

## The man who saved a million lives

In the Second World War, only military action killed more Britons than cigarettes. The tobacco industry wouldn't accept it - and the government couldn't afford to. But in Oxford, one scientist was about to prove the cancer link that changed the course of medical history.

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It is hard to say precisely how many lives Sir Richard Doll has saved in his career, but a million may be considered a conservative estimate. The true figure probably lies in the steel filing cabinets in his small office at the Radcliffe Infirmary in Oxford, or among the stacks of medical journals that surround him, soon to be packed in crates and transported to a sparkling new glass and concrete home in a different part of the city. Sir Richard does not plan to visit the new building very often - he doesn't drive, and the new place isn't within walking distance. There is, therefore, a certain irony in the fact that the unofficial retirement, at the age of 92, of one of the greatest medical detectives in the world will be caused by the opening of the building that will proudly bear his name.

The Richard Doll Building, in Headington, on the outskirts of Oxford, will house several research and medical departments whose work over the past half-century has been significantly influenced by Professor Doll's endeavours, not least the Cancer Research UK Epidemiology Unit. Professor Doll did not set out in life to be a medical statistician in search of the causes of disease, but he will leave the profession as its most famous British practitioner. He has studied diet, radon gas, HIV, ulcers and radioactivity, but he will be widely remembered for just one thing: as the man who proved that smoking causes lung cancer.

He did not achieve this feat alone, and it has taken 50 years to complete the study, but his work bears comparison with the greatest discoveries of the modern age. Because the detrimental effects of smoking are largely self-inflicted, and because 90 per cent of lung cancers are caused by smoking, Professor Doll's work amounts to a cure, albeit one notoriously difficult to self-administer.

Those who call on him for the first time may be struck by the fact that this slightly stooping elderly man with tweed jacket and a semi-halo of white hair is keen to meet visitors at the lift, and then prepare a drink for them with an old kettle in a corner of his office. No American medical institution would allow one of its stars to behave in such a way. There is, in fact, a departmental secretary who assists with his diary and emails. There is no computer in his room, and a job dependent on complex comparative data and the constant flow of information is carried on much as it was when its occupier first made a name for himself in the early Fifties. As for his emails, 'At least 48 out of 50 of them are junk,' the statistician says.

Richard Doll was born in 1912, at a time when smoking was just becoming popular. His father, who was a GP near the family home in Hampton, Middlesex, promised his son £50 if he refrained from smoking until he was 21, not because he thought it was harmful, but because it was a waste of money. 'I was determined to get it,' Doll says, 'but I had a brother, seven years younger than me, and whenever we had friends in the house he would say, "Oh, Richard's not going to smoke until he's 21!" And I finally said, "I can't stand this any longer - give me a cigarette!"'

He consumed two ounces of pipe tobacco a week and five cigarettes a day during his time as a medical student and an officer during the Second World War. 'In the Thirties, none of my teachers said smoking was harmful,' he remembers. The medical textbooks of the Forties made brief reference to cancers of the lip and tongue, and blindness caused by the combination of pipe smoke and malnutrition.

The incidence of lung cancer had increased steadily throughout the Thirties, but no one knew why. Hospital beds filled up with people who arrived with choking coughs and soon graduated to emphysema and mouths full of blood, and during the war this became the second biggest cause of death after military action.

When the conflict ended, Richard Doll began working for the Medical Research Council, on the causes of gastric duodenal ulcers. But the MRC had also become concerned with the lung cancer rates, and had asked Bradford Hill, an epidemiologist at the London School of Hygiene, to conduct a brief study. Hill had become aware of Doll's patience and analytical skills and asked him to assist. At the time, the most likely cause of lung disease was believed to be atmospheric pollution. Doll's own hunch was that it was caused by the increase in the tarring of roads.

In 1949, Doll and Hill visited hundreds of patients in London hospitals who had been diagnosed with lung cancer or were suspected of it. Most patients presented before they were very ill, and were able to answer a detailed questionnaire. They were asked about their family history, diet and previous diseases, and whether they had ever worked on the roads. Doll then returned to the hospitals in the following months to examine their diagnoses. 'The most striking thing was that if the person was a non-smoker, the diagnosis would always change,' Doll says. 'But if they were a heavy smoker it was usually lung cancer. It was changed occasionally, but not very often. In 649 cases of lung cancer there were two non-smokers.'

Today, we may regard these results as obvious and predictable, but the epidemiologists were astonished. German doctors working for the Nazis had suspected a link before the war, and other surveys in Britain and the US had voiced suspicions. But Doll and Hill's numbers were so striking that what others had regarded as an association, they could already claim to be a causation. Doll was so struck by the certainty of his research that he instantly gave up smoking. 'It wasn't so difficult.'

Others were harder to convince. In 1950, when the first survey was complete, the secretary of the MRC suggested that the results might apply only to London. Doll and Hill thought this unlikely, but agreed to spread their research to Cambridge, Bristol, Leeds and Newcastle. Now the records of 5,000 patients were examined.

'And, of course, we got exactly the same results.'

Then something strange happened. When the results were published in 1952, no one took much notice. The same thing happened when a similar study appeared in the United States. The survey was still considered to be quite small, and the results seemed too simple. Even the most eminent health officials refused to believe that lung cancer was largely self-inflicted. 'This wasn't a result of pressure from the tobacco industry,' Doll says, 'although they did make sure that if ever there was an article about it it was accompanied by another one from a doctor who said that the link was a load of nonsense.' The tobacco industry had an unusual ally. The cancer advisory committee of the Department of Health suggested a period of inaction. Doll remembers being told: 'You shouldn't frighten people into thinking that smoking might be dangerous.'

Doll and Hill thought there was little use repeating their survey among other lung cancer patients, so they chose another group of people whom the medical profession might regard as more reliable: doctors. In October 1951, the epidemiologists wrote to 59,600 doctors asking very simple questions about whether they smoked, and, if so, when they began and how much they consumed - and 40,500 replied. They kept a close track of their health in the following years. By 1954, Doll and Hill were getting similar results to their hospital patients, and they published their first findings in the British Medical Journal. This five-page report was such a significant document that in June last year, 50 years after its original publication, the BMJ reprinted the first page on its cover. The incidence of doctors dying from lung cancer was still small in 1954 (36 deaths in men and women over the age of 35 in the 29 months between the start and first reporting of the survey, out of a total death toll of 789). This may explain why, once again, the findings failed to have much impact on the media and general public. But some doctors began to take note, particularly the heavy smokers who believed their health was deteriorating and had witnessed the effects on their colleagues. The wise ones began to warn their patients. Follow-up surveys continued to be returned to Doll and Hill in the following years, and by 1956 the results were unmistakable. More than 200 heavy smokers had died of lung cancer in a four-year period, whereas the incidence among non-smokers was negligible. Only in later years would the effects of passive smoking also be seen.

The Department of Health considered the results for a year. 'They set up an inter-departmental committee to advise on what should be done,' Professor Doll recalls. 'This said - and I've seen the report - that it would be very serious if smoking was reduced, not because tax would decrease, but because they like people to die off at 65 to save their pensions. The committee was chaired by the Treasury. And as a result it was decided to do nothing.' But in 1957, the Department of Health did call a press conference to share what it regarded as potentially worrying news. 'And the minister who announced it,' Doll remembers, 'was smoking a cigarette at the same time.'

Doll drinks his coffee with a steady hand. As far as he's aware, coffee has no long-term detrimental effects, although the evidence is conflicting. He has other things to worry about. His hearing is still excellent, but his eyesight is failing. 'My brain is not as sharp as it was,' he says. 'I certainly don't feel I can keep up, which is

why I'm pulling out. People ask me to referee things, and I don't really feel now that I have adequate knowledge of developments in cancer biology. But I still feel up to date with the epidemiology.' His wife died three years ago, 'which limits one's life substantially.'

On his desk are notes for a talk he was preparing to give at the Royal Society of Medicine on the Great Killers, an event which would also include papers on the black death, TB, HIV and obesity. Doll's address was entitled 'The Identification of Smoking as a Killer', and he rehearses the topic for my benefit in his office. 'By 1956, the tobacco industry had started to react,' he says. 'They didn't put any pressure on us, but they were initially bemused by the findings and wanted to show that we were mistaken.' When their first report was published, Doll and Hill held a meeting at the London School of Hygiene with three representatives from the cigarette companies, and the smokers maintained that lung cancer was caused by the fumes from cars and under-regulated factory emissions (the Clean Air Act was passed only in 1956, partly as a result of the great London smog of 1952). According to Doll, Hill replied: 'Go away and prove it, because we can't.' By 1957, the year after Doll and Hill published their second and more substantial report, the civil mood of that first meeting had changed. 'There was a war on, and they had the ear of the media because of all their advertising.' The message received by the public was confused, and a process of claim and counter-claim persisted for more than a decade. The Royal College of Physicians published a damning report on the effects of smoking in 1962, but it wasn't until 1970 that the media became convinced, resulting in great increases in the amount of smokers quitting and the first social shift in the treatment of smokers as pariahs. Restaurants and public transport began to offer non-smoking sections, and forward-thinking hotels provided non-smoking floors. By then, of course, it was clear that smoking did a lot more than just cause cancer of the lung.

Sir Richard Doll's reputation does not rest on his smoking work alone. In the mid-Fifties, the testing of the hydrogen bomb in the Pacific prompted the MRC to conduct research on the carcinogenic effects of ionising radiation. The common view was that only large doses caused cancer, and Doll and his colleague William Court-Brown devised a study to gauge the incidence of leukaemia among a group of almost 14,000 hospital patients who had received radiotherapy for a benign condition known as ankylosing spondylitis. 'The MRC said we could have all the resources we required,' Doll says, 'but they wanted the results in six months. We got them the answer in six months, but it turned out to be the wrong answer.' Doll and Court-Brown concluded that a small dose didn't have a significant effect, but a radiation specialist then realised they had misinterpreted the results. They hadn't considered the dose in the bone marrow; when they did this, they found a proportional, linear relationship between radiation levels and leukaemia; the more radiation one receives, the greater the risk, but even relatively small amounts can have an effect. 'Unfortunately, this has frightened the public in a disproportionate way,' Doll says, 'and people suspect that the very small doses that one gets from a nuclear power station could be having some effect, but in fact the doses are so small that it's quite impossible for them to have any detectable effect at all. I spend most of my time saying, "No, this is nonsense - this cluster of leukaemias isn't due to radiation."'

Doll's work on the effects of radon gas in the home has caused less dispute. Radon is a naturally occurring, colourless and odourless gas found at varying levels in all houses throughout the UK, and accounts for about half of all non-medical radiation exposure. At higher levels it can be lethal, causing about 1,000 lung cancer deaths in the UK each year, and about 20,000 in the European Union. As disintegrating radon erodes the cell linings of the lung, it is particularly damaging to smokers, who may already have weakened cell walls. This study, published at the end of last year, was led by Doll's Oxford colleague, Professor Sarah Darby, with whom he also collaborated on work with haemophiliacs in the mid-Eighties that helped to confirm the link between HIV and Aids.

The catalogue of significant historical inquiries goes on: in the late Nineties, Doll and colleagues conducted a survey among 2,700 retired men and women in Oxford and East Anglia which concluded that regular intake of a vitamin D supplement may reduce the risk of fractures after a fall. In 2002, he co-authored a report in the British Journal of Cancer that broke new ground in distinguishing the effects of alcohol and tobacco on breast cancer. The study drew on the experiences of 150,000 women, and its findings were surprising but unequivocal: smoking has no direct effect, but the risk of breast cancer increases by 6 per cent for every extra alcoholic drink consumed on a daily basis. It was estimated that alcohol consumption was responsible for about 2,000 cases of breast cancer in the UK each year.

'Richard Doll's influence has been massive,' Professor Jeffrey Tobias, a consultant oncologist at University College London Hospital, told me recently. 'He has the most remarkable tenacity, and he continues to make highly valuable contributions.' Tobias, who chairs the Tobacco Advisory Group at Cancer Research UK, calls it 'an international scandal' that Doll has not been awarded the Nobel Prize for Medicine. 'If the prize is intended in a Benthamite way to honour a person who brought the greatest happiness to the greatest number, then I cannot imagine there is an individual on the surface of the planet who is better qualified or more deserving.' There is one plausible explanation for the omission: in some quarters, epidemiology is still not regarded as hardcore science; Doll's work does not involve looking down a microscope. 'But we benefit substantially from stepping back from the microscope,' Professor Tobias reasons. 'You step back and you get the whole patient, and then you step back further and you get epidemiology.'

I put the question to Professor Doll towards the end of our meeting, and for the first time he seemed a little uncomfortable. 'I know I have been nominated for it, but it didn't get any further than that. It's not something I'm worried about. I've had more than enough recognition.' There is little evidence of it in his office, but somewhere a shelf is groaning: in 1962, a United Nations award for cancer research; in 1974, the New York Academy of Science Presidential Award; the Gold Medal from the British Medical Association (1983); the Royal Medal from the Royal Society (1986); Norway's King Olaf V Award (2002); the King Faisal International Prize for Medicine (with Sir Richard Peto) earlier this year. He was knighted in 1971, and was made a Companion of Honour 25 years later. I mentioned to him that Professor Tobias considered the absence of the Nobel scandalous. 'He's not alone on that. But, oh well, that's something I'd prefer not

to discuss.'

Professor Doll has also received enough recognition in his life to acknowledge his occasional misjudgments. Twenty-five years ago, when researching the relationship between diet and cancer for a book, he believed that certain factors were undeniable. 'Now,' he says, 'I probably know less about it than I did then. Everyone was always pretty confident that what you ate had something to do with cancer of the bowel. But the evidence has been very confused. The hypothesis about the lack of fibre causing cancer in the large bowel was enthusiastically accepted, and we believed it in 1980, but ever since then it's become less clear that it has much effect.' The same doubts cloud the correlation between a high-fat diet and breast cancer.

A strong association was accepted for years, but larger, more recent studies have suggested otherwise. He is still certain of one link: the consumption of fruit and vegetables does help prevent cancer of the stomach.

Doll's work on smoking came to an unofficial end last year, when, on precisely the 50th anniversary of his preliminary BMJ paper of 1954, he and his colleagues published their final follow-up report. In all, 34,000 doctors had continued to take part in the 50-year study. The final report was no longer concerned with causation, but with comparative mortality rates between smokers and non-smokers. Men born between 1900 and 1930, who smoked only cigarettes and continued smoking throughout their lives, died on average about 10 years younger than lifelong non-smokers. Those who gave up at age 60, 50, 40 or 30 years gained, respectively, about three, six, nine or 10 years of life expectancy. The probability of dying in middle age (35 to 69) for smokers born in the Twenties was 43 per cent, compared with 15 per cent for non-smokers. Cessation at age 50 halved the risk of contracting lung cancer, and stopping at 30 avoided almost all of it. The study also exposed the extent to which smoking hastened the onset of many other fatal diseases. Indeed, lung cancer accounted for less than half of the comparatively early mortality among smokers.

But Doll's greatest legacy lies instead among the statistical files and graphs at Cancer Research UK. Here, there is clear evidence that the decrease in smoking from the Seventies onwards has had a distinct impact on both incidence and mortality. CRUK estimates that 6.3m people have died from smoking-related diseases in the past half-century. Forty-two per cent of deaths in middle-aged men were caused by smoking during this period, while in the Sixties the figure was 50 per cent. For women, the figure was 16 per cent, but 24 per cent in the Eighties. The figures were particularly high in Scotland. The good news is that the figures are falling: in 2000 the percentage of deaths caused by tobacco in middle-aged men was 25 per cent, and 21 per cent in women.

In 2001, there were 37,450 new cases of lung cancer registered in the UK, accounting for 14 per cent of all new cancers that year and making it the second most prevalent type after breast cancer (41,080 cases). More than 120,000 people die from all smoking-related causes, about one fifth of all deaths. The UK rates compare favourably with many other countries in the EU, where there are an estimated 347,000 deaths from lung cancer each year, with a particularly high proportion in Hungary, Belgium, Poland and Holland. (The UK comes 16th in the table of deaths as a proportion of population, marginally above Spain, France and

Germany.)

The percentage of adults who smoke cigarettes in the UK fell from 45 per cent in 1974 to 35 per cent in 1982; today, just over a quarter of adults smoke.

Undoubtedly, much of the decrease has been caused by a combination of better education, higher tobacco taxes, restrictions on advertising and the partial ban on smoking in public places. When, in the mid-Seventies, Denis Healey became the first Chancellor of the Exchequer to announce that he was deliberately raising the tax on tobacco to discourage smoking, Richard Doll sent him a letter of congratulation.

Doll was less impressed last year when the government failed to follow the example set in Ireland and ban smoking from all public places (rather than just those which serve food). But he has consciously never been a campaigner. 'I've always believed that a research worker should not proselytise and should not concern himself with what was done as a result of his research,' he told me. 'It was your job to get the facts right, and if you say, "You must do so-and-so because of this" you will then find it difficult to change your mind if you were wrong.

Epidemiologists should publicise the research of other people, not their own.' Three years ago on Desert Island Discs, Professor Doll said he had formulated a new strategy towards health education: 'Find out what the tobacco industry supports and don't do it, and find out what they object to and do it.' He chose Rhapsody in Blue, Beethoven's 9th, an excerpt from the old radio comedy The Glums, and a down pillow as his luxury item. At the end of the programme he told Sue Lawley something that came as a surprise to those who knew him well. He said the effect of someone lighting up a cigarette in his presence 'is so small that it doesn't worry me', a comment which some interpreted as a denial of the impact of passive smoking. In fact, he had just published a study from 12 European countries suggesting the opposite: it was estimated that non-smokers exposed to second-hand smoke are between 20 and 30 per cent more likely to develop lung cancer. In other words, the damage first detected by a young doctor 55 years ago has turned out to be far worse than anyone ever imagined.

The Richard Doll Building is almost finished. Viewed from a certain angle it looks like an ocean liner from the beginning of the last century, a sharp white prow suggesting fleetness and fortitude. It is a place that, at an estimated cost of £22m, announces itself as a venue for important business. As well as the CRUK Epidemiology Unit it will also bring together the offices and laboratories of Oxford's Clinical Trials Service Unit and the Department of Public Health and Primary Care.

In March of last year, the man responsible for its name and for defining the entire field of population-based study of disease, put on his black peaked cap and performed the topping-out ceremony on the roof. Its position on the edge of the city is a little too far for Professor Doll to visit every day when the rest of his office moves there on 10 June. I asked him how he would use the additional spare time. The same as usual, he said: reading novels, seeing friends. 'I've spent so much of my life working that I don't really have hobbies as such.' After thinking for a while he concluded that he wouldn't mind doing a little more research into the effects of diet on cancer. 'It's something that can still have a great effect on people's lives,' he said. 'So long as you've got the facts absolutely right.'

Richard Doll died in July 2005.