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Obituary

Sir Richard Doll, 1912–2005

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Abbreviation: MRC, Medical Research Council.

Sir Richard Doll, who died on July 24, 2005, will long be remembered for carrying out epidemiologic studies that improved health and saved lives throughout the world. Over a remarkable career that began in the 1940s and extended up to the time of his death at age 92, he made seminal observations on the causes of cancer, quantified the risks of radiation, anchored collaborative research projects, and tirelessly served on expert panels concerned with the translation of epidemiologic evidence into public policy. Although best known for his research on cancer, his curriculum vitae lists key papers on gastrointestinal diseases, asthma, and cardiovascular diseases.

His imprint will be lasting not only because of his scholarly contributions but also because of the many colleagues and trainees who flourished under his direction at Oxford University and earlier in the Medical Research Council's (MRC's) Statistical Research Unit, which he directed from 1961 through 1969. At Oxford, he was the Regius Professor of Medicine, a title once held by William Osler, and for many years he served as the Director of the Imperial Cancer Research Fund's Cancer Epidemiology and Clinical Trials Unit. Many leading epidemiologists worked and trained with Richard, including Richard Peto, Malcolm Pike, Martin Vessey, Sarah Darby, Nicholas Wald, and one of us (F. E. S.). By example, his influence was global, and epidemiologists worldwide have long cited him as one of the field's leaders and exemplars.

Eloquent obituaries have described Richard's long and full life; and a personal and engaging account of his career was published in 2003 in the ''Voices'' series in *Epidemiology* (1). Headed for a career in mathematics, he failed the qualifying examination for a scholarship at Cambridge and turned to medicine, following his father. He served in the military during World War II and was present at the Battle of Dunkirk; he reported to one of us (J. M. S.) that in recent years, he had more often been approached by the media to recount the evacuation of Dunkirk, as one of the few survivors, than to address his research findings. After the war, he took a training course in medical statistics and met Sir Austin (Tony) Bradford Hill, who was to have a strong influence on his career (1). Richard began working with Hill in the MRC's Statistical Research Unit at the time that research programs on environmental causes of disease were being implemented. From this point onward, his career spanned over a half century and resulted in more than 500 publications.

In this commentary, we offer a selective overview of these publications, highlighting some of Richard's most significant contributions in broad research areas—including tobacco use, risks of ionizing radiation, asbestos and lung cancer, cancer epidemiology, and asthma—and his collaborative activities. We also cite some of his key publications. Richard published two papers in the *American Journal of Epidemiology* (2, 3).

TOBACCO USE

Of his contributions to medicine, Richard's studies of the consequences of tobacco smoking are the best known. Many people have mistakenly attributed the first identification of smoking as a cause of lung cancer to the 1950 *British Medical Journal* report on the initial findings of the case-control study he and Hill initiated (4, 5). However, two case-control studies had been previously conducted by German investigators, although their findings were not widely circulated (6) and were not fully known to Doll and Hill in 1950

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(7, 8); reports from four other case-control studies were also published that year. In fact, the publication of two studies in the *Journal of the American Medical Association* earlier in the year motivated Doll and Hill to move ahead and provide their first report on the findings in London (7, 9, 10). This study was extended to over 1,000 patients, with the addition of patients from other parts of England, to deal with the potential criticism that some phenomena related to living in air-polluted London could have biased the findings (3).

Following their initial report on smoking and lung cancer from the case-control study, Doll and Hill quickly recognized that prospectively collected data were needed to complement the retrospective and then-novel case-control approach. They wisely selected British physicians for the cohort, recognizing that this group would be cooperative and readily tracked; and at the time, smoking was as frequent among physicians as in the general population (11). This same rationale led US epidemiologists, who had been influenced by Richard, to establish studies involving health care professionals: the Nurses' Health Study, the Physicians' Health Study, and the Health Professionals Follow-up Study. In fact, during a visit to the United States, Richard convinced one of us (F. E. S.) that pilot data were sufficiently promising to proceed with the development of a cohort study, eventually to become the Nurses' Health Study.

Remarkably, although the British doctor cohort was established in 1951, Doll and Hill published initial findings only 3 years later, in 1954 (11), confirming the increased risk of lung cancer in smokers that had already been shown in case-control studies. Follow-up of the cohort has continued for 50 years, and Richard himself was the first author of ''Mortality in relation to smoking: 50 years' observations on male British doctors,'' published in the *British Medical Journal* in 2004, 50 years to the day after the first paper (12). The British Doctors' Study has provided many key findings concerning smoking and disease risk. Along with other early cohort studies, it provided the first indications of the many now-identified causal associations between smoking and disease. With its lengthy follow-up, the study also addressed temporal dimensions of the risks of smoking, showing a decline in the relative risk of lung cancer mortality for persons who successfully quit but increasing relative risks among smokers in the later years of follow-up. With its rich longitudinal data, the study also proved useful for modeling the risk of lung cancer in relation to quantitative dimensions of smoking (13).

Richard described these studies and the evolution of the evidence on smoking in several eloquent essays (7, 14). As he succinctly stated, ''That so many diseases—major and minor—should be related to smoking is one of the most remarkable medical research findings of the present century'' (14, p. 112). Although not an advocate, he saw the need to oppose the tobacco industry's attempts to dismiss the fully convincing epidemiologic findings and contributed vigorously to tobacco control through his influential presence on key panels; he also served as an expert in litigation against the industry. He chaired the 1986 meeting that led to ''Tobacco Smoking,'' monograph 38 in the series published by the International Agency for Research on Cancer (15), and in 2002, he was an active contributor to monograph 83, which covered active and involuntary smoking (16). He chaired the United Kingdom's Scientific Committee on Tobacco as well (17). He also gave key testimony in litigation in Australia on passive smoking (18) and contributed to the litigation in the United States.

IONIZING RADIATION

Richard's work on the risks of radiation began in the 1950s as research emphasis shifted from the acute consequences of radiation, including acute leukemia, to longer-term risks, particularly cancer (19). To measure these risks, epidemiologists set up cohort studies of radiation-exposed groups so that cancer risks could be prospectively determined in relation to radiation dose. In the 1950s, the still-ongoing study of survivors of the atomic bomb blasts in Japan was initiated, and Richard, along with William Court-Brown, began studies of two populations that also continue: persons with ankylosing spondylitis given x-ray treatment and British radiologists (20, 21).

The original cohort of ankylosing spondylitis patients included over 14,000 persons who had been treated with x-rays for the disease between 1935 and 1954. The initial findings showed increased risk of leukemia (21), and later analyses showed that risk was greatest in a time window of 3–5 years after treatment (22). Subsequent analyses of the data further explored the timing of risk in relation to dose and applied biology-based risk models to quantify risk in relation to dose. The study of British radiologists analyzed their mortality in relation to the year of their registration as radiologists, a surrogate measure for dose. By adding successive waves of cohort members, Richard and his colleagues were able to track changing patterns of mortality as radiation protection became progressively more stringent (23). In the most recent follow-up, radiologists registered after 1954 did not have excess cancer mortality.

Richard's work extended to more contemporary issues in radiation epidemiology: the consequences of fallout (24), risks to veterans who had participated in nuclear testing exercises (25, 26), and indoor radon (27). Because of his long-term perspective on radiation epidemiology, Richard engaged in a number of controversial areas of policy and litigation. His most notable testimony was as an expert for British Nuclear Fuels in litigation regarding causation of leukemia among children of workers at the Sellafield nuclear power plant. This litigation pitted him against Martin Gardner, whose research on a childhood leukemia cluster led to a hypothesized role for paternal occupational exposure to radiation at the plant as a risk factor (28). Richard judged this hypothesis to be wrong and testified for British Nuclear Fuels, which won its case (29).

CANCER EPIDEMIOLOGY

The prospective cohort study of smoking in doctors and its initial focus on lung cancer mortality set the stage for much of Richard's subsequent work. Richard Doll's name will be forever linked to the development of cancer epidemiology. Richard started work in the MRC Statistical

Research Unit with Hill in 1948, and remarkably, within 2 years they had designed, collected, and analyzed the data and had published their first paper on smoking and carcinoma of the lung (2). Within another year, the cohort study of physicians was under way. Richard quickly expanded his research on environmental causes of cancer. By the late 1950s, he had carried out retrospective cohort assessments of lung cancer risks among nickel workers (30), asbestos workers (31) (see below), and coal gas workers (32).

This research was distinguished by rigorous design and simple but effective analyses, captured in remarkably clear and precise reports that are still a model for other investigators. Certainly by the mid-1960s, with the publication of *Cancer in Five Continents* (33), Richard was established as the world's preeminent cancer epidemiologist. By then, the causal relation between smoking and lung cancer, along with several other cancers, was well-established. However, he continued to refine and define the relation between exposure to various environmental and occupational carcinogens and cancer to provide insights into the biology of cancer risk. He characterized the relation between age (duration of exposure) and risk of cancer (34, 35). To assess the consequences of quitting smoking, he tracked cancer risk after cessation of smoking, showing that substantial reduction of lung cancer risk followed (36).

In 1981, in collaboration with Richard Peto, he published a monograph entitled *The Causes of Cancer* (37). This monograph was commissioned by the Office of Technology Assessment of the US Congress to produce quantitative estimates of avoidable cancer risks in the United States as of 1980. The report came at a time of great controversy in the United States concerning the extent to which environmental factors, particularly chemicals, were contributing to rapidly rising cancer rates. Doll and Peto found that there were sufficient valid data to attribute 30 percent of the total cancer burden to tobacco smoking (37). Another 35 percent was attributed, albeit with somewhat less certainty, to aspects of diet, an additional 7 percent to reproductive and sexual behavior, and finally, up to 5 percent to occupational exposure. Overall, they estimated that nearly two thirds of all cancer cases in the United States were preventable, giving great impetus to cancer control measures. Importantly, this document offered a framework for epidemiologic research that has guided investigators around the world. It remains useful today and has now been cited in more than 240 books and countless peer-reviewed articles.

While Richard has long been recognized as one of the first epidemiologists to document the smoking-lung cancer link, his identification of asbestos as a cause of lung cancer has been more obscure. In 1955, in a singly authored paper published in the *British Journal of Industrial Medicine*, he described findings from 105 autopsies of workers at an ''asbestos works,'' a textile factory (31). Of 18 autopsied workers with lung cancer, 15 were found to have had asbestosis as well. In the same paper, he also reported the results of a retrospective cohort study among the workers, finding 11 cases of lung cancer with asbestosis as compared with a negligible number expected based on the general population. He stated, ''From the data it can be concluded that lung cancer was a specific industrial hazard of certain asbestos workers. . . .'' (31, p. 86). The cohort was subsequently expanded to include more recent workers, and the evolution of the excess lung cancer risk was tracked and quantified (38, 39).

Richard also recognized that epidemiologic data on cancer could be analyzed to gain biologic insights into underlying carcinogenic processes. In 1954, with Peter Armitage, he published a landmark publication on what is now referred to as the ''Armitage-Doll multistage model of carcinogenesis'' (40). Based on the relation between age and cancer occurrence, Armitage and Doll postulated that the development of cancer reflects a multistage process, with a cell going through a series of transformations as it moves from being normal to fully malignant. They offered a mathematical formulation for this process that is still in use. With Peto, Richard applied this approach to data from the British Doctors' Study to better characterize the quantitative determinants of lung cancer risk in smokers (13).

Over the last 25 years, Richard Doll continued to publish reports regularly on original investigations of risk factors for a wide variety of cancers, as well as to participate in developing the reports of expert committees charged with setting public policy in regard to cancer control. Invariably, his participation gave heightened weight to the conclusions of these panels.

ASTHMA

Richard wrote his first paper on asthma based on work done as a medical student after one of his professors tried to interest him in respiratory physiology (41). The report, on a clinical case series, describes the effects of helium in the treatment of hospitalized persons with severe asthma. Over the years he remained somewhat involved in lung disease research, mostly through his support of Sir Charles Fletcher. He encouraged Fletcher to conduct a prospective cohort study of middle-aged men to understand the risk factors for chronic obstructive pulmonary disease and to describe its natural history (42). In the early 1960s, through the Statistical Research Unit, Richard supplied the statistical and computing support necessary for analyses of data sets involving repeated measures taken in approximately 1,000 working men. The data set posed new analytic challenges that were taken on by Richard Peto, whom Richard assigned to the project. The study was Peto's introduction to epidemiologic research.

In the mid-1960s, with the recognition of an epidemic of asthma deaths among young people in England, Richard took on the role of mentor for one of us (F. E. S.) and outlined a series of studies that were conducted over the ensuing 5 years (43–46). These studies eventually showed that the excess of mortality in young people was attributable in large part to overuse of pressurized aerosols of sympathomimetics by young asthmatics. The results of this series of studies led to public health warnings that were subsequently estimated to have saved the lives of over 3,500 children.

The MRC's style of functioning at that time allowed Richard, with a single phone call, to convene a meeting of the heads of several units that brought together experts in

physiology, pharmacology, and epidemiology. He was able to secure modest funding and initiate the basic work that identified factors associated with this excess mortality.

REFLECTIONS

When Richard Doll began medical school in the late 1930s, he was struck almost immediately by the differences in clinical care and outcome according to patients' social standing. Most doctors, himself included, had little knowledge of the circumstances of poor people, who were often prescribed unaffordable drugs and unrealistic therapeutic regimens. His social conscience led him, with other concerned colleagues, to found the St. Thomas's Socialist Society, which became part of an Interhospital Socialist Society. Even at this early phase of his career, Richard recognized that medicine would need to acknowledge social determinants of disease and the relevance of these factors to treatment. At that time, few opportunities existed to conduct research that would now be termed population-based and that addressed social and behavioral determinants of disease. Richard entered this arena through his relationship with Joan Faulkner, who was working at MRC headquarters (and who subsequently became not only the second-highest-ranking woman physician in the MRC but also Richard's wife). She identified a job for him at the Central Middlesex Hospital with Dr. Avery Jones, who had received a grant to study occupational causes of gastric ulcers. Richard reported some of the preliminary findings of this study to an MRC committee that included Sir Austin Bradford Hill. Hill saw Richard's promise and subsequently offered him a job in the Statistical Research Unit, launching his long career.

Richard became Director of the Statistical Research Unit upon Hill's retirement in 1961, and one of us (F. E. S.) worked there during 1966–1968. The unit brought together equal numbers of epidemiologists and statisticians to work on research related to occupational and environmental cancers and leukemias, as well as on clinical trials in the treatment of tuberculosis and gastric and peptic ulcers, studies of the effects of oral contraceptives on the cardiovascular system, and research on the role of infectious agents in a wide variety of other chronic diseases. Weekly seminars alternated between statisticians and epidemiologists, each presenting a point of view that made collaboration between them all the more engaging. Richard's mastery in developing research approaches, organizing data collection, and directing analyses was remarkable.

In 1969, when Richard was named Regius Professor of Medicine at Oxford, the most prestigious medical position in Great Britain, he questioned whether he would ever again conduct original research. Fortunately, his research continued. To develop the field of population-based research, Richard brought Martin Vessey and Richard Peto, among others from London, to join him in Oxford. The research unit was most appropriately set up in the old Radcliffe Infirmary, the site of one of the first clinical studies on the use of penicillin. Richard and Joan chose to live in the Osler house, which had been donated to the University by Sir William Osler. Visiting and staying in the house or its adjacent apartment was an always-memorable experience that often included discussions continuing late into the night on issues such as health care reform in the United States and relations among Britain, the United States, and Russia.

During his years as Regius Professor, Richard developed the concept for a new college oriented toward all aspects of medical care and public health that would add to the richness of Oxford University. He convinced both the University and external funders (the principal one being Cecil Green, the former chief executive officer of the company that became Texas Instruments) to establish the college. In 1979, he gave up his post as Regius Professor and became Warden of Green College. In this role, he and Joan changed the culture of medical education at Oxford University. As before upon assuming a new administrative challenge, he questioned whether he could continue to do research, but again he persisted as he took on the position of Director of the Imperial Cancer Research Fund's Cancer Epidemiology and Clinical Trials Unit.

Over the last 20 years of his life, Richard not only continued to write prolifically on cancer but also began to travel extensively, to appear before commissions as an expert, to give significant invited lectures, and to receive honors. A short list of these honors, recently summarized by one of us (47), included honorary degrees from universities in Great Britain (including Newcastle, Belfast, Birmingham, London, and Oxford), the United States (including Harvard and Stony Brook), and countries such as Jamaica, Tasmania, Australia, and Norway. Professional honors included being named a Fellow of the Royal Society, a Senior Member of the US Institute of Medicine, a Foreign Associate of the US National Academy of Sciences, and a Foreign Member of the American Epidemiological Society. He was also named an honorary fellow of the Royal Statistical Society, the American College of Epidemiology, and the New York Academy of Medicine. For his important contributions to research on cancer and the effects of smoking, he received the United Nations Award for Cancer Research, the Nuffield Medal of the Royal Society of Medicine, the General Motors Cancer Fund Charles Mott Prize for Cancer Research, the Alton Ochsner Award, the Erkki Saxen Medal of the Cancer Society of Finland, the Nathan Davis International Award from the American Medical Association, and, more recently, the Shaw Prize in Life Science and Medicine and the King Faisal Award for Medicine. He received numerous other awards and honors.

Both of us had numerous opportunities to see Richard in action. He always thoroughly understood any topic he chose to talk about. He had a keen mind and an ability to relate facts from a variety of perspectives. Underlying much of his approach were the lessons he had learned as a medical student—particularly that prevention based on science could have a direct impact on populations that could never be achieved by curative medicine alone. One obvious proof was the millions of premature deaths avoided by the tobacco control measures that were initiated by his findings on smoking and lung cancer. On numerous occasions over the last few years, he reflected on his successes and on the difficulties that epidemiologists will face in the 21st century.

In retrospect, his research in determining the impact of smoking on lung cancer risk may seem ''easy.'' The risks were large, and little else caused the disease of interest. He also began his career in an era when there was an absence of administrative barriers separating investigators and research participants. Trust between the parties was required, however, and he often spoke of the concern that this trust could not be legislated.

Richard's work demonstrated the power of long-term prospective investigation with large cohorts. He recognized the ongoing need for these kinds of studies and was concerned as to how future cadres of investigators would be trained to work on them and to grow academically. He also recognized the need to develop funding for the infrastructure required to support such studies. Oxford University has just opened a new building, the Richard Doll Building, appropriately devoted to population-based research. Richard's legacy is large, and like this new building, it will stand.

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