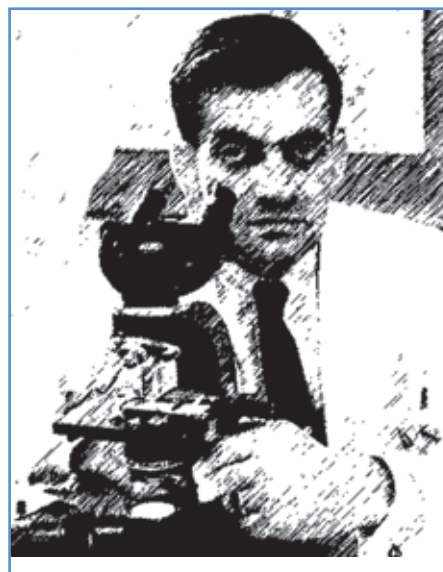


Public Health and Medical Humanities History Corner

Ernst L. Wynder: A pioneer of no tobacco world



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ABSTRACT

Ernst L Wynder was a great epidemiologist who devoted his career to investigate harmful effects of tobacco smoke, in particular his studies represent a landmark in the history of epidemiological research on lung cancer.

The commitment of Ernst Wynder was not limited to the risk factors related to tobacco. In fact, he studied also the role of nutritional factors in the incidence of tumors.

His talent, enthusiasm and tireless energy have allowed him to obtain a complete victory despite the difficulties and the initial loneliness.

“Of those who not accept existing evidence, I should like to know what evidence would be acceptable. If one criticizes epidemiology for being statistical, if one criticizes animal research for being unrelated to the human problem and if one criticizes chemical identification of carcinogens as not having any bearing to the human disease, I should like to ask if there is a form of evidence that would be accepted as being conclusive. If were humanly possible we would at once set up a study that could yield such evidence. If it is humanly impossible, it is not a constructive kind of suggestion, that would advance scientific knowledge”.

E.L. Wynder, NEJM, 264:1240 (1961)

Ernst L. Wynder was born in Herford, Germany, on April 30, 1923. His family, like many others, was forced to flee as a result of Nazi persecution. The racist madness of the Third Reich led many illustrious minds of his time to enrich the scientific landscape of other countries. In our section we have already encountered the forced migration, for example, in the similar history of Alessandro Seppilli [1]. Wynder came to the U.S. with his parents and his sister in 1938 and in 1943 became an American citizen. His refined wit and perfect knowledge of German led him back in Germany as intelligence officer of the United States Army from 1943 to 1945. When the war ended, he decided to follow his father's footsteps in the medical career. So he began to study medicine at Washington University in St. Louis, Missouri, with the famous thoracic surgeon Evarts A. Graham.

The starting point of his research is now recognized in 1948, while he was working as a summer student at New York University. He took part in an autopsy of a lung cancer patient (42 years old), smoker of two packs of cigarettes per day for many years. He decided to methodically gather information about him and his family. Then Wynder devised a questionnaire and interviewed some patients with and without lung cancer. Thus an epidemiological study was born and it was soon evident a correlation between cigarette smoking and lung cancer [2]. It was not the first time someone questioned the harmful effects of tobacco smoke. Previously in 1645 Giovanni Giacomo Cuffari, a doctor of Palermo, Sicily [2], wrote a booklet in which he stated that tobacco use is harmful and deadly, even without symptoms at the beginning. Cuffari hoped that this habit would end and described his observations (brain damage, left heart disease and a "black thing near the diaphragm", likely lung cancer).

In Italy, much later, in 1906, an article by Domenico Mocchi, of the Royal College of Obstetrics in Milan [2] drew attention to the harmful effect of exposure to tobacco during pregnancy, highlighting the increased risk of miscarriages and stillbirths among women who worked in the cigar manufacture. Mocchi also introduced the topic to the International Congress for Diseases of Labour, in Milan, June 9-14, 1906 [2].

Indeed in many countries and at different times tobacco use was considered harmful. To limit ourselves to the physicians observations, Samuel Thomas von Soemmering, the famous German anatomist who discovered the retinal macula in the human body in 1795, Christoph Wilhelm Hufeland, doctor of Goethe and member of the Royal Prussian Academy of Sciences in Berlin in 1798 and Robert Abbe, pioneer of radiology in the United States in 1915 [2] expressed great concern about the use of tobacco in their time.

When Ernst Wynder returned to Washington University, persuaded Evarts Graham to allow him to continue the research with Graham's patients. Eventually, with the help of Graham, Wynder obtained a scholarship from the American Cancer Society, to complete his studies.

In 1950, after collecting data and histories of 684 cases of lung cancer, Wynder and Graham published their study in JAMA in an article that is now considered a landmark in the history of epidemiological research on lung cancer. They concluded that "the excessive and prolonged use of tobacco, especially through the cigarette smoke, seems to be an important factor in the induction of bronchogenic cancer" [3]. Since that time, Wynder devoted himself tirelessly to study the causes of cancer and, by his great talent as a communicator, he hardly worked to persuade people to move away from tobacco to protect their own health.

Wynder also worked at Sloan-Kettering Institute for Cancer Research in New York. One of the great merits of Ernst Wynder was to seek support for the hypothesis that smoking is a major cause of cancer. He realized that it was necessary to combine epidemiology with biology, chemistry and biochemistry

to demonstrate smoking-related carcinogenesis. So he initiated important collaborations. In addition to his mentor Graham, he invited researchers with various skills to collaborate with him, including Dietrich Hoffmann, from German Max Planck Institute and Stephen Hecht. Together with his younger colleagues, Wynder constituted a formidable team that studied the origin of tumors for 40 years. They identified, for the first time, carcinogen benzo-(a)-pyrene and other polycyclic aromatic hydrocarbons present in tar. In 1959 the Wynder's team enjoyed strong support by the great statistical Jerome Cornfield, a prestigious researcher, who from 1947 was part of a group that provided advice to the National Institutes of Health (NIH). The question that the researchers of the NIH had addressed was: why do so many people die for lung cancer in 1950, but 50 years before there have been so few reported cases? Several explanations were possible: the improvement of the diagnostic method, increased industrial pollution, increased life span of the population. Among the possible explanations there was also an increase in tobacco smoke. The retrospective case-control studies of Richard Doll and Bradford Hill in the UK had linked lung cancer to cigarette smoke, but Cornfield wanted a strong conclusion, not a simple correlation but a definite cause-effect relationship. Cornfield was a formidable statistical convinced user of Bayesian rules to assess the risk that a smoker will develop lung cancer. Using Bayes' rule, he was able to combine the results of Doll and Hill with data from the NIH. The result of his research was that smokers are many times more likely to develop lung cancer than non-smokers and about this topic he published a landmark article in the Journal of the National Cancer Institute [4].

Cornfield was initially lonely and hindered in his battle against tobacco. The influential Sir Ronald Fisher (great smoker, consultant paid by the tobacco industry, fervent anti-Bayesian) was against him. But Cornfield, with the same determination of Wynder, successfully defended his methods and results. From this moment, very few people with any serious knowledge of the subject did not agree on the identification of smoking as a cause of cancer. The causality of the relationship, however, was not accepted in a uniform manner and the tobacco industry still managed for years to prevent serious action against tobacco smoke.

OBSTACLES

In the summer of 1961, Wynder and Clarence Cook Little, his teacher on the genetics of cancer, had a public debate on the pages of the New England Journal of Medicine. The debate, however, was presented by an editorial rather lukewarm, which ended with the formula "the search for truth continues". But the truth had already been found and the major researchers in this field knew it well! The cautious attitude of a prestigious magazine as NEJM shows how the tobacco industry power frightened people at the time and difficulty of the work of Ernst Wynder.

The situation deteriorated further the following year. The new director of the Sloan-Kettering, Frank Horsfall, said that Wynder's conclusions about the causal relationship between smoking and lung cancer were irresponsible and that all future publications from his research group would have to be forbidden. Wynder replied, with a good sense of humor, describing the new hostile director in a meeting: "I first met Dr. Frank Horsfall a few months later at a cocktail party, he had a drink in one hand and a cigarette in the other, and he told me that he did not believe in my work relative to smoking and lung cancer" [5].

Only Peyton Rous, a distinguished scientist at Rockefeller University and member of the Board of Foundation of the Sloan-Kettering Institute, helped Wynder, declaring immediately that he would propose the issue of censorship

at the Board. The censorship was withdrawn but funding for the section of epidemiology and associated laboratories was gradually reduced.

So in 1969 Wynder decided that his future research would have to take place elsewhere.

So Wynder turned to the National Cancer Institute and the American Cancer Society, which obtained funds from trusts and private benefactors. The new center for research was therefore the American Health Foundation and Wynder became medical director and president.

The well-equipped laboratories and a team of valid epidemiologists enabled important discoveries, including the carcinogenic tobacco-specific nitrosamines. The nitrosamines were detected not only in tobacco smoke but also in chewing tobacco. This finding provided an explanation for the carcinogenicity of tobacco quids and smoking-related pancreatic and esophageal cancers.

During the following 30 years, Wynder tirelessly continued his epidemiological studies. His maxim was: "My lab is the world". But he also continued a strong defence by tobacco companies. A new area of discussion was the theory of the "safe cigarette" and that of "less harmful" and therefore acceptable cigarette.

The carcinogenicity of tar provided by Wynder led industries to pursue the path of the "safe cigarette" by removing a sufficient amount of smoke tar through the use of lighter tobacco and by a filter inserted by the manufacturer at the height of cigarettes. What could be the acceptable limit of tar? Wynder himself stated that a filter able to stop 40% of the tar would be a step in the right direction and would have favoured a significant reduction in the risk of cancer.

In 1978 the National Cancer Institute Task Force "The Less Hazardous Cigarette Working Group", after a 10 years research (since 1969) to find a cigarette able to reduce the risk of death, defined a "socially tolerable" limit of 20 mg tar and 1 mg of nicotine per cigarette. The publication of this theory led smokers to buy cigarettes with lower tar with an increase of sales in 1979 by 50%. But the anti-tobacco movement stated that these conclusion have brought the fight against cigarette smoke back many years. It argued, rightly, that smokers of lighter cigarettes compensated for the decrease in nicotine and tar consuming a greater number of cigarettes by inhaling the smoke more deeply and smoking a cigarette down to the filter. It was finally the good time to validate the idea of Wynder also in the public debate: the only cigarette "safe" is the non-cigarette!

ERNST WYNDER: ALSO A PUBLIC HEALTH LEADER

Wynder didn't only study the risk factors related to tobacco. He extended his interest to the study of nutritional factors associated with the incidence of tumors, such as the relationship between low consumption of saturated fat and low incidence of myocardial infarction and breast cancer, or between high consumption of fibers and low incidence of colon cancer. Wynder found that 80 to 95% of cases of cancer and various other chronic diseases were related to bad behavior and therefore avoidable. He was confident, for example, that a diet with low fat and wide use of the fiber, which has been proven effective in laboratory tests, would

prevent a second primary breast cancer in women with breast cancer.

Wynder was really a protagonist also in Public Health. He considered the prevention of major chronic diseases, especially cancers related to tobacco and nutrition, as a Public Health priority and founded the Journal of Preventive Medicine. Wynder was tireless in his efforts to convince politicians to take the necessary measures to reduce tobacco smoking and to involve the food industry in promoting healthy nutrition. For this purpose he founded the American Health Foundation in New York. He was also a firm believer in the importance

of Health Education. The social impact of cancer and its relationship with tobacco use and diet, as well as the low rate of success of many methods of intervention, convinced him that Health Education was the only way to stop the epidemic of cancer related to tobacco use and unhealthy diet. He therefore devised programs for school as "Know Your Body" to promote a better lifestyle since childhood. Wynder believed that each school needed a teacher specifically responsible for good health practice, and that the habits consciously adopted in childhood can last all life long.

His formidable personality hindered collaboration with some important epidemiologists, but his group were faithful and Wynder earned a record of 770 publications that describe the epidemiology of cancer in the world in relation to risk factors, including tobacco, nutrition and other environmental influences, as well as laboratory studies, strategies for prevention and health policies. Many people call Ernst Wynder "the conscience of the nation's health" because of his incessant incitement to government authorities and social institutions to engage in prevention of chronic diseases and health promotion [6].

REFLECTIONS

Only Wynder's enthusiasm, his tireless energy, communication skills and innate entrepreneurial spirit have allowed him to obtain a complete victory.

Wynder himself offers significant insights on his great scientific adventure [5]. His reflections didn't spare anyone. Wynder affirmed that the most part of doctors felt more important to be healers of disease than prevent disease. The journalists, because the interests of the tobacco industry influenced the articles of many of them and the media, were reluctant to do anything against their best advertisers. Also Wynder sustained that the interests of the tobacco lobby in the U.S. Congress and concerns on national and state tobacco taxes have blocked legislation until the beginning of 90s. Perhaps, recognized Wynder, part of the problem was that doctors had generally a critical opinion of epidemiology. In fact for a long time they considered that the statistical correlation did not feel enough of the causation. As late as 1997, the New York Times celebrated the figure of the pathologist Oscar Auerbach by the words of Lawrence Garfinkel who celebrated Auerbach research methods and explained that "many physicians, policymakers and smokers took his findings more seriously than earlier reports of a smoking-cancer link" (a man "who could look at 2 000 slides a day, when others were looking at 200 a day. One Auerbach's paper was based on 22 000 slides, about 50 slides from each patient"). It is clear that this way of conceiving the research is far from benevolent towards the epidemiology and biostatistics!

But Wynder also revealed an interesting backstory. In a letter dated January 8 1997 he asked Sir Richard Doll to express his view on why the health professionals didn't sustain his work on risk factors of lung cancer in 1950 [7]. Doll replied, on January 13 1997, with typical British humor: "I think the skeptical reaction of doctors occurred in part because they smoke and partly because they are not accustomed to the interpretation of epidemiological data and tended to judge the causality from Koch's postulates". When they were called as government advisers physicians showed a pathological fear to spread cancer phobia in the population, and refused to recognize the urgency to plan initiatives for early diagnosis. At the same time government was worried about the effects of the reduction of sales tax income. The desire to work with the tobacco industry prevailed on the need to speak out against it.

The correspondence between two great epidemiologists continued again

and from it emerged a common belief: the consensus among experts was not sufficient to create actions. To produce checks and preventive actions to protect people's health, a joint action between experts, government, media and educators was necessary. Wynder has strongly criticized the tobacco industries because since 1950 they were aware that smoking was the leading cause of major types of cancer in men and women and that adversely affected a number of diseases, including the myocardial infarction and emphysema.

Before then, in 1975 Renato Dulbecco in his Nobel Lecture made a strong attack to the role of tobacco in the field of cancer: "according to epidemiological evidence tobacco smoke is the agent of lung cancer in man, which in Britain is responsible for one in eight of all male deaths. Yet only mild sanctions have been imposed on tobacco products, such as a vague health warning on cigarette packets, which sounds rather like an official endorsement. Any limitation on the use of tobacco is left to the individual, although it is clear that the individual cannot easily exercise voluntary restraint in the face of very effective advertisements, especially as he does not usually appreciate the danger of a cumulative action over a long period of time" [8].

Ernst Wynder concluded bitterly that few men are favourable to be actively involved in a dispute, especially if the opponent is strong. It is part of human nature but it also caused that anyone who struggled to prove that smoking causes cancer, was often alone. We hope that this research gladiator could be an example for young scientists when they discover a strong evidence of risk and are called to fight an unpopular battle against a very strong enemy. They must remember what Ernst Wynder has left us, as a testimony of life and as personal conviction: "What has always attracted me to science is that when the evidence is strong, it will, in due time, be accepted because scientific truth in the long time always triumphs! Importantly, in public health issues that affect millions of people, scientists have a moral obligation to be involved proactively".

Ernst Ludwig Wynder died on July 14, 1999, for thyroid cancer. The legacy of Ernst Wynder as a pioneer of the prevention of multifactorial diseases is a precious gift for future generations.

In fact during the last years, in particular, a growing interest on prevention tobacco smoking involved several countries. In the United States a strategic action plan to improve the tobacco prevention and control reducing the burden of tobacco dependence has been developed [9]. This plan aims to reduce the adult smoking rate to 12% meeting the *Healthy People* objective [10]. *The Healthy Weight 2010* objective is to reduce adult smoking to 12 percent. *The Healthy Weight 2020* objectives are still in draft form, but this tobacco use objective will likely remain unchanged [10].

On June 22 2009, president Barack Obama signed a law to regulate tobacco product to protect the public health: "Our work to protect our children and improve the public's health is not complete. Today, tobacco is the leading preventable cause of death not just in America, but also in the world."

Elaborazione grafica dell'immagine a cura di Alice Mannocci

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