally in foods. Knowledge of this subject is not changing very rapidly and good reviews have been published elsewhere.

It is hoped that this monograph, which is based on papers presented at the International Symposium on Nutrition and Drug Interrelations held at Iowa State University, August 4-6, 1976, will become a much needed benchmark publication in the subject. No previous symposium or publication has incorporated such a wide range of topics in this subject with this intensity. We hope that this publication will prove useful to nutritionists, pharmacologists, dietitians, and physicians, and also stimulate further research.

We wish to express our thanks to the Iowa State University Nutritional Sciences Council, especially M. Allison, W. Brewer, R. Ewan, N. Jacobson, W. Runyan, A. Trenkle, and J. Young, for help in planning, organizing, and hosting the symposium. Also, we gladly acknowledge the financial and organization support from the Nutrition Foundation, and the advice and encouragement given by Dr. William J. Darby, without which the symposium and this monograph would not have been possible.

*John N. Hathcock
Julius Coon*

NUTRITION AND DRUG INTERRELATIONS

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1

The Agile Role of Food: Some Historical Reflections

JAMES HARVEY YOUNG

I. Food as Patriotism	1
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I. FOOD AS PATRIOTISM

Father and I went down to camp,
Along with Captain Gooding,
And there we see the men and boys
As thick as hasty pudding.*

(Sonneck, 1972; Evans, 1903-1959)

In these bicentennial days it seems appropriate to begin some reflections on the agile role of food in history by pointing to a vivid food simile appearing in "Yankee Doodle," a popular song of the American Revolution. Food and the Revolution, moreover, are bound together by ties more substantial than similes. "I know not why," John Adams wrote after the new nation had become established, "we should blush to confess that molasses was an essential ingredient in American independence"

*Sonneck dates a broadside containing this verse to 1775 or 1776, although other authorities believe the first published version appeared as late as 1793.

(Schlesinger, 1949, p. 239). British tax measures involving molasses, sugar, and tea had much to do with provoking the expanding discontent that eventually led to war.

Indeed, the psychohistorian Lloyd DeMause has recently termed the Boston Tea Party the “real turning point” in a “group fantasy” (Seabrook, 1976). Puritan mothers, according to his interpretation, gave their children the harsh discipline traditional in England, but moderated it with a much greater measure of love, thus rearing children who possessed the psychic strength to be rebellious enough to challenge the mother country’s rule. “England was jamming food down America’s throat,” DeMause asserts, “just as mothers used to jam pap down their babies’ throats until they threw up.” In the Boston Tea Party, “the colonists didn’t take it lying down.”

An historian of an earlier generation, Arthur M. Schlesinger, Sr., saw economic rather than child-rearing reasons underlying American confidence in challenging Great Britain, but these reasons also related to food. The colonies possessed a food supply that was not only self-sufficient, encouraging self-reliance, but that was also ample enough for export. In his famous pamphlet *Common Sense*, Thomas Paine wryly noted that a free American nation would “always have a market while eating is the custom of Europe” (Schlesinger, 1949, pp. 238–240).

Despite America’s potential food abundance, the turmoil of the Revolutionary War led to shortages and drab diets, even in the armies. John Adams complained that “Our frying-pans and gridirons slay more than the sword” (Greene, 1943). At Valley Forge the troops came close to mutiny because of poor rations. George Washington besought his chief cook to devise a meal that might enhance morale. Combining tripe, vegetables, and peppercorns, the cook invented Philadelphia Pepper Pot, which boosted the spirit of the troops considerably (Hoag, 1976).

A broader and more significant impact came from the French alliance. French military chefs began to introduce new vegetables, the practice of serving vegetables in separate dishes, and new modes of cooking food. Moments of *contretemps* did occur. In Cambridge, Massachusetts, Nathaniel Tracy, revealing that a little knowledge of another country’s cuisine can be a dangerous thing, entertained the admiral and officers of the French fleet for dinner and served them a soup containing whole frogs (Cummings, 1941, pp. 30–31).

Food and Uncle Sam, the major figure symbolizing the nation, bear a relationship. In 1774 when Paul Revere copied for an American magazine a British cartoon showing the British prime minister forcing a draught of tea down the throat of a reluctant America, the symbol for

America was a half-naked Indian maiden.† After independence, a descendant of Yankee Doodle named Brother Jonathan supplanted the maiden. In turn Brother Jonathan was pushed aside in the 1850's by Uncle Sam, who had first made his appearance in the War of 1812, patterned after a real man who supplied meat to the armies (Murrell, 1933). When Uncle Sam took over as a symbol, he looked just like the typical American male described by a procession of European aristocrats who wrote travel books about the United States. Americans ate heavy, starchy, salty, fat-fried food and suffered from a lack of milk, fresh fruits, and leafy vegetables. They also bolted their meals; the national motto, one traveler said, should be "gobble, gulp, and go." The result, in the words of another traveler, was "a nation of moody dyspeptics" (Cummings, 1941, pp. 4 and 23-24; Schlesinger, 1949, pp. 240-242). An American observer, writing for *Harper's* in 1856, concurred in the grim judgments of the travelers from abroad (Anonymous, 1856). "We are fast becoming . . . a nation of invalids," he charged. "Foreigners already effect to see in us a degenerate offspring of a nobler race, and with them a skeleton frame, a yellow-died bilious face, an uncomfortable dyspeptic expression, an uneasy spasmodic motion, and a general ghost-like charnel-house aspect, serve to make up a type of the species Yankee." This description would serve for countless cartoon renderings of Uncle Sam (Schlesinger, 1949, pp. 241-242).

Thus food and patriotism endlessly interact and intertwine. Nor should this be at all surprising. For, like the air we breathe, but in a more complex and varied way, food is an indispensable ingredient of life. Playing for us so crucial a role, food inevitably mingles with other important ingredients in life's vast pot. Schlesinger argued that, of countless clues to the past, food is "the most basic of all" (Schlesinger, 1949, p. 234). "Men must have food if they are to think and act. Here is a want which precedes and conditions other hopes, aims and achievements." If monistic interpretations of history would serve, a dietary interpretation of history would make the most persuasive sense.

II. THE VAST VARIETY OF FOOD IMAGE AND ROLE

On the individual level, the Gestalt psychologist Fritz Perls has suggested the act of eating as a revelation of the entire personality.

†The cartoon, in the American Antiquarian Society, was entitled "The Able Doctor, or America Swallowing the British Draught," and appeared in the June 1774 issue of the *Royal American Magazine*.

“How . . . do you eat?” queries a popularizer of this point of view. “How do you take the world into yourself? Do you choose food carefully for its aesthetic and nutritional value? Do you pay attention to taste and texture? Chew carefully? Read when eating? As you incorporate nourishment, so you will take in and digest the world which surrounds you” (Keen, 1970).

“If you doubt this,” suggests the popularizer, “give full attention to your style of eating for one week and try drawing parallels to the way in which you read, listen, think, understand, and relate to persons.”

Through the ages the central importance of food to man has led him to use food as a mirror held up to reveal nature—and indeed the cosmic realms beyond. A recent issue of *Speculum* contains an article by Patrick Gallacher entitled “Food, Laxatives, and Catharsis in Chaucer’s Nun’s Priest’s Tale” (Gallacher, 1976). Gallacher makes manifest how, not only for Chaucer, but for numerous important theorists from Plato on into the fourteenth century, eating and elimination, and efforts to accomplish both so as to keep the humors balanced and thus retain or regain health, form a fundamental analogy for the most sweeping “metaphorical, moral, and theological meanings.” Man’s knottiest problems are confronted, such as the relation between “free will and divine foreknowledge.” Starting with food, these august thinkers construct “a model of total continuous intelligibility in the universe.”

The relation of food to the mind of God transcends the relation of food to patriotism, the theme with which I began. Countless other lesser linkages have existed between food and the diverse concerns of humankind. The way in which man perceived food until less than a century ago has tended to foster such linkages.

From the earliest times man has employed the same botanicals as both food and drugs. This was certainly true at both ends of the Fertile Crescent, in ancient Egypt and in Mesopotamia. “The borderline between dietetic and pharmacological treatment,” Henry Sigerist wrote, “was by no means sharp” (Sigerist, 1951, p. 486). In the Western tradition, this fusion became especially strong because of the key role given by the Hippocratic corpus to diet in the physician’s effort to help his patient (Sigerist, 1951, pp. 335–336; 1961, pp. 240–241). During the medieval and Renaissance periods, spices doubled as food condiments and as drugs. One scholar points out that “the terms spices, drugs, and aromatics were generic and interchangeable through all these years” (Guerra, 1966). The late sixteenth century English herbalist, John Gerard, summed up the double role: “In the first ages of the world, . . . [plants] were the ordinary meate of men, and have continued ever since of necessary

use both for meates to maintaine life, and for medicine to recover health.” (Gerard, 1636).*

The striking historical circumstance, in the consideration of the same products of nature in their dual role as both food and drugs, is that, when regarded as a drug, each product might fulfill a multitude of therapeutic functions, whereas when used as food, all products were believed to serve the same single purpose. Within a decade after the appearance of Gerard’s herbal, Francis Bacon wrote: “In the body there are three degrees of that we receive into it, aliment, medicine and poison.”† His use of the word “aliment” revealed the continuing potency of the Hippocratic assumption that all foods contained a single principle made available to the body by digestion to repair its tissues and provide it with energy. Nor did this received doctrine suffer major challenge and revision until the nineteenth century. In 1837 Ralph Waldo Emerson could still express the general view: “The human body can be nourished on any food” (Emerson, 1903).

The perspective that nutritionally, so to speak, all foods served the same purpose had important intellectual consequences.** First, it put a damper on the development of healthy suspicion that some disease conditions might be related to the *absence* from the diet of some type of food. To be sure, here and there some people acted empirically as if vaguely harboring such a suspicion, as in the eating of fish livers by the early fishing folk of northern Europe. The single aliment notion had a second important result: if all foods were equally valuable for nourishment, then a whole host of secondary and sometimes specious reasons could develop for choosing and for rejecting individual foods. Food has served also, among other roles, as taboo, as poison, as potent marvel, as status symbol, and as handmaiden to beauty.

All major religions have had to concern themselves with something as important as food, and many ancient taboos still exercise powerful influence. The Mosaic injunction to the Jews against pork is an example. The explanation that this taboo rested on an empirical base, a sensing that eating pork might harm the health, does not seem persuasive, because the link between infected pork and trichinosis is too remote for such observational detection. A more likely reason for the taboo, Magnus Pyke argues, lies in the circumstance that the Jews were a nomadic people and pigs did not herd easily over long distances (Pyke, 1968, p.

*First edition appeared in 1597.

†Bacon is cited under “Aliment” in the “Oxford English Dictionary.”

**I first explored this effort to pattern ideas in food history in Blix (1970).

12). Jealous of more settled groups who could raise pigs and eat pork, the Jews put that meat beyond the pale. The power of religious food beliefs may be suggested by another example, a quotation from a Western physician who recently practiced in India among the vegetarian Hindus (Simeons, 1968). "I know from personal experience," he writes, "that it is not uncommon for an orthodox Hindu to prefer dying of pernicious anemia to taking liver extract."

Foods have been deemed poisonous in settings solely secular. In his herbal Gerard mentioned that recent import, the potato, brought from America by Sir Walter Raleigh, and cited a Burgundian belief that its tubers caused leprosy (Gerard, 1636). European farmers generally came to share this fear. The flesh-colored nodules extending their finger-like growths made men think of the deformed hands and pale skin of leprosy. Despite many efforts to dispel this groundless suspicion, nearly 2 centuries elapsed before the potato became an accepted English field crop (Pyke, 1968, pp. 25-27). And British America from whence the potato had gone to England, brought back from the mother country traces of the fear which the potato had generated. Even after eating potatoes became acceptable, a popular American superstition held that if one ate them every day he could not live out 7 years (Weigley, 1967). In Europe, turnips, beets, and tomatoes in their day, all faced initial hostility (Renner, 1944, pp. 166-70, and 204). Only after livestock had devoured them safely for a long time did people generally take them up.

Contrariwise, other novel and exotic foods and drinks grabbed the imagination of regions into which they were newly introduced as marvelous wonders, panaceas, foods for or from the gods. So it was with maple sugar and pineapple, asparagus and celery (Young, 1961). And so it was with coffee. The Arabs drank coffee as early as the year 1000, according to one chronicler, perhaps more as a medicine than as a drink (Renner, 1944, p. 215). When coffee first appeared in Western Europe, a somewhat therapeutic mantle garbed it. "It is said to be healthy when drunk hot . . .," wrote Sir T. H. Herbert in 1626. "It destroys melancholy, dries the tears, softens anger and produces joyful feelings. Nevertheless, the Persians would not estimate it so highly, if there were not the tradition: Invented and produced by Gabriel for restoring the sinking Mohammed." In England and on the continent coffee drinking became a sudden vogue (Renner, 1944).

Tea, the drink destined to oust coffee as England's national drink, illustrates food as status symbol. In the early eighteenth century, the urban wealthy considered tea an occasional luxury. As the years passed, each lower economic level began to desire what those above in the hierarchy increasingly drank, and by 1850 tea had become the national

beverage. During the same period a similar trend occurred with respect to bread. For centuries the higher the social ranking, the whiter the bread. In the early nineteenth century, urban workers aspired to the whiter bread of their betters and, as with tea, increasingly bought it. White bread and tea entered the diets of the poor not without great social cost. "What had been mere adjuncts at the tables of the wealthy," a recent scholar states, "now constituted virtually the total diet of those who could afford no more" (Burnett, 1966, pp. 2-3).

Standards of beauty also influenced attitudes toward food. In the romantic age of the nineteenth century, a particular vision of beauty prevailed. For both men and women, paleness, frailness, slenderness became the vogue. One might achieve such an appearance by falling victim to tuberculosis and gradually waning away, becoming more ethereal the closer death approached.* Remember the heroines of all those romantic operas. If a person were not destined to contract consumption, the same ideal of beauty could be achieved by dieting. In 1824 a British magazine published advice on "Beauty Training for Ladies" which forbade them to consume milk, cream, butter, cheese, fish, or any vegetable except potatoes (Burnett, 1966, pp. 56-57). Similar dietary counsel for the same esthetic purposes enjoyed a vogue in the United States (Cummings, 1941, p. 34).

These examples illustrate the numerous secondary roles which food could play in the minds of men when food as nourishment was restricted to the single alimental role. Nor would such a vast and complex body of food folklore wither away when, during the second half of the nineteenth century, food scientists split that one universal aliment into a nutritional trinity of protein, carbohydrates, and fats.

Food in its role as medicine also contributed mightily to the massive folk tradition. Indeed, therapeutic uses for foods treasured and employed in ancient Egypt and Mesopotamia persist into our own day (Sigerist, 1951, p. 248; 1961, p. 244). Garlic, for example, served as both food and medicine for the Egyptians, the Greeks, the Romans, for medieval man, and for man ever since (Raspadori, 1966). One of Dioscorides' (1959) "herbs with a sharpe qualitie," garlic cleared out the arteries, the Greek medical writer asserted. In the 1950's garlic could still perform this indispensable healing function, if one believed the spiel of a taxi driver turned food lecturer who traveled widely in these United States (Young, 1967, pp. 333-357). Within the last year or so, an airline magazine has run an article hailing garlic's mystic healing potency.

*Perceptive attention to the social image of tuberculosis is paid in Dubos (1952).

III. THE AMERICAN VERSION OF FOOD FOLKLORE

Before the day of scientific nutrition, the American version of food folklore acquired its own special hue of a coloration tinting food folklore throughout the Western world. "The atmosphere of the [Romantic] age," Grete de Francesco has written, "was favourable to all sorts of nature cures, and to the development of a new kind of imposture: a falsification of Nature through overemphasis on the natural" (Francesco, 1939). All over Europe and America, lay healers in rustic settings employed all sort of "natural" remedies, water being especially prominent. Among those bemoaning the increasing artificiality of life, there began a great preoccupation with the "natural" diet.

American cultural soil permitted such ideas to grow with unusual vigor. The romantic movement furnished one impetus, and there were many others, for a major multifaceted reform movement flourished in the United States during the second quarter of the nineteenth century. Freedom's ferment expanded political democracy during the age of Andrew Jackson and addressed the rights of women and of slaves (Tyler, 1944). Health practices, from the heroic bleeding and purging prescribed by orthodox practitioners to the tightly laced corsets decreed by fashion, met challenge from reformers (Walker, 1955).

Nor were the nation's eating habits exempt from criticism. That "back to nature" should constitute the major message in appeals for food reform conformed with the basic way by which citizens of the United States sought to explain themselves. The central developing myth envisioned the nation as a garden, indeed a new opportunity for mankind almost as significant as the original Garden of Eden (Smith, 1950; Lewis, 1955; Marx, 1964). The new Adam was the American yeoman farmer. In time, the historian Frederick Jackson Turner, a native of Wisconsin, converted the garden myth into respectable historiography. His frontier hypothesis, enunciated at the Chicago Columbian Exposition in 1893 (Turner, 1920), remained the virtually unchallenged explanation of American uniqueness for 40 years. The hypothesis attributed everything good about the nation to the frontier. The converse of this idealization of nature was suspicion of too much civilization, especially that site of noisy machinery, epidemic ailments, and processed foods, the city. Intellectuals and common citizens alike shared this distrust of urban life (White and White, 1962).

In the first great urbanizing-industrializing period, coinciding with those years of freedom's ferment, Sylvester Graham became the nation's first great champion of natural foods (Shryock, 1966). A clergyman, Graham found his ideal standard of diet in the Garden of Eden. "Fruits,

nuts, farinaceous seeds, and roots,” he wrote in 1839, “with perhaps some milk, and it may be honey . . . constituted the food of the first family and the first generation of mankind” (Graham, 1883, p. 316).^{*} During this Golden Age, Graham said, no “artificial preparation” was necessary except for shelling the nuts.

The way Americans ate in Graham’s day deserved rebuke, as I have already suggested. So Graham made much sense. But some of his ideas went far astray. He made a panacea of bread baked from a kind of flour that still bears his name. He termed all meat taboo. And he came close to suggesting that his dietary regimen might bring back the Garden of Eden. “The simpler, plainer, and more natural the food of man is,” Graham wrote, “. . . the more healthy, vigorous, and long-lived will be the body, the more perfect will be all the senses, and the more active and powerful may the intellectual and moral faculties be rendered by suitable cultivation” (Graham, 1883, p. 309).

Graham’s doctrines had much influence on the dietary practice of new religious sects arising in the nation and shortly upon commerce as well. Ronald Numbers has recently published a biography of Ellen G. White, the founder of one of those new sects, the Seventh Day Adventists (Numbers, 1976). The dry cereal industry that arose in Battle Creek, Michigan, a center of Adventist strength, initially promoted itself with food reform ideas. That form of corn flakes later known as Post Toasties first bore the name of Elijah’s Manna (Carson, 1957).

Packaged cereals formed one sector of an increasingly important processed food industry, made possible by advances in science and technology and made necessary by burgeoning urban population, remote from the gardens and orchards of rural America. The technology often revealed inadequacies, and the processors sometimes exhibited ethical shortcomings which they shared with other types of entrepreneurs during the Gilded Age. A vigorous critique arose, attacking food adulteration that might go so far as to fabricate so-called “strawberry jam” from apple scraps and hayseeds, and condemning the use of a host of new and perhaps dangerous preservatives. Food, in this extreme of agility, could equal fraud (Cummings, 1941, pp. 96–103; Keuchel, 1972, 1973; Anderson, 1958).

Some critics, recognizing the necessity for processed foods in an increasingly urbanized society, sought to restrain abuses through the enactment of pure food and drug laws. A small but vocal minority, however, echoed Sylvester Graham’s plea of half a century earlier to return to nature.

^{*}Graham’s lectures were originally published in 1839.

Prime prophet of this doctrine during the early twentieth century was a Missouri farm boy who preached how to go back to nature in the city (Macfadden and Gauvreau, 1953; Young, 1977). Bernarr Macfadden learned better than had Graham the technique of self-promotion. He set up a magazine called *Physical Culture* to propagandize his version of nature's way, and on the streets of New York City he exhibited his own muscled body as his most potent advertisement. His regimen, long on exercise, short on clothing, condemned "the baneful habit of over-eating" (Macfadden, 1903). Like Graham, Macfadden thought ill of meat and well of raw vegetables. The carrot became for him a sort of trademark.

IV. THE NEWER NUTRITION AND ITS MANIPULATION

Macfadden, who had attended grade school only briefly, drew his ideas about food from the vast body of popular lore that had developed through the centuries when nutritional concepts were simple. He propagated his gospel during the very years that nutrition was becoming established as a true science. "In 1900," Elmer McCollum has said, "we were [still] almost blind to the relation of food to health" (McCollum, 1957). The single universal aliment had become a trinity, but as of 1900 observations and research were just building toward an awareness of the infinitely greater complexity that existed in the nexus between food and health. Charles Rosenberg (1976) has recently helped clarify how difficult a research frontier the nutritional borderlands were to enter upon. Professional specialization had already reached the point at which the clinical physician and the organic chemist did not know enough about what the other was doing, about what techniques the other was using. America's initial contributions to the newer nutrition, the discovery of vitamin A, for example, came not from medical men concerned about deficiency diseases, but from organic chemists at agricultural experiment stations concerned about the feeding of cattle. Even after early successes by the organic chemists, physicians assimilated only slowly the concept of dietary deficiency diseases. The germ theory attributed illness to the presence of unwanted invaders from outside the body, and research concentrated on tracking down all such intruders. To think of diseases as caused by an absence in the body of elusive substances that should be there required a contrasting mind-set only gradually acquired. Before this audience there is no need to trace the nutritional revolution to its major plateau about 1940, by which time more than forty vitamins and other nutrients had been proved necessary for an adequate diet in

man. For the nutritional scientist, food had assumed the role of multiple nutrient.

What of the layman, be he ordinary mortal, cultist, or wily entrepreneur? For him also the nutrition revolution ushered in the dawn of a new day. To the great mythic storehouse deriving from ancient alimental days, a second vast vision relating food to health became added, bearing the imprimatur of science. Too complex for easy grasping, the new doctrine, like the older simpler one, could be easily twisted and distorted. Its basic premise readily provoked alarm. Even while eating enough of what you usually ate, you might get sick. To stay healthy some mysterious extras might be needed. You couldn't see them and you couldn't taste them, but without them you might acquire horrendous symptoms or else just wither away.

Grant that Graham and Macfadden believed fervently in their own food gospels, both the old lore and the new science offered boundless opportunities for shady commercial exploitation. Before the first World War, a form of dried cottage cheese, parading under the name of Sanatogen, was marketed claiming to be "The Re-Creator of Lost Health," "a nerve and tissue food for which the brain, spinal cord and the nerves have a special predilection" (American Medical Association, 1912). During the 1920's the word vitamin appeared with increasing frequency in food advertising, even for chocolate bars (Young, 1967, p. 335). Multivitamin panaceas began to receive widespread promotion, one of them called Catalyn, made of wheat bran, milk sugar, and epinephrine, its label boasting potency in all vitamins from A through G and claiming to cure high and low blood pressure, Bright's disease, dropsy, and goiter (U.S. v. Lee, 1939).

After World War II a new wave of questionable promotions got under way. The wartime enrichment program decreed by the Food and Nutrition Board of the National Academy of Sciences had further publicized vitamins, expanding public interest. The Food and Drug Administration, using new powers acquired in the New Deal revision of its basic law, began a vigorous campaign against traditional forms of quackery. Some hard-pressed promoters moved into the greener pastures of "nutrition."

To succeed most effectively, these vitamin vendors needed to undermine faith in the regular food supply. They sought to do this through books, pamphlets, mail-order catalogs, radio and television broadcasts, lectures, door-to-door pitches, and conversations in health food stores (Young, 1967, pp. 333-359). An integrated myth emerged of considerable persuasiveness: improper diet caused all disease; food wasn't what it used to be because of worn-out soil; chemical fertilizers poisoned the land and hence the food grown on it; pesticides heaped on more poison;

food processing destroyed nutrients; you might not realize you were sick, but you really were, suffering from subclinical deficiencies (Bell, 1958). But a way lay open to counter all these hazards: take wonder mixes of ingredients and stay out of "the marble orchard." These mixtures often wedded the ancient lore and the new science. Garlic continued to possess its marvelous curative properties known to the Egyptians. Vitamins soared beyond the value attributed to them by nutritional scientists and offered laymen a magical route to super-health and super-happiness. Promoters were clever too at turning an occasional true problem of the regular food supply to their account: an instance of excessive pesticide residue, some problems with a food additive, the discovery of mercury in fish.

Events of the 1960's expanded the nation's receptivity to food faddism and charlatanism. For then we saw, especially among the young, an upsurge of neoromanticism, a wave of disillusion with civilization and its discontents, a skepticism of big government, big business, big science, and, indeed, of the intellectual approach underlying science, rational thought. This temper drew strength from the fact that big science had invented the atomic bomb and environment-threatening chemicals, although the mood had been coming on for a long time. When reason is distrusted, unreason becomes glamorized. Romantics, depending on intuitions, always worry about their health, and are ready to intuit a variety of unorthodox cures. Romanticism, as we have seen from earlier eras, leads back to nature—in our day, sometimes all the way back to a remote rural commune, sometimes only so far as so-called organic foods for sale at a health food store. In such a climate, billions have been made by promoters preying on the susceptible.

On a case-by-case basis, the Food and Drug Administration attacked the largest and most outrageous pseudonutritional promotions right from the start (Young, 1967, pp. 206–208 and 338–359). Since World War II the regulatory task has proved especially difficult, because such a high proportion of the exaggeration has consisted of the spoken word. A printed label, primly circumspect, acquires overtones of magic when interpreted by a spieler or a clerk in a health food store. I have a bottle of multivitamin tablets given me by a student to whose uncle it was sold. Recovering from a broken leg, the uncle had hobbled to his front door to confront an itinerant salesman who took one look and then insisted that the vitamins he vended would speed the mending of the fracture. For a time after tape recorders came on the market, the courts permitted the FDA to present as evidence recordings of false and misleading claims made orally by promoters and recorded without their knowledge. In due

course such recordings came to be considered unwarranted invasions of privacy. Thus enormous difficulties continue to plague regulators.

V. THE VITAMIN AMENDMENTS OF 1976

Indeed, the most recent chapter of the story seems to me to possess elements of tragedy. Powerful popular currents, shrewdly exploited by special interest groups, have led to a significant weakening of protection against promoters of nutritional nonsense. The neoromantic tide with its back-to-nature currents has been mentioned. Suspicion of bureaucracy has also mounted mightily in the last few years, certainly for some legitimate reasons, with the impact of suspicion, however, falling on the heads of both the unjust and the just. The ecological movement, while sorely needed, at times has magnified individual incidents and produced exaggerated alarm. In such an atmosphere purveyors of the food myth have found an increasing number of common citizens ready to be persuaded that our ordinary food supply is dangerously tainted and that only magical mixtures of twentieth century vitamins and dawn-age botanicals can save the nation (National Analysts, Inc., 1972).^{*} Thus food with agility assumes a Janus-image as poison and perfecter.

Striving to combat the growing market which depends on deceptions and distortions relating to food, the Food and Drug Administration has itself fallen victim to the power of the health food industry and the vast number of American citizens who have been persuaded to swallow whole the nutrition myth. In 1962 the FDA sought to bolster the case-by-case method by revising its regulations, 2 decades old and seriously out-moded, so as to introduce scientific rationality into the marketing of vitamins, minerals, and other dietary supplements. Some 54,000 pieces of mail flooded the FDA opposing its proposals, including 40,000 protesting postcards generated by the major trade association in the health food industry, the National Health Federation (Public Health and Environment Subcommittee, 1973, pp. 1-5). A new version of the proposed regulations issued in 1966 was the subject of marathon hearings between 1968 and 1970, amassing 32,000 pages of testimony. In 1973 the FDA published final regulations, and elements of the health food industry took the FDA to court. In due course a Circuit Court of Appeals re-

^{*}According to a survey sponsored by federal agencies, three out of four adult Americans were persuaded that, no matter how nutritionally adequate their diets, extra vitamins would provide them with increased energy.

quired some modification of the regulations and ruled that one issue be given renewed hearings, held this year (National Nutritional Foods Association *v.* Food and Drug Administration, 1974; Davidson, 1976). But in the main the court supported both the FDA's authority and its approach to regulating special dietary supplements. Indeed, the Court asserted that some of the most effective evidence showing the need for new regulations came from the 50,000 letters the FDA had received protesting the regulations.

The battle, however, had shifted to another front. No doubt anticipating that the courts might let the FDA set standards which, if not met, automatically brought products into violation of the law, the health food industry turned its attention to the Congress. A new law was needed, the industry asserted, because bureaucrats intended to trample the consumer's freedom of choice, depriving him of the right to buy vitamins without a prescription from a doctor (Public Health and Environment Subcommittee, 1973, pp. 5-7). Such charges were untrue, except for potentially toxic levels of vitamins A and D. Under the new regulations, consumers would retain freedom to buy individual vitamins other than A and D and to purchase other single food supplements at any level of strength (Public Health and Environment Subcommittee, 1973, pp. 11-18; Anonymous, 1974). For multi-ingredient products, to be sure, standards of identity would provide for more rational combinations than those on the market, the yardstick of rationality derived from the Recommended Daily Allowances as determined by the Food and Nutrition Board of the National Academy of Sciences. The regulations also would decree more informative labeling to help consumers buy more wisely.

Why did the Congress respond so favorably to the health food industry's attack upon the FDA? For one thing, Congressmen were buried under an avalanche of mail. The industry generated over two million letters—the issue was said to have spurred more mail than Watergate—protesting the FDA regulations and demanding a law to stay the agency's hand (Kline and Davis, 1975; Anonymous, 1973). Moreover, we may assume, like some of their constituents, key members of the Congress had been beguiled into putting personal trust in facets of the nutrition myth. Also, skepticism of bureaucratic agencies was rising in the legislative branch. So during 1973 various bills were introduced, one of them co-sponsored by over 150 members of the House of Representatives (Congressional Record, 1973; Young, 1974). The bill would not only negate the FDA's proposed regulations, but would also curtail seriously the agency's legislative authority to regulate food supplements, given it by the Congress in the law of 1938. One such bill received Senate ap-

proval during the 93rd Congress (Congressional Record, 1974). The size of the vote indicated the way the wind was blowing: the bill passed 81 to 10.

In the 94th Congress, a somewhat revised Senate version of the vitamin bill was attached as a rider to a “must” bill which had almost no opposition, the National Heart and Lung Act. The House heart and lung bill passed without the vitamin rider, but the conference committee accepted it, as did, in April 1976, both Houses of the Congress. The President quickly signed the measure into law (U.S. Senate, 1975; Congressional Record, 1975, 1976).*

The Congress can not be said to have given the issue the consideration it deserved. The devious parliamentary strategy indicates this. Moreover, the 94th Congress did not even hold public hearings on the bill, despite opposition to the food supplement measure from such a wide spectrum of groups as the American Society of Clinical Nutrition, the Committee on Nutrition of the American Academy of Pediatrics, the American Association of Retired Persons, Consumers Union, and Ralph Nader’s associates (Public Health and Environment Subcommittee 1973, pp. 52–56; Health Subcommittee, 1974; Holliday, 1975; Butterworth, 1975). A trade newsletter deemed the course of events “one of the ‘legislative miracles’ in a lifetime” (*F-D-C Reports*, 1975).

The 1976 amendments to the 1938 act represent the first retrogressive step in federal legislation respecting self-treatment wares since the initial Pure Food and Drugs Act became law in 1906. The amendments will prevent the Food and Drug Administration from: “Limiting the potency of vitamins and minerals in dietary supplements to nutritionally useful levels; classifying a vitamin or mineral preparation as a “drug” because it exceeds a nutritionally rational or useful potency; requiring the presence in dietary supplements of nutritionally essential vitamins and minerals; [and] prohibiting the inclusion in dietary supplements of useless ingredients with no nutritional value” (Food and Drug Administration, 1976; Hopkins, 1976).

During the course of this legislative adventure, Food and Drug Commissioner Alexander M. Schmidt spoke of the then pending bill as “a charlatan’s dream” (Food and Drug Administration, 1976).

The biochemical interrelations in the human body of what we term foods and what we deem drugs, the theme of our symposium, constitutes one front of the ongoing, complex, careful, scientific inquiry regarding nutrition. That inquiry, it has been the burden of my remarks to illustrate, takes place in a bigger real world, one in which food has been and

*The enacted bill became Public Law 94-278.

will be a kaleidoscopic concept, the facets of which possess great power to spur the actions of men, often in bizarre ways inharmonious with the tenets prevailing in a nutrition laboratory.

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Section I

DRUG EFFECTS ON NUTRIENT INTAKE, FUNCTION, AND REQUIREMENT

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2

Appetite Regulation and Its Modulation by Drugs

ANN C. SULLIVAN and LORRAINE CHENG

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I. INTRODUCTION

Feeding is so crucial to the survival of the species that we should not be surprised at the multitude of regulatory tactics involved in the control of appetite. Feeding behavior certainly reflects a multiplicity of inputs and the control of appetite is undoubtedly regulated by a succession of oral, gastric, intestinal, parenteral, and ultimately central processes. Peripheral (outside the brain) factors influence feeding and include taste, smell, stomach distention, osmoreception, gastrointestinal and

hepatic chemoreception, metabolites, ions, hormones, and temperature. Metabolic processes influence, coordinate, and integrate peripheral factors with neural elements and the animal starts, continues, or stops eating. Regulation of food intake is believed to encompass both a short-term and a long-term component. The former consists of "factors" which influence and modify individual meals, i.e., short-term satiety, and the latter includes "factors" which reflect the state of body nutrient stores and are concerned with the long-term regulation of feeding. Normal feeding behavior is intimately linked to energy balance, and animals maintain an optimal level of body weight through appropriate alterations in caloric intake. Hyperphagic obesity and anorexia nervosa represent the two major types of feeding disorders, involving significant overeating and undereating in relation to energy requirements, respectively. Anorectic agents decrease food intake and are employed in the treatment of hyperphagic obesity; orectic agents stimulate appetite and are frequently used in a therapeutic regimen for anorexia nervosa. The majority of drugs that have been demonstrated to influence food intake apparently act centrally by influencing various components involved in the neural regulation of appetite. However, other agents might reduce appetite by acting predominantly at peripheral sites believed to be involved in feeding control.

The following review presents current concepts of the neural and peripheral components of appetite regulation as well as metabolic elements which might integrate and influence these areas. Disorders of appetite regulation will be discussed, and anorectic and orectic drugs affecting appetite will be described with emphasis on their mechanism(s) and site(s) of action.

II. REGULATION OF FOOD INTAKE

A. Neural Regulation of Food Intake

The vast majority of investigations on the regulation of food intake have centered around two major syndromes of abnormal feeding: ventromedial hypothalamic hyperphagia (Brobeck *et al.*, 1943) and lateral hypothalamic aphagia (Anand and Brobeck, 1951). From these studies the concept of a bilateral "satiety center" localized in the ventromedial hypothalamus, and a bilateral "feeding center" located in the lateral hypothalamus emerged (Stellar, 1954). This model proposed that the motivation to eat was proportional to the activity of the "feeding center" in the lateral hypothalamus, and that the "satiety center" in the ventromedial hypothalamus influenced feeding by exerting inhibitory ef-

fects on the “feeding center”. These centers are believed to collect neural and chemical information regarding the nutritional state of the animal, and to receive input from peripheral sources as well as other regions of the brain (Grossman, 1975).

The involvement of neurotransmitters in these two abnormal syndromes, and in normal appetite regulation in general, has emerged from the development of several important techniques: (1) application of neurotransmitters directly into specific sites in the brain, thus extending the classical work of Grossman (1960, 1962a,b); (2) anatomic visualization and identification of monoamine systems in the brain (Anden *et al.*, 1966); and (3) selective destruction of catecholamine systems in the brain (Ungerstedt, 1971). Through the applications of these techniques, spe-

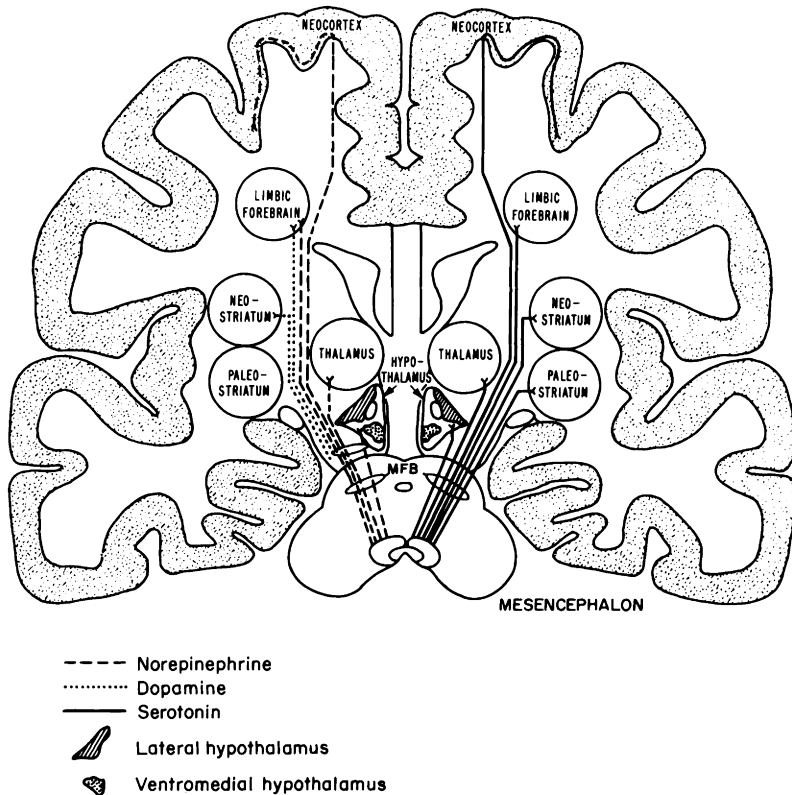


Fig. 1. Diagrammatic representation of the brain, illustrating biogenic amine pathways of three major neurotransmitters (norepinephrine, dopamine, serotonin) and two important anatomical locations (lateral hypothalamus and ventromedial hypothalamus) involved in appetite regulation.

cific transmitter systems in the brain are believed to be critical links in the transmission of various types of information to the aforementioned appetite centers, and a more integrated view of the neural regulation of food intake has emerged. The anatomical location of the important brain centers involved in appetite regulation (ventromedial and lateral hypothalamic areas) and the neurotransmitter nerve fiber systems (norepinephrine, dopamine, and serotonin) are illustrated in Fig. 1. The following discussion will describe these brain centers and the neurotransmitters believed to be involved in appetite control. Several excellent reviews (Epstein, 1971; Hoebel, 1971; Rabin, 1972; Baile, 1974; Panksepp, 1974; Grossman, 1975; Teitelbaum and Wolgin, 1975) should be consulted for further details.

1. *Brain Sites*

a. Ventromedial Hypothalamus. As first reported by Hetherington and Ranson (1940), small bilateral lesions in the ventromedial hypothalamus of rats produced overeating which led to obesity. The marked increase in body weight produced by ventromedial hypothalamic lesions is illustrated in Fig. 2. Several well-documented cases of patients with hypothalamic tumors in this same area, who developed hyperphagia and obesity were reported (Reeves and Plum, 1969; Heldenberg *et al.*, 1972). The ventromedial hypothalamus is considered an inhibitory "satiety center" since stimulation of this site resulted in cessation of feeding, while its destruction produced overeating (Table I). Hyperphagia ceased when the lateral hypothalamus was subsequently destroyed bilaterally, suggesting that the ventromedial hypothalamic region inhibited activity in the lateral hypothalamus (Anand and Brobeck, 1951).

Many investigators have analyzed the behavioral and biochemical results of ventromedial hypothalamic lesions in animals, partly because remarkable similarities existed between the behavior of obese humans and the behavior of animals that became obese after lesions of the ventromedial hypothalamus (Nisbett, 1968, 1972a; Schacter, 1971). Rats with ventromedial lesions eventually reached a "static" phase and no longer continually increased their food intake; body weight was maintained at a high but stable value. When starved back to normal body weight, however, rats returned to a "dynamic state" (similar to that observed after lesioning) and became hyperphagic (Brobeck, 1946). If prior to lesioning, an animal was made obese either by insulin administration or force-feeding, the subsequent destruction of the ventromedial hypothalamus caused little overeating and weight gain (Hoebel and

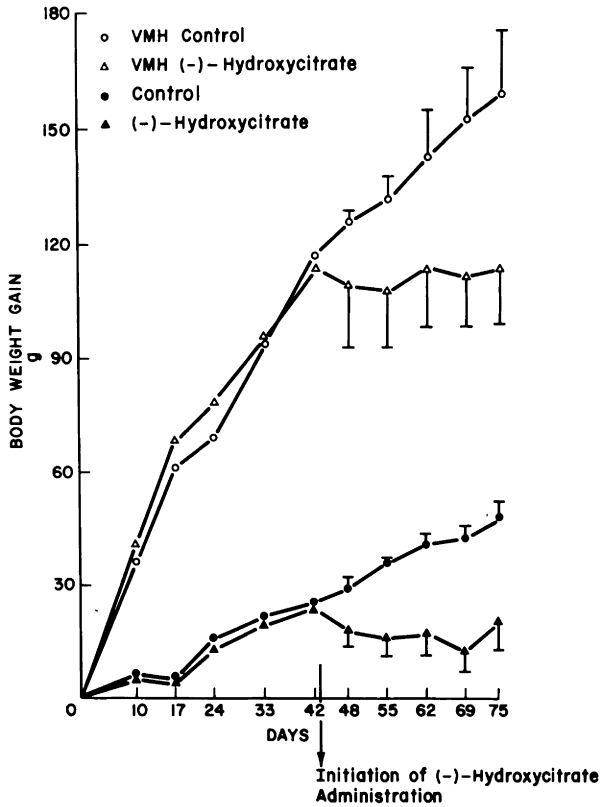


Fig. 2. Comparison of the effect of (—)-hydroxycitrate on cumulative body weight gain in ventromedial hypothalamic-lesioned and nonlesioned rats. The ventromedial hypothalamic region of 10 rats was destroyed bilaterally by electrocauterization with radiofrequency current. Ten lesioned rats and 15 nonlesioned rats were fed ad libitum a 70% glucose diet for 42 days, and on day 43 one-half of each group was given (—)-hydroxycitrate, tri-sodium salt (52.6 mmoles/kg diet) as a dietary admixture for 33 days. Vertical bar indicates the SE of the mean. (Sullivan and Triscari, 1977).

TABLE I
Food Intake Following Experimental Manipulation^a

Brain region	Surgical or chemical lesion	Electrical or chemical stimulation
Ventromedial hypothalamus	↑	↓
Lateral hypothalamus	↓	↑

^a Adapted from Epstein (1960).