

Milestones... in Investigative Pathology

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Whistleblowers of the 1950s: Epidemiologists and the Association between Cigarette Smoking and Increased Risk of Lung Carcinoma

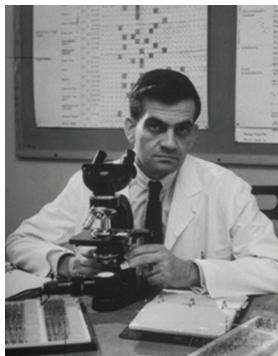


Figure 1: Dr. Ernst Ludwig Wynder
Wynder
(http://www.allposters.com/-sp/Cancer-Specialist-Dr-Ernest-L-Wynder-at-Microscope-in-His-Office-Posters_i5282512_.html)



Figure 2: Sir Richard Doll
(<https://www.ctsu.ox.ac.uk/researchers/richard-doll-biography>)

Wynder EL and Graham EA:
Tobacco Smoking as a Possible
Etiologic Factor in Bronchiogenic
Carcinoma: A Study of Six
Hundred and Eighty-Four Cases.
JAMA 1950, 143:329.

Doll R and Hill AB: Smoking and
Carcinoma of the Lung:
Preliminary Report. Br Med J
1950, 2:739-48.

As you review your slides to find yet another new case of lung primary squamous cell carcinoma or small cell carcinoma, you may ask yourself if you are being passively complicit in an epidemic of disease caused by carcinogenic-rich dusts from inhaled tobacco smoke from cheap, high-quality commercial cigarettes. We physicians and scientists are so used to treating problems and putting out fires that perhaps we have become desensitized to the notion that somebody else might be creating some of these problems, and that identification and elimination of certain etiologic

agents might prevent certain diseases. This **Milestones** article features the 1950 publications of Wynder/Graham¹ and Doll/Hill², which present sound data pointing to inhaled cigarette smoke as the etiology of most primary lung carcinomas. A previous *ASIP Pathways Milestones* article³ by the first **Milestones** editor, **Richard G. Lynch**, was published in 2003 and featured the 1957 publications of **Oscar Auerbach** and his colleagues^{4,5}.

Tobacco smoking in pipes had been associated with lip and oral cavity carcinoma in the 19th century⁶. The elucidation of cigarette smoking's association with lung carcinomas was confounded by non-specific plain film lung radiographs (tuberculosis was common), high frequency of smoking in men, infrequency of lung carcinoma, and the lag time for development of lung carcinoma in smokers⁶. Now is a

good time to discuss preventable cigarette smoke-associated lung carcinomas, as we recognize the 100th anniversary of packaged cigarettes (**RJ Reynolds'** 'Camel' brand, Oct 1913⁷). Commercial cigarettes have caused an epidemic of death and disability due to primary medical and surgical diseases of lung, arterial tree, gut, and bladder, as well as secondary diseases in affiliated non-smokers. A combination of commercial profitability, willing government subsidization, lax public health oversight, wide legal moats, addictive components in the commercial product, and individual users' willingness to downplay the inherent risk of cigarette smoking, has led to this 100-year epidemic of acquired, preventable diseases.

Mortality due to primary lung carcinoma in men in the United States (US) in 1950 was about 20 per 100,000, at the time representing a 30-fold increase during the first half of the 20th century. The increased mortality rate due to lung carcinoma was recognized early in the 20th century (e.g. Adler⁸), with subsequent discussion of multiple potential etiologies, including air pollution, insecticides, arsenic, and 'irritants' in cigarette smoke⁶. The sound statistical associations between cigarette smoking and increased risk of lung carcinoma were detailed in the 1950 by Drs. Wynder and Graham from the US¹, and by Drs. Doll and Hill from the United Kingdom². These statistical associations led to subsequent studies over the last 65 years that have dissected the step-wise morphologic and molecular pathogenesis of small cell and non-small cell lung carcinoma due to cigarette smoke. 100 years after the introduction of 'Camel,' although the biomedical research community understands much about the pathogenesis of tobacco-associated diseases, we still have not developed effective programs to extinguish the morbid and mortal diseases that are associated with inhalation of cigarette smoke.

The whistle-blowers of this preventable epidemic were **Ernest Wynder** and his chest surgeon collaborator, **Evarts Graham**, and epidemiologists **Richard Doll** and **A. Bradford Hill**. The challenge was to collect and analyze data sufficient to demonstrate a difference in lung carcinoma incidence between smokers and non-smokers at a time when >50% of men in these countries smoked.

Before Wynder, Doll, and Auerbach, there were Henle and his protégé Koch, the anatomist and microbiologist who articulated the logical principles behind demonstration of causality in bacterial infectious disease ("Koch's postulates⁹"), namely:

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- 1) The presumptive etiologic agent would be present in every case of the disease.
- 2) The agent would not occur in other diseases as a non-pathogen.
- 3) The agent can be purified.
- 4) The purified agent can induce the disease anew.

Strict adherence to these Henle/Koch guidelines makes sense for culturable agents like *Streptococcus pyogenes* and *Mycobacterium tuberculosis*, but it is a problem to apply these criteria to putative etiologic agents in neoplastic diseases. The papers by Wynder/Graham¹ and Doll/Hill² associated increased cigarette smoke exposure with increased risk of lung carcinoma, but multiple discoveries (DNA crystal structure, organic chemistry of cigarette smoke, DNA replication chemistry, DNA repair chemistry, DNA codon-to-amino acid translation rules, cytogenetics, distortion of signaling biochemistry by mutations of oncogenes and tumor suppressor genes, immunohistochemistry, DNA sequencing chemistry, DNA methylation measurement, copy number variation measurement, mRNA cluster analysis), were subsequently required to define the etiologic agents in the cigarette smoke, and the step-wise pathogenesis of the different types of lung carcinomas.

Alfred Evans summarized the challenges to strict interpretation of the Henle/Koch postulates as they relate to determination of etiologic agents in viral and non-infectious diseases in the Thomas Parran lecture published in the *American Journal of Epidemiology* in 1978¹⁰. Evans recommended use of the following criteria for demonstrating causality of both infectious and chronic diseases:

- 1) Prevalence of the disease should be higher in those exposed than in those not exposed.
- 2) Exposure to the putative cause should be present more commonly in those with the disease than in those without the disease.
- 3) The incidence should be higher in persons who are so exposed than in those not exposed, as shown in prospective studies.
- 4) Exposure to the suspected factor should precede the disease.
- 5) There should be a measurable biologic spectrum of host responses.
- 6) Experimental reproduction of the disease should be demonstrated.
- 7) Elimination of the putative cause should decrease the incidence of the disease.
- 8) Prevention or modification of the host response should decrease or eliminate the expression of the disease.

Data from the articles of Wynder/Graham¹ and Doll/Hill² support several of the Evans criteria:

- 1) Wynder and Graham¹ found that cigarette smoking preceded development of squamous and small cell undifferentiated lung carcinomas in 99% of (605) men. It seems foreign to us now, but 85% of the (780) men in their “general hospital” control group without lung carcinoma smoked as well. Doll and Hill² found that cigarette smoking preceded development of lung carcinoma in 99.7% of (647) men. Similar to the US control group, 96% of the (622) men in their “non-cancer” control group smoked as well. This difference was statistically significant at $p < 10^{-5}$. Both papers considered potential biases, concluded that lung carcinoma did not precede smoking habituation, and that there was no obvious etiology that could cause both smoking habituation and lung carcinoma. These data argue that cigarette smoking is an “important factor in the production of carcinoma of the lung” (Doll and Hill²).
- 2) Wynder and Graham¹ found that male lung carcinoma patients had higher smoke exposures than their general hospital control group (Fig. 3), $p < 0.0001$.

	n	% smokers	>10 pk-yrs	>16 pk-yrs	>21 pk-yrs	>35 pk-yrs
Ca Lung	605	99%	96%	86%	51%	20%
Gen Hosp	780	85%	74%	55%	19%	8%

Doll and Hill² also found that male lung carcinoma patients had higher smoke exposures than their non-cancer control group. (Table V), $p < 0.001$.

	n	1 cig/day	5 cigs/day	15 cigs/day	25 cigs/day	50 cigs/day
Ca Lung	647	5%	39%	30%	21%	5%
Non-Ca	622	9%	47%	30%	11%	2%

These data argue that higher and/or longer cigarette smoke exposure increases the risk of development of lung carcinomas. Because cigarettes are standardized doses, Proctor⁶ estimated that one new lung carcinoma is generated for every three million cigarettes smoked.

One of the challenges of assigning a direct causal relationship between a putative etiologic agent and the disease phenotype is the lag time between initial exposure (or deficiency) and subsequent disease. This is true for a variety of diseases ranging from infectious disease (e.g. tuberculosis), to neoplastic diseases (e.g. cigarette smoke

associated lung carcinoma, asbestos-associated mesothelioma, and aniline dye-associated bladder carcinoma), to vitamin deficiencies. In the Wynder and Graham¹ cohort of 605 male lung carcinoma patients, cigarette smoking histories ranged from 15 to 65 years, with a mode of 40 to 44 years; 96% had smoked for more than 20 years. In the Doll and Hill² cohort, 95% of 688 male lung carcinoma patients had smoked for more than 20 years.

Wynder, Graham, Doll, and Hill are good early examples of epidemiologists who sought to identify preventable diseases, and work such as theirs has triggered the development of adequately powered sample sizes, new trial designs, and statistical methods for comparison of patient treatments and outcomes.

Wynder, Graham, Doll, and Hill were correct – increased cigarette consumption leads to increased incidence and mortality due to lung carcinoma. Perhaps the most telling subsequent data are the similar curves for global cigarette consumption and lung carcinoma mortality from 1900 to 2000, offset by about 30 years⁶. Lung carcinoma mortality in men peaked in the US in about 1990, at 4 to 5 times the mortality rate seen in the 1940s by the whistleblower authors featured in this **Milestones** article. Proctor⁶ estimated that 100 million deaths were attributable to lung carcinoma in the 20th century, and wondered whether the 21st century will set a new mortality record of 1 billion lung carcinoma deaths. We are currently clocking 1.6 million deaths due to lung carcinoma worldwide each year, on par with AIDS and tuberculosis.

Aside from the institutional embarrassment attendant to our scientific/medical/public health community's unwillingness/inability to confront and eliminate cigarettes from the marketplace, these data beg the question of why humans take unnecessary risks. Slovic¹¹ makes the point that experts and consumers estimate risk differently. Experts use statistical data to estimate risk, e.g., annual mortality rates attributable to the behavior. For example, experts would rank cigarette smoking as the 2nd riskiest behavior (1st place goes to motor vehicles).

Consumers, on the other hand, consider emotional factors like dread of catastrophe, impact on future generations, and their voluntary decision to participate, such that cigarette smoking ranks as less risky to non-experts than handguns, motor vehicles, and nuclear power. Voluntariness may be the most interesting aspect of human perception of risk. For example, a person may downplay the risk of a voluntary activity such as cigarette smoking, while exaggerating the risk of involuntary activities like consumption of perceived-hazardous food preservatives. Thus, the voluntary decision to smoke cigarettes, as well as the delayed development of the smoking-associated disease phenotypes, means that

20% of the adult US population (men and women) still consider the benefits of cigarette smoking to outweigh the risks. Don't even get me started on the contribution of cigarette smoking to the development of emphysema, myocardial infarction, or stroke.

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