NUTRACEUTICALS: DESIGNER FOODS III GARLIC, SOY AND LICORICE

Edited by

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DEDICATION

This book is dedicated to the memory of Dr. Herbert F. Pierson Jr., born 7 August 1952 in Trenton, New Jersey, who earned degrees in biochemistry and pharmacognosy.

As a scientist in the Diet and Cancer Prevention Branch, National Cancer Institute, he was Project Leader of the novel initiative to fingerprint the cancer-preventing compounds found in food. With boundless enthusiasm and energy, in 1989, he coined the descriptor "Designer Foods" to not only recognize the role of phytochemicals in thwarting disease pathogenesis, but to stimulate the food and pharmaceutical industries to research and to market existing and new foods "designed" to benefit the health of humans.

He was very closely allied to the three "Designer Foods"short courses held at Rutgers. By the time of the third Designer Foods short course, he had resigned his position at NCI to establish his own consulting business "Preventive Nutrition Consultants" in Woodinville, WA. In addition, he became involved, along with his wife, with the continuing education of pharmacist in this emerging field of herbals and designer or functional foods, which in the USA are grouped as Nutraceuticals.

He fought valiantly with lymphoma but his Creator called him home 14 March 1996.

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PREFACE

The term "Designer Foods" was the programmatic and funding term of the National Cancer Institute and can be briefly defined as the study of one or more phytochemical components(s) acting individually, additively or synergistically, usually as component(s) of whole food, that have the characteristic of providing protective, preventative and possibly curative roles in the pathogenesis of cancer and other chronic disease progressions. The observation of benefits may be based on the results of one or more epidemiological, *in vitro* and/or *in vivo* cellular, organ system or whole organism assays, and may include human clinical experiences and trials. Other terms have emerged to describe "designer foods." The University of Illinois has evolved a coordinated phytochemical research effort entitled "Functional Foods for Health." Dr. Stephen DeFelice of the Foundation for Innovative Medicine coined the term "Nutraceutical" to describe beneficial phytochemicals. This term has gained considerable acceptance because it is unique, concise and somewhat descriptive of the intended field of endeavor.

Rutgers held the first short course on Designer Foods in January 1990, and the second in March 1993, with the third being held 23-25 May 1994 at Georgetown University of which these are the proceedings.

In contrast to the field of Pharmacognosy and the discovery of drugs from natural products, nutraceutical research discovers substances that are considered a food or a part of a food and which provide health or even medical benefits. Such substances are invariably phytochemicals and may range from being isolated nutrients to other non-nutrient phytochemicals that act directly, or may exert biochemical activity directly, or by modulating genomic materials. Food, be it commodity, or herb, or spice, is any substance that is eaten or otherwise taken into the body (e.g., ostomy) to sustain psychological and physiological life, provide energy and promote the biochemical and physiological interactions that are nutrition. The substance of food is a vast array of chemicals of which a very small number are essential to life and are recognized and classified as nutrients. In contrast a vast array of food chemicals provide flavor, color and texture attributes, while others are key to the metabolism of the food (e.g., enzymes). Of the functions of food, nine are psychological and only three are physiological. Nutraceuticals are naturally-occurring and if determined to be beneficial could be biotechnologically-enhanced.

A paradigm I have evolved to give dimension to the breadth and potential of the implications of nutraceuticals is shown in Fig. P.1. There are four major components to the paradigm. First is the recognition that a major consideration in the risk of any disease developing is our genetic make-up revealed to some degree by our family history. Secondly, there is no question

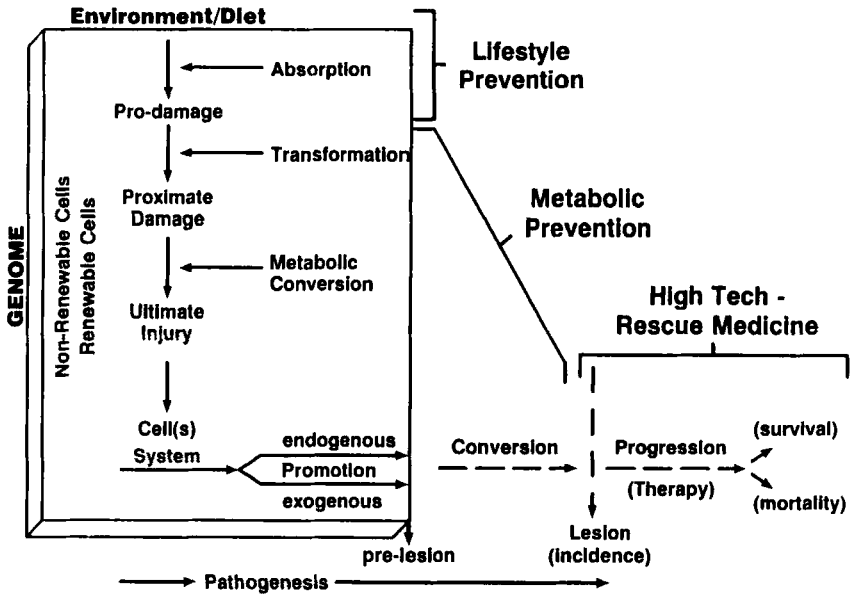

FIG. P.1. PARADIGM OF METABOLIC PREVENTION ROLE FOR NUTRACEUTICALS

The paradigm utilizes concepts of phases in cancer induction recognizing that a genetic predisposition exists. In addition renewable cells are more prone to pathology. The predominate philosophy is treatment *after* recognition of the pathology at the high costs associated with high-tech-rescue medicine. Lifestyle practices, such as exposure to smoking and antioxidant dietary composition, can induce, accelerate or thwart partially or completely the initiation of the pathogenesis. Nutraceuticals function at the metabolic prevention level to block, inhibit or suppress promotion, thus thwarting pathogenesis and the cost of pathology and its consequences.

that our exposure to the environment, including smoking, and to various favorable and unfavorable diet components can be partially counterbalanced by our choice of lifestyle practices, such as consuming no less than five servings of fruit and vegetables per day and regular exercise. Thirdly, today's medical care system is devoted to the remediation of disease that is already pathological, and thus we experience a very costly practice of high-tech-rescue medicine. The fourth dimension encompasses the overlooked numerous metabolic steps in the transformation of normal cellular events into damaged events (e.g., oxidized or precancerous lesions), which nutraceuticals at the proper dose can block or suppress, or metabolically transform, thus setting the stage to prevent, or even revert pathology. The mechanisms of action of the various nutraceuticals may be one or several. For example, free radical scavenger and antioxidant

nutraceuticals can nullify damage by any number of biochemical mechanisms, but some also exert benefit by enhancing immune function. Table P.1 lists the broad classes of compounds that have nutraceutical activity, and there are very likely more classes of compounds that have nutraceutical activity. It is very likely there are many other nutraceutical components, as well as interactions, yet to be discovered.

TABLE P.1
PHYTOCHEMICALS: THE NEXT FRONTIER

Phytochemical Family	**Food Sources**
Allyl Sulfides	Onions, garlic, leeks, chives
Indoles	Cruciferous vegetables (broccoli, cabbage, kale, cauliflower)
Isoflavones	Soybeans (tofu, soy milk)
Isothiocyanates	Cruciferous vegetables
Phenolic Acids (ellagic acid, ferulic acid)	Tomatoes, citrus fruits, carrots, whole grains, nuts
Polyphenols	Green tea, grapes, wine
Saponins	Beans and legumes
Terpenes (perillyl alcohol, limonene)	Cherries, citrus fruit peel

A very conservative 1993 economic analysis of solely hospital care costs and the role that three nutrient antioxidants could exert on cardiovascular disease, breast cancer and cataracts is presented in Table P.2. It is common knowledge that billions of dollars are expended each year for hospital cost relating to breast, lung, stomach and other cancers, cardiovascular disease and cataracts. The study[1] considers the potential impact of only three antioxidants, namely vitamin C, vitamin E and beta carotene; the annual savings in hospital care costs alone would exceed 8 billion dollars. Expert public health physicians[2] believe that as much as 70% of disease is in fact preventable!

TABLE P.2
U.S. HOSPITALIZATION EXPENDITURES

	Total Expenditures ($ Mil)	Percentage Preventable from Increased Antioxidants (Vits. C,E, Beta-Carotene)	Estimated Medicare Cost Savings ($ Mil)	Estimated Total Savings ($ Mil)
Cancer				
Breast	1,088.3	16	27.4	174.1
Lung	3,263.7	21	125.4	685.4
Stomach	538.0	30	43.6	161.4
Cardiovascular Disease	30,823.7	25	1,500.0	7,705.9
Cataracts	98.5	50	7.1	49.3
TOTAL	35,812.3		1,676.6	8,776.1 Annual

Source: Pracon Inc. Economic Analysis (1993)

The papers in this symposium were organized to reveal the existing and emerging knowledge of the nutraceuticals found in garlic, soy and licorice. The lead paper discusses the epidemiological evidence, and the papers following present and discuss chemical or biochemical evidence at the cellular level; and some clinical data are presented.

I'm indebted to the late Dr. Herbert Peirson, who first headed up the Designer Foods Program for the National Cancer Institute and later had the courage and foresight to start a consulting business in this area. His suggestions as to relevant investigators were invaluable, as was his assistance in gaining funding to support the symposium/short course. He served as co-chair of the meeting and these proceedings which I have chosen to dedicate to his memory. We in turn are indebted to the authors who provided succinct texts of their presentations to serve as a status summary of the current state of the available knowledge.

A major conclusion of the overall effort is that the science is very incomplete, but that the findings to date have great promise. The problem is that marketing persons are trying to capitalize on the "promise" of the existing knowledge, but often to a degree that the existing data cannot support. In the interim, the consumer needs to increase their intakes of conventional fruits and

vegetables and some cereal grain products, but otherwise should "beware" of the false and misleading promises.

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CONTENTS

SECTION I

PERSPECTIVES

CHAPTER 1

PLANT FOODS IN DISEASE PREVENTION — STUDY OF PROCEDURE LESSONS FROM EASTERN VERSUS WESTERN DIET

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ABSTRACT

A synopsis is presented of two publications concerning disease prevention associated with plant food constituents. Human breast cancer is increasing worldwide. Total lifetime exposure to estrogen is a risk factor; 16 alpha hydroxyestrone increases tumor growth. Indole-2-carbinol and genestein promote an alternate favorable pathway to 2-hydroxyestrone. Natural products are evidently sources of potent anticarcinogens but require research.

Some Clues about Plant Foods in Disease Prevention

These remarks introduce reprints of two recent papers pertinent to the subject of opportunities for disease prevention through plant foods. Before presenting these papers, I want to recapitulate the theory that some portion of breast cancer today may be due to avoidable exposures to some xenoestrogenic materials, and that other xenoestrogenic materials, which are natural products and plant foods, may help to prevent breast cancer. This work has been developed with H. Leon Bradlow, of Cornell Medical Center, Mary Wolff of Mt. Sinai Medical Center, and other colleagues who are part of the Breast Cancer Prevention Collaborative Research Group (BCPCRG). The BCPCRG is an informal network of clinical, toxicologic, and epidemiologic researchers who

work chiefly on the Internet and by Fax to exchange late-breaking developments pertinent to the identification of avoidable causes of breast cancer.

Breast Cancer

Though breast cancer mortality has recently fallen in younger white women, mortality and incidence have risen substantially for African American women of all ages and for all women over 65 in the U.S. and U.K. Worldwide patterns also reveal growing breast cancer incidence and mortality. Geographic and time trend analysis provide an especially intriguing part of the breast cancer puzzle, and bolster the notion that a substantial portion of breast cancer should be avoidable. Women and men in Japan and Asia have rates of new cases and deaths from breast cancer that are consistently about five times lower than those in other industrial countries. Breast cancer mortality for women ages 45 to 84 in 15 major industrial countries from 1968 to 1986, grouped into six major global regions, rose between 0.2 and 2% annually. While rates are highest in U.K. and U.S., the fastest rate of growth is evident in East Asia and Eastern Europe, two regions where mammographic screening cannot generally be conducted. Thus, breast cancer deaths in all countries appear to be on the rise, growing most in regions where improved diagnostic technology does not play a role.

For breast cancer, and possibly other hormonally mediated cancers, such as testicular, prostate, and endometrium, the common factor which links most known risk factors is total lifetime exposure to estrogen. Based on epidemiologic studies and on previous experimental research that found that many of the same materials which increase breast tumor development in animals are also estrogenic, we have recently hypothesized that some breast cancer cases are due to avoidable environmental exposures that increase estrogen levels and alter overall metabolism. We have termed these materials "xenoestrogens." They include some organochlorine pesticides, pharmaceuticals, fuels, plastics, and natural products — all of which have been found to affect the amounts and types of estrogen produced.

Experimental studies on the ability of a wide variety of materials to affect estrogen production have been conducted for more than two decades in several medical laboratories. For breast and other hormonally mediated cancers, agents which affect the body's natural levels of estrogen may thereby affect the risk of breast cancer. With respect to PCBs, a number of isomers are anti--estrogenic, while others are potent estrogens. The picture is complex and incomplete, but clearly indicates that a number of widely used compounds affect estrogen production and metabolism and other hormonally mediated biologic activities.

We have hypothesized that two competing enzyme systems can alter metabolism of the 18-carbon estradiol by contending for two mutually exclusive pathways. Pathway I inserts a hydroxyl (OH•) radical at the 2-carbon position and yields the catechol estrogen 2-hydroxyestrone (2-OHE_1), a weakly anti-estrogenic metabolite. Pathway II adds an OH• at the 16 position and yields 16α-hydroxyestrone (16α-OHE_1); this creates a fully potent metabolite which increases tumor growth, DNA damage and cell proliferation. While many of the synthetic materials identified as xenoestrogens to date promote the cell proliferative pathway, several natural products, such as indole-2-carbinol and genistein, appear to promote the beneficial pathway. Studies underway in laboratories across the country will clarify the relative role of these materials in helping reduce the risk of recurrence in women with breast cancer, as well as in reducing the risk of the disease overall. David Zava and others have recently speculated that genistein and related compounds may work by keying into estrogen receptors, and blocking its activation by more potent estradiol. In fact, most xenoestrogens identified to date are thousands of times less potent than the body's own estradiol. But, materials such as genistein can occur with circulating levels that are thousands of times higher than those of the body's own estradiol, especially in Asian women whose diets are rich in soy products.

Papers Published

The first paper[1] reviews in vitro and in vivo evidence that a number of common natural products function as potent anticarcinogens. The second paper[2] assesses patterns of cancer in farmers as clues to preventable causes of the disease.

Both papers[1,2] present evidence that current patterns of cancer may be linked, in part, to avoidable exposures. We know that it is feasible to prevent cancer because the rates of the disease vary substantially, even within the industrial world. The rates of brain cancer, multiple myeloma, and breast cancer are all three to five times higher in the United States for males and females than in Japan. This variation in patterns between countries suggests that there are preventable factors.

Consider what is generally known about cancer. Genetics, which gets a lot of front-page coverage, explains, in some sense, all about cancer. But, only a small proportion of cancer is in fact inherited. Most cancer is acquired in a lifetime through interaction of normal genes with the environment, which obviously includes nutrition as a major component. We have to ask what in the environment interacts with the inherited genes that most people have to cause the development of cancer. Food, air, and water sustain life and are also critical components of the environment to which we are all exposed every day of our lives. This essential microenvironment contains both natural and synthetic carcinogens and anticarcinogens.

As to other major causes of cancer, smoking is the single most important preventable cause in industrial countries. Food is a very important factor, both in terms of preventing and causing cancer. Contamination with mycotoxins and fungal molds in the developing world is an important factor, which explains some of the high rates of esophageal, liver and stomach cancer that are endemic in parts of Asia and Africa.

Chemicals, as dusts and fumes, have been clearly characterized as important causes of cancer in highly exposed workers. Sexual practices are relevant to AIDS, but are also relevant to cervical cancer. Viruses, except for the AIDS virus, have not yet been identified as clear viral causes of human cancer, but have been implicated for stomach cancer, as well as cervix. And of course, radiation — both ionizing and non-ionizing — is important, as it can ionize cells and lead to direct mutations.

With my colleagues, David Hoel and Gregg Dinse, I published in 1994[3] a relevant article in the *Journal of the American Medical Association*. We found that baby-boomer males had three times higher rates of cancer not related to smoking than we estimate occurred for their grandfathers. Many of the tumors that have occurred at greater rates in these men, also have occurred more often in farmers; the latter are reviewed in reference number 2. And baby-boomer females have a 50% higher rate of new cases of cancer compared to their grandmothers. We took away the smoking-related cancers to do this analysis, as we wanted to see whether causes other than smoking appeared to be operating.

Taken together with the theory of xenoestrogens, these three publications provide evidence that some segment of cancer is preventable. Variations in cancer rates may very well be linked to parts of the environment, including foods as protective factors and as sources of contaminants. We have to ask what we control as a society that will reduce the risk of cancer? We all recognize that food policy is a vital part of preventative public health programs. In the past, ketchup was proposed as a vegetable in the school lunch program. New guidelines have been developed that provide for more consumption of fruits and vegetables, less consumption of salt and animal fat. Other ways to effect positive food policy changes will include programs or subsidies that we can change. Thus, beef is now graded as to fat content. And subsidies could be developed to reward those who produce healthier produce. Rather than subsidize and stockpile butter, we could develop economic incentives to encourage the production of more healthful crops, such as soy, and to discourage tobacco, which could prove quite valuable in advancing public health.

The rationale for pursuing opportunities to prevent cancer and other diseases grows stronger day by day. New cases of cancer in young persons continue to increase for reasons that are unclear. And rates of deaths from cancer have increased in persons over 65. Along with other efforts to promote

health and prevent disease, the development of foods rich in anticarcinogens could play a critical role in ensuring that fewer cases of cancer occur in the first place.

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CHAPTER 2

SAPONINS IN *ALLIUM* VEGETABLES

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ABSTRACT

The saponins of the genus Allium *have been little explored either chemically or biologically, possibly because of the intense interest in the more obvious classes of* Allium *compounds, the thiols and flavonoids. This brief survey demonstrates the chemical complexity of* Allium *saponins in an attempt to direct researchers' attention to this little recognized class of dietary compounds.*

INTRODUCTION

Allium species are among the most widely used of all of the flowering plants. Consider first that one or more members of this widespread genus are an integral component in almost every cuisine. As Table 2.1 shows, the most prominent members of the genus are recognized as foods by almost all of the races of man. A less commonly acknowledged, but almost as universal, fact is the use of these plants for a variety of medical conditions. In the United States this unacknowledged fact has developed into a large and lucrative but somewhat underground market. Though openly sold for "medical" uses, to the tune of millions of dollars per year, the Food and Drug Administration (FDA) has yet to sanction, or conduct a detailed investigation into the use of, any *Allium* product for any specific medical condition. This is unfortunate in view of the extensive peer-reviewed, yet highly variable, experimental/medical literature that surrounds these plants and the chemical compounds that they contain. In this brief review, we will examine in some detail the chemical, taxonomic and biological range of one of the minor classes of compounds that is found in these plants, namely, saponins. This class of compounds may hold the key to some of the medical claims and may explain the variability of the published results, since

different preparation protocols will either concentrate or remove them from the final product.

Allium Taxonomy

The genus *Allium*, in the family Amaryllidaceae, is a genus of perennial herbs usually with bulbous rootstocks. Their leaves are simple and more-or-less linear. There are some 300 defined species, many of which are human dietary components (see Table 2.1). Some are horticulturally ornamental. Only a small portion of the known species have been chemically examined.

TABLE 2.1
COMMONLY CONSUMED *ALLIUM* SPECIES

Species	Common name
Allium cepa	Onion
Allium sativum	Garlic
Allium ascalonium	Shallot
Allium ampelorasum	Leek
Allium fistulosum	Scallion
Allium schoenprasum	Chive

Allium Chemistry

The chemistry (and medicine) of alliums has been dominated by the various thiols that contribute most tellingly to the pungency of individual species. These recently reviewed compounds (Fig. 2.1a) provide the pronounced and distinctive odors to onions, garlic and their like.[1] Possibly because of high (olfactory) profile, they have been the subject of much investigation and have been shown to contribute to some of the recognized biology of the crude extracts of the plant material. Thus, compounds such as ajoene and allicin have been widely investigated and shown to be antitumor-promoter[2], antifungal[3], and anti-inflammatory, possibly due to an inhibition of phospholipase.[4] A second class of compounds that are present in many of these species, the flavonoids (Fig. 2.1b) are well known as antioxidants and anti-inflammatory compounds.[5] Their presence in some *Allium* species has recently been noted as onions may be the single biggest source of flavonoids in the human diet.[6]

Because of the prominence of the above two groups, it is at first surprising to recognize that saponins are commonly present throughout the genus, since saponins are generally assumed to be associated with toxicity or