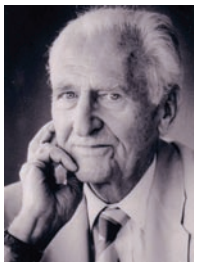

Richard Doll: Science will always win in the end

➜ Interview by Anna Wagstaff

In 1950, Richard Doll showed the world that smoking causes lung cancer. Today, aged 92, a word from him can still cause anxiety in the Nokia boardroom or have us counting our portions of fruit and veg. He carries the responsibility lightly, because he believes in the power of evidence. After all, when it comes to the causality of cancer, he wrote the rules.

Lung cancer had been rising sharply for decades before your groundbreaking report showed, with only a one in a million scintilla of doubt, that smoking is a cause of lung cancer. Why did such a strong association take so long to identify?

RICHARD DOLL Cigarette smoke had first been suspected in the 1920s, but some pathologists tried to produce skin cancer in mice by smearing them with cigarette smoke tar. When there was no response, smoking was ruled out as a possible carcinogen, and researchers turned their attention to other possible causes.

The technique of testing for carcinogens by exposing animals to them had only been introduced in about 1919, in Japan, and for the next two or three decades, scientists thought that's the way we discover the causes of cancers, by getting suspect materials and putting them on the skin of mice.

I myself did not expect to find smoking was a major problem. If I'd had to bet money at that time, I would have put it on something to do with the roads and motorcars.

Was yours the first epidemiological study on lung cancer?

RICHARD DOLL There were a few others, but we were the first to have sufficient confidence in our findings to state that "We conclude that smoking is a cause and an important cause of the disease."

A couple of very primitive studies had been carried out in Germany, but they were very flawed. For example, one used the average age of lung cancer patients as a basis for selecting control patients – so if the average age of the lung cancer patients was 54, they interviewed a lot of people aged 54. You really need to have the separate experiences of a 70-year-old and a 30-year-old, you can't assume that the experience of a 54-year-old is representative.

Then there was a US study that came out about the same time as ours and had similar findings, but because they had used less rigorous techniques, they were more cautious about drawing conclusions from their data, and merely concluded that there was an association they'd found which might imply causality.

With Richard Peto, who became known in the cancer world as the man behind the Oxford Early Breast Cancer Collaborative Group, which first proved the benefits of adjuvant therapy. Doll brought Peto with him to Oxford when he took up his post as Regius Professor of Medicine at the University in 1969

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The trouble was that, until then, epidemiology had been concerned almost entirely with infectious diseases, which required very different methods and tended to look at differences between entire populations – differences in rainfall, temperature, things like that. With cancer and chronic diseases, you need to compare individuals with the disease against those without. There are all sorts of biases that can affect this kind of epidemiological study, and that was not understood at the time. A person being interviewed, for instance, will tend to overemphasise something that they think might be useful. It took some time to establish and find techniques to eliminate all the biases that can affect the results.

We were confident of our data because we had taken steps to ensure that our results were robust. Chance you could cut out immediately, because you were talking about odds of less than one in a million of getting our results by chance. Then you had to show that your results weren't biased, and then you had to show that the results were not due to what is now called confounding; that it was not smoking that caused the disease, but smoking was associated with something else that did. For example lung cancer is associated with drinking alcohol – smokers tend to drink more alcohol.

Then we checked our results against ecological evidence, to see what sense it made in the world at large. If smoking is the cause, we ought to find that wherever the disease was common, smoking should be common, and vice versa. So where people didn't smoke there shouldn't be much lung cancer. And that's what we found when we looked round the world.

Was the medical world convinced?

RICHARD DOLL Not at all. Sir Harold Himsworth, the Secretary of the Medical Research Council (MRC), who had commissioned the study, accepted the results straight off. But most cancer research workers did not accept it, and in fact they advised the Department of Health that they shouldn't take any action because they were uncertain about what it meant.

It wasn't until 1957, when the Government asked the MRC for a formal opinion as to whether our conclusion was correct or not, that the MRC formally considered it and said it was correct and advised the Government to that effect. The result was that the Minister of Health in 1957 called a press conference to announce the results of the MRC consultation. He announced that the MRC had advised them that smoking was the cause of the great increase in lung cancer. While he was reporting this to the media, he was smoking a cigarette himself!

One of the problems we found in trying to convince the scientific community was that thinking at that time was dominated by the discovery of bacteria such as diphtheria, typhoid, and the tubercle, which had been the basis for the big advances in medicine in the last decades of the 19th century.

When it came to drawing conclusions from an epidemiology study, scientists tended to use

While the minister announced that smoking caused lung cancer, he was smoking himself

the rules that had been used to show that a particular germ was the cause of an infectious disease – Koch's three postulates. Koch was a great German pathologist who discovered the tubercle bacillus, and one of his postulates was that you must always find the organism in every case of the disease.

When we did our study on lung cancer and smoking, 50 years later, a number of scientists thought this applied to the cause of chronic diseases. A lot of people said, "Smoking can't be the cause of lung cancer because I have seen a case in a non-smoker, and therefore by Koch's postulate smoking is not the cause."

But, of course, nobody was saying it was *the* cause; what we were saying is that it is *a* cause. People didn't realise that these chronic diseases could have multiple causes. And smoking is only one cause of lung cancer – it happens to be much the most important cause, however.

How did you convince the doubters?

RICHARD DOLL When we saw that, apart from Sir Harold Himsworth and one or two others, practically no-one believed our conclusions, we thought it's no good repeating the study. So we designed another one, using a different method. We decided to look at people's smoking habits and see whether that could predict who would contract lung cancer.

We chose doctors as our sample, principally because they were easy to follow up, and we planned to do the study for five years. But within two and a half years, we already had 37 deaths from lung cancer – none in non-smokers, and a high incidence in heavy smokers. The association was very clear. It turned out to have been very fortunate to have chosen doctors, from a number of points of view. One was that the medical profession in this country became convinced of the findings quicker than anywhere else. They said, "Goodness! Smoking kills doctors, it must be very serious," and, of course, a very high proportion gave up.

After five years we had around 70 cases, but by this time, our results were beginning to show that smoking was also associated with a number of other diseases, particularly with heart disease, so we decided to continue the study, though this had never been the initial plan.

Your findings have implications for us all. Do you get drawn in to discussions about people's lifestyles?

RICHARD DOLL My job has been to try to find out what the causes are, or what is the efficient treatment. If I then go round telling people what they should do, I may get prejudiced because I'm committed to a particular opinion, and as a scientist you must always be prepared to change your mind if the evidence changes.

I am now committed to the viewpoint that people shouldn't smoke, but that's 50 years after the first observation. I never gave any advice for the first 30 years. But it is so established now that there is no question of my being prejudiced.

People can also over-react. Radiation is an example – people are ridiculously frightened of

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Tobacco bosses in 1950 were horrified by the idea that what they were selling was killing people

it. I also think we've gone too far in eliminating asbestos – I mean the less dangerous white type, which carefully handled probably does more good than harm. Several hundred British sailors died in the Falklands War who needn't have, because they hadn't got the adequate fire control that you had with asbestos.

Fifty years ago you showed the world that smoking can kill. Why do you think so many youngsters are still not getting the message?

RICHARD DOLL Young people will always behave a bit recklessly. That's why it's so important that we now can show that giving up smoking early in life is really effective. I think we're going to save more lives by persuading people to give up than we are by stopping people from starting.

Obviously you try to educate children and young people, but you know you are not going to win with all of them. Even my own children smoked. My son smoked from about age 12 to 16. My daughter didn't stop till she was 30.

Did you personally come up against the tobacco industry?

RICHARD DOLL What you've got to remember is that the directors of the tobacco companies in 1950 were responsible people, insofar as the directors of any firm were, and they were horrified by the idea that what they were selling was killing people. They made serious efforts, perfectly reasonably, to disprove the claim, but their own statistical advisor after a few years told them that it was a waste of time and that he was convinced that smoking caused lung cancer.

I remember he rang me up and said that he agreed with my findings and that he was going to have to leave his job.

He wanted to take the opportunity of his final two weeks' of expenses allowance to invite me and my wife out to dinner. As it happened, his employers accepted his advice, and he agreed to continue working for them on the basis that they would never publicly deny that smoking caused lung cancer.

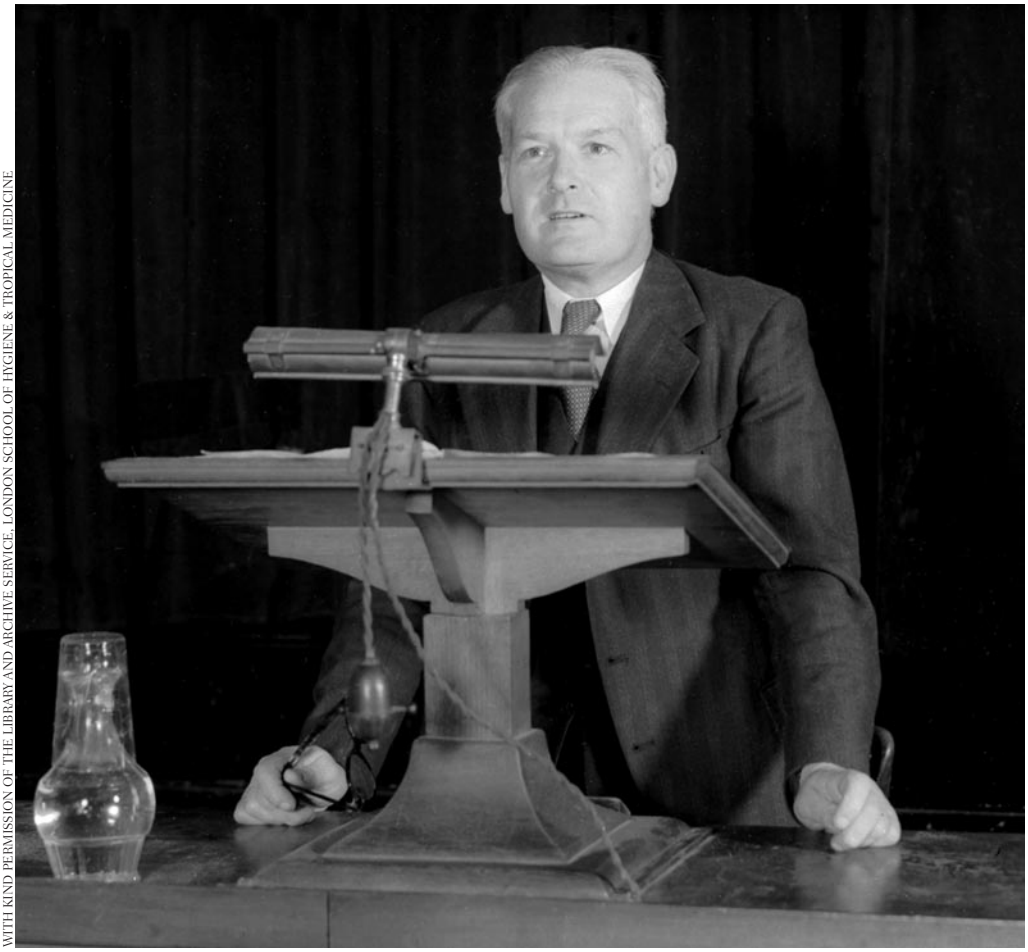
It's a different case with today's directors of the tobacco industry. They have gone into it knowing perfectly well that they are selling something that is a lethal material, and they are to my mind thoroughly immoral people. But that wasn't true of the directors of 1950.

The tobacco industry in America did not react at all in the same way, and they tried to get a colleague of mine, Ernest Wynder, sacked from his job with the Sloan-Kettering. They put pressure on the Director not to allow Wynder to publish anything that claimed smoking caused disease, and the Director did try to suppress his studies. Wynder, however, responded by setting up his own organisation and getting support from somebody else to carry on doing the research. So when he published his results, they didn't have the Sloan-Kettering stamp. Sloan-Kettering came out of it very badly.

However, despite this sort of pressure, the leading epidemiologists in America all got together fairly early on – in the late 1950s – and said they regarded it as proved that smoking causes disease. The trouble was the American law courts. The industry made it so expensive to sue them that it wasn't for some years that you got very wealthy groups of lawyers who were prepared to take them on. The industry could make it so expensive by raising objections and making it last a very long time.

Did you feel a sense of triumph when the courts finally found against the mighty tobacco industry?

RICHARD DOLL Science will always win in the end.



WITH KIND PERMISSION OF THE LIBRARY AND ARCHIVE SERVICE, LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

Sir Austin Bradford Hill – grandfather of modern epidemiology and Richard Doll's boss and teacher. As Professor of Medical Statistics at the London School of Hygiene & Tropical Medicine, he was the man the Medical Research Council turned to as the death toll from lung cancer rose ever higher. Together, he and Doll worked out the techniques that fingered smoking as the culprit. Bradford Hill wanted to be a doctor, but World War I ended his hopes and would probably have ended his life, had his service as a fighter pilot not been cut short when he contracted tuberculosis. He pulled through, but it was too late to start a medical career, so he went into statistics and applied it to medicine. The rest is history

What we're left with now are the smaller risk factors such as alcohol for breast cancer

Your discovery that smoking causes lung cancer was the preventive equivalent of the 'magic bullet'. Are there any more major factors that we don't yet know about?

RICHARD DOLL No there are not. We've eliminated so many causes of cancer. What people don't realise now is how many occupational cancers there used to be. They've all been cleared up. 2-naphthylamine, for instance, which was used in dyes and in the preparation of rubber, led to a very high incidence of bladder cancer among those who worked with it. That's gone. Road workers would get skin cancer from tar, or lung cancer from the fumes. Many oils used for lubricating machinery would result in skin cancer or cancer of the scrotum. Asbestos. All these work-related cancers have now been eliminated. We've also made huge strides identifying which cancers have an infectious origin. We now know,

Tamoxifen, for instance, was not being used in this country until Peto's collaborative analysis in 1988

for instance, that cervical cancer has a viral origin, and we shall have a vaccine against it in a few years' time. We are beginning to find other cancers with viral origins. Hepatitis B and C are major causes of liver cancer in many parts of the world, the Epstein Barr virus causes some rare cancers in the Far East, but is also responsible for some cases of Hodgkin's disease. And we now know that gastric cancer, which dropped dramatically in incidence during the last century, is largely caused by the helicobacter pylori bacterium. What we're left with now are the smaller risk factors, such as alcohol for breast cancer, which can only be detected by collaborative studies looking at populations of tens of thousands rather than the hundreds that we used to use. This sort of work has been pioneered by Richard Peto, whom I brought with me from London when I took up my position of Regius Professor at Oxford University. This has to my mind been his really major contribution. These large-scale studies were undreamed of until he demonstrated the possibility by collaborating with different people in different countries.

The increased effectiveness of new treatments can also be too small to measure except through this sort of study. Tamoxifen, for instance, was not being used in this country until Peto's collaborative analysis in 1988. The evidence was all there but it was in little bits and contradictory. It wasn't until the evidence was all put together that you could say "Look! It's absolutely clear that giving women tamoxifen after the operation reduces their mortality by about 10–15%. You saw a very clear answer, and people changed their habits overnight. Very few people had been using it, or they had only been using it for a year. After this study everyone started using it and they realised they had to continue using it for up to five years.

What do you see as your legacy to the world of epidemiology?

RICHARD DOLL Sir Austin Bradford Hill has largely been forgotten about nowadays because he is dead. But he was my boss and my teacher, and the methods and techniques we developed together in order to find out why lung cancer was increasing so dramatically are still used to this day.

Bradford Hill later codified these into what he termed "nine guidelines", (often wrongly referred to as "criteria") which are universally accepted now. They are cited in courts of law.

I wrote an article about three years ago on proof of causality – proof that something is actually a cause of a disease – which made use of what I'd learnt from Bradford Hill, and which is now used as a reference point for epidemiologists.

And of course our report that established smoking as an important cause of lung cancer was very important. That was the first serious epidemiological study ever done into cancer, at a time when there were probably no more than a dozen of us working on this issue worldwide. Looking back with the benefit of more than 50 years' hindsight, I can honestly say that we did a good job.

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