Contributions of Ernst L. Wynder to chronic disease control worldwide and to preventive medicine

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Abstract

Ernst L. Wynder is internationally known for his important discoveries in the field of human chronic disease causation, that is the underlying mechanisms, studied in various animal models, as a foundation for recommendations on the prevention of these diseases. These include coronary heart disease, and the main human cancers including cancer of the lung, caused by traditional smoking habits, and the nutritionally linked cancers, namely cancer of the breast, prostate, colon, pancreas, and urinary bladder. Much of this research was performed in a chronic disease prevention institution—created by Dr. Wynder—the American Health Foundation. There were outreach programs to educate people about proper lifestyles to secure disease prevention, including beginning health education in children.

Keywords: Lung cancer; Tobacco; Nutritional habits; Causes of heart diseases; Breast cancer; Colon cancer; Prostate cancer; Prevention; International research; Japan; Italy.

After migrating from Germany, Ernst Wynder earned a B.A. degree from New York University in 1943. Upon graduation, Ernst Wynder served in the U.S. Army Intelligence Corps from 1943 to 1945. Upon discharge, he moved to St. Louis, MO, where he earned a Bachelor in Medical Science in 1950 and graduated from Washington University, St. Louis, with an M.D. degree, also in 1950.

During his studies in St. Louis, beginning in 1948, he asked the question about causes of lung cancer. At that time, the dogma had it that all cancers were caused by exposure to harmful chemicals. In contrast, Wynder discovered that 93% of the lung cancer cases in humans he studied were observed in traditional cigarette smokers. Thus, a major discovery in the field of cancer causation was made. A preliminary finding was presented at a meeting (Wynder and Graham, 1949). The definitive results were published in JAMA (Wynder and Graham, 1950), reprinted as a landmark article, Wynder and Graham, 1985).

At the time these discoveries were published in 1950, about 78% of American men were smokers, but only 3 or 4% of women were smokers. In contrast, about the year 2000, only 22% of men were regular smokers. Consequently, in the United States, the rate of lung cancer has dropped dramatically in men. However, Garfinkle and Stellman (1988) reported that there were more women smokers (28%), and their lung cancer incidence and mortality from cancer of the lung have increased sharply. Thus, lung cancer kills more women than the much feared breast cancer.

In addition to federal agencies, the U.S. Public Health Service, and the several Surgeon Generals Dr. Wynder frequently visited, he also convinced members of Congress to introduce legislation on chronic disease prevention. He influenced the smoking and health programs of the National Cancer Institute, National Institutes of Health, as well as private programs such as those of the American Cancer Society, and volunteer organizations like Action Smoking and Health, that encouraged recently the Chicago City Council to ban smoking in all workplaces, and the Council did so by voting 40 to 1 for this action. It was shown that passive inhalation was hazardous (Correa et al., 1983; Hirayama, 1981). Thus, research on smoking cessation provided a means to eliminate the risk of smoking (Kabat and Wynder, 1987; Wynder, 1992).

While smoking is decreasing in the United States, under the effective actions of Dr. Wynder, it is increasing in other areas of the world. It is expected that lung cancer rates in those areas will rise substantially, at great financial and personal cost.

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Some cancers of the lung can be cured by surgical removal of either the lung bearing the tumor, or at least part of the lung that is affected. Despite advances in therapy of many types of cancer, the therapy of lung cancer is still difficult. Yet, the individuals affected, their families, and even their doctors are making efforts to cure the patient. This leads to prolonged hospitalizations with the attendant high cost. Thus, smoking habits contribute in great part to the high cost of medical care (Kristen et al., 1977).

The fact that a “natural product,” tobacco, could cause cancer was the subject of reservations by many in cancer research. Thus, Dr. Wynder, with his colleague, Dr. D. Hoffmann whom he recruited from Professor Butenandi’s laboratory in Munich, Germany, conducted studies in mice to which they applied extract of tobacco smoke and discovered the formation of cancers at the point of application. This research paralleled the findings of a British laboratory, demonstrating that skin tumors developed in mice after applications of coal tar. Therefore, Wynder’s laboratory provided the evidence that there were carcinogens in tobacco tar, and hence in tobacco smoke. This work was performed at the Sloan-Kettering Institute in New York City. The leadership of this research center, mostly concerned with treatment methods of cancer at that time, was not enchanted with Wynder’s research. Therefore, he decided to leave and establish an independent research center, the American Health Foundation (AHF). His official title was President and Medical Director.

Initially, the research of the American Health Foundation was conducted in temporary quarters in New York City, in the neighborhood of the Memorial Cancer Center and Cornell University Medical School.

In addition to Dr. Hoffmann, Dr. Wynder recruited Dr. B. S. Reddy from the Lobund Laboratory, part of Notre Dame University. Dr. Reddy was trained in the field of colon cancer research, under the direction of Dr. Morris Pollard. Dr. Wynder realized that colon cancer was a major disease in the United States and the Western world, and he thought that the American Health Foundation should be concerned with research on other important diseases, in addition to lung cancer (Reddy et al., 1980).

With the expansion of the staff, Dr. Wynder recruited Dr. John H. Weisburger, a U.S. Public Health Officer, serving at the U.S. National Cancer Institute. Dr. Weisburger assumed responsibility for research in the new American Health Foundation, as Vice President for Research. With further recruitment and enlargement of the staff to perform research on the causation and prevention of major chronic diseases, both tobacco-related and nutritionally linked, Dr. Wynder convinced Mrs. Eleanor Naylor Dana, the wealthy widow of Mr. Charles A. Dana to provide major funding for a new research facility to be located on the campus of the Westchester Medical Center and New York Medical College. The entire staff then moved to this new facility in the Spring of 1974. Dr. Wynder persuaded Westchester County and the Medical Center, located there, to name the road adjoining the building for AHF research, Dana Road, in honor of the Dana family.

Wynder’s original findings that lung cancer was induced by tobacco smoke in humans and confirmed in animal models was the basis for new research on the mechanisms of action of tobacco smoke. Under the leadership of Dr. D. Hoffmann, a chemist, painstaking experiments were performed to isolate and identify the chemicals that might be associated with cancer causation. Initially, they found a series of polycyclic aromatic hydrocarbons, in part similar to those in coal tar. A major discovery was made in 1977 by Dr. Hoffmann’s team, that now included Dr. S. Hecht, Dr. K. El-Bayoumy, and others, that tobacco tar contained nicotine-derived, tobacco-specific nitrosamines. These were powerful carcinogens upon exposure of mice, hamsters, and rats. It would seem that these tobacco-associated nitrosamines would account for a sizable number of lung cancers in humans, in addition to the polycyclic hydrocarbons (Hoffmann and Hecht, 1985; Hoffmann et al., 1977; Hecht et al., 1993). The tobacco-specific nitrosamines induced not only lung cancer, but also other cancers such as in the pancreas (Rivenson et al., 1988).

Smokers of cigarettes are also at a higher risk of coronary heart disease, especially in the Western world, where the agents from cigarettes combined with nutritional factors, and, especially, reactive oxygen species associated with smoking (Taioli et al., 1991; Walter et al., 1988). This research, using the techniques of metabolic epidemiology, was extended to determine the plasma cholesterol levels of 6850 children, as part of the “Know Your Body” screening program (Resnicow et al., 1989a); see later a discussion of the “Know Your Body” research activities.

Successes from the laboratory of Dr. Reddy in colon cancer research led to the recruitment of other scientists to study what is now known as nutritionally linked factors for breast, prostate, ovary, and pancreas cancers. Patients with pancreatic cancer displayed a higher incidence in smokers, compared to non-smokers, which suggested that both nutritional habits and smoking combined to account for this higher risk.

Dr. Wynder was also interested in the decline of fatal stomach cancer in the United States since the 1920s. The laboratory of Dr. Weisburger also became concerned with this unexpected decline of a major cancer. He collaborated with Dr. Wynder, and they discovered that, with the introduction of refrigerated food storage, the previously needed salting and pickling for food preservation could be eliminated. Therefore, they concluded that the intake of salted and pickled food might well be a cause of stomach cancer (Howson et al., 1986). Incidentally, Professors Joossens and Kesteloot from Leuven, Belgium, had demonstrated this mechanism for stomach cancer occurrence at about that time.

In addition to the laboratory center called the Naylor Dana Institute for Disease Prevention, in honor of Mrs. Dana who provided much of the funding to construct this center, Dr. Wynder maintained laboratories in New York City for clinical investigations and attempts to change people’s lifestyles. For example, there were smoking withdrawal clinics and nutrition education activities for adults and also for children. Dr. Wynder emphasized that poor lifestyle habits, especially nutritional patterns, developed early in life, and thus children should
become acquainted with healthy lifestyles. He recruited Christine Williams, M.D., to direct these programs called "Know Your Body," or KYB (Resnicow et al., 1989b; Williams et al., 1980). Also, he created the WIN (Women’s Intervention Nutrition Study), a program to educate adult women about proper lifestyles for chronic disease prevention with emphasis on breast cancer. A recent report demonstrated the validity of this approach (Chlebowski et al., 1993). Participants regularly received a WIN newsletter. A Clinical Nutrition Research Unit (CNRU) was developed through the leadership of Dr. Rivlin, and under the auspices of the American Health Foundation, Memorial Sloan-Kettering Cancer Center, Weill Medical College of Cornell University, the Rockefeller University and its Strang Cancer Prevention Center, and, in Westchester County, the Medical Center and New York Medical College. For males, a similar program (PINS) was established for the prevention of prostate cancer.

In addition to smoking-related diseases, Dr. Wynder felt that the Institute should also study the main chronic diseases associated with nutritional habits. Like Dr. Weishburger, who trained at the NCI with his mentors, Dr. Harold Stewart and Dr. Michael Shimkin, in the field of geographic pathology, Dr. Wynder shared these views. Thus, the staff of the Institute, such as Dr. Reddy, an expert in colon cancer, developed research programs on nutrition-associated diseases including breast cancer, pancreas cancer, and prostate cancer, mostly funded by the National Cancer Institute, NIH, in Bethesda, Maryland (Reddy et al., 1980; Rose et al., 1986; Parkin et al., 1999; Greenwald et al., 2001). These types of neoplasms showed vastly different incidence rates across the world (Greenwald et al., 2001; Parkin et al., 1999). They were high in North America, Ireland, and Great Britain, as well as in the other Anglo Saxon countries. They were low in Asia, such as Japan and China. A low rate also prevailed in most of India, but an exception was the Parsi population in Western India. Israel was an interesting area for study. Indeed, in Israel, there are the Ashkenazi Jews, mostly from Europe, who had a high incidence of the Western diseases. In contrast, the Sephardic Jews, from North Africa and Ethiopia, had a low incidence, because they consumed a low fat, high fiber diet. An obvious conclusion stemming from these contrasting occurrences indicates that the "environment" often alleged to relate to cancer risk is not likely to be responsible for these cancers. In fact, Israel is a small country, and the environment is identical throughout Israel. It can be concluded that personal lifestyle habits such as nutritional and smoking traditions played a major role in the occurrence of these types of cancers, and indeed also of the risk of coronary heart disease.

Another example of systematic studies in geographic pathology was the case of Finland, where the population displayed a high incidence of heart disease, but, in contrast, they had a low rate of breast and colon cancer. Research by Dr. Wynder, Dr. Reddy, and staff (Reddy et al., 1978) demonstrated that the fat and protein intake in populations of Kupio, in rural Finland, was similar to that in the New York reference group. However, in Kupio, people consumed much more cereal and bread, such as Finnish rye bread, which is rich in bran cereal fiber. Consequently, this led to an increased stool bulk, diluting bile acids which were demonstrated in separate research to promote colon cancer and to favor the excretion of estrogen glucuronides. Both of these factors account for the decreased rate of breast and distal colon cancer. In conclusion, this research by Wynder’s group demonstrated the importance of consuming cereals and breads high in fiber, leading to a large stool bulk, and to the excretion of products that would have adverse effects on colon and breast tissues.

The decline of stomach cancer was discussed above. This disease used to have a high incidence in Japan, due to the fact that eating and cooking traditions in Japan involved as much as 30g of salt and pickled foods per day. In 1982, at the time Mr. Nakasone was Prime Minister, the President of the National Cancer Center, Professor Takashi Sugimura, was asked to meet with the Prime Minister on a monthly basis. Sugimura explained to the Prime Minister that the high rate of gastric cancer in Japan was associated with the high daily salt intake, a view shared by Dr. Weishburger and Dr. Wynder. Thus, a 10-year plan to progressively reduce the salt intake of the Japanese people was implemented. The program continues currently, and gastric cancer in Japan displays lower rates. This plan was continued for another 10 years and in 2002, it was still in progress. The data suggest that the daily intake of salt in Japan is now less than 10g a day. In the United States, about 3–4g of salt are currently used, and educational efforts are under way to lower it still somewhat more, to the range of about 2g per day. In Japan, the decreased salt intake has been reflected in reduced incidence of stomach cancer and of the related high blood pressure. Regrettably, as documented by collaborators of Dr. Wynder, at the Aichi Cancer Center in Nagoya, Japan, many of the young Japanese people began to eat Western style, with a progressive increased rate of the types of chronic diseases prevalent in North America.

This writer is not aware of which measures are being taken in this regard in China. It is known that, in this large country, different provinces and distinct populations display considerably diverse eating habits. As is true in Japan, there is a tendency to switch to Western food habits, with the introduction of inexpensive fast food restaurants. Consequently, there is a trend in China, as is true in Japan, toward an increase of the chronic diseases, such as coronary heart disease, and the types of cancers discussed above.

Geographic pathology also led to research, together with Italian collaborators, on the role of the Mediterranean lifestyle on health including heart disease and the Western nutritionally linked cancers (Chan et al., 1977; Cohen and Wynder, 1990; Rose et al., 1986). Indeed, in Italy and particularly in Southern Italy, the rate of heart disease and of cancers of the breast, prostate, pancreas, and colon was lower than in North America or in Northern Italy, Germany, and France. Investigation showed that the Italian population used exclusively olive oil. Laboratory studies under the direction of Dr. Wynder at the Valhalla research center showed that rats given a colon or mammary gland carcinogen and fed various oils, demonstrated that when they were on olive oil, a monounsaturated fat, compared to the omega 6-polyunsaturated oils, they had a much lower rate of these cancers (Chan et al., 1977; Cohen and
Wynder, 1990). Therefore, one explanation for the lower rate in Southern Italy was the type of fat used. In addition, the Italians consumed many more vegetables and fruits. The main meat used was veal that was not heavily fried or browned. We found that typically used meats in North America were beef that upon browning, displayed a new class of chemicals, heterocyclic amines. This type of compound was discovered originally in the laboratory of Professor T. Sugimura (Nagao and Sugimura, 2000). We found that these kinds of compounds could induce cancer of the colon and of the mammary gland in animal models. Also, the laboratory of Dr. Ito and Dr. Shirai in Nagoya (Shirai et al., 1997) extended these findings to cancer of the prostate as well as mammary gland and pancreas, as we had demonstrated. Therefore, the findings at the American Health Foundation in the United States, in Japan, and in Italy, showed that specific eating habits can lead to major types of cancer. In addition, these international studies showed that regular exercise, at any age, was beneficial in lowering the risk of the major chronic diseases.

Studies in Italy also demonstrated that extensive intake of cooked tomatoes lowered the rate of prostate cancer. At the American Health Foundation, systematic studies on vegetables, such as cooked tomatoes and broccoli, showed that these were chemopreventive agents for various types of cancer, accounting for the findings in Italy (Taioli et al., 1991). A symposium on this topic was held at the American Health Foundation.

Furthermore, in the context of eating habits, the staff under Dr. Weisburger’s leadership examined the role of beverages. He and the laboratory of Dr. F.-L. Chung, found that black and green tea blocked the formation of cancers at various significant sites and determined the mechanisms of action of these beverages. They organized a symposium on tea at the Manhattan facilities of the American Health Foundation. The resulting manuscripts were published in Preventive Medicine, in May and July 1992.

Dr. Wynder traveled to Washington, DC, frequently and interacted with the staff at the National Cancer Institute and the NIH, as well as with members of Congress. Dr. Wynder’s convincing arguments led to the introduction of legislation, mainly by Senators Hatch and McGovern, to amend the U.S. Public Health Service Act to emphasize prevention, mediated by establishing the position of an Assistant Director for Prevention at the NIH.

The American Health Foundation declared that “February is National Cancer Prevention Month,” Preventive Medicine (2004), 38, 250. Also, occasional pamphlets for the public were published, such as “High Cholesterol, a risk you can live without” or “Looking good, feeling great, ten ways to a longer, healthier life.”

At the time Dr. Wynder recruited Dr. Weisburger, he simply asked the question: What about a journal? Dr. Weisburger had been Chairman of the Board of Publications of the Society of Toxicology, and, as such, he had been working with Dr. James Barsky, Vice President, Academic Press for journals. A short telephone call by Dr. Wynder to Dr. Barsky led to this preliminary approval of a new journal, that was to be called Preventive Medicine, the journal currently edited by Dr. Alfredo Morabia, who years ago was an international research fellow in Dr. Wynder’s laboratory.

Dr. Wynder published an editorial in this journal entitled “Preventive Medicine: A Reaffirmation.” It concluded “it was clear in 1972, and it is clear today, that the most effective medicine is preventive medicine”; Wynder, E.L. 1988, Preventive Medicine, 17, 774–775.

Dr. Wynder was honored by professional societies in many parts of the world. He was featured on the front cover of Cancer Research a number of times, as was the staff of the American Health Foundation.

Dr. Wynder’s pleasure consisted in performing research and constructing facilities for staff to develop the field of preventive medicine. Despite his busy life, he fell in love with Sandra Miller, and they were married in 1991.

Ernst Wynder died on July 14, 1999, at the age of 77. He was buried in a cemetery in Valhalla, NY, near the Research Center he created in 1975.

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References


