CANCER
RISKS AND PREVENTION

Edited by M.P. VESSEY and MUIR GRAY

Cancer Risks and Prevention

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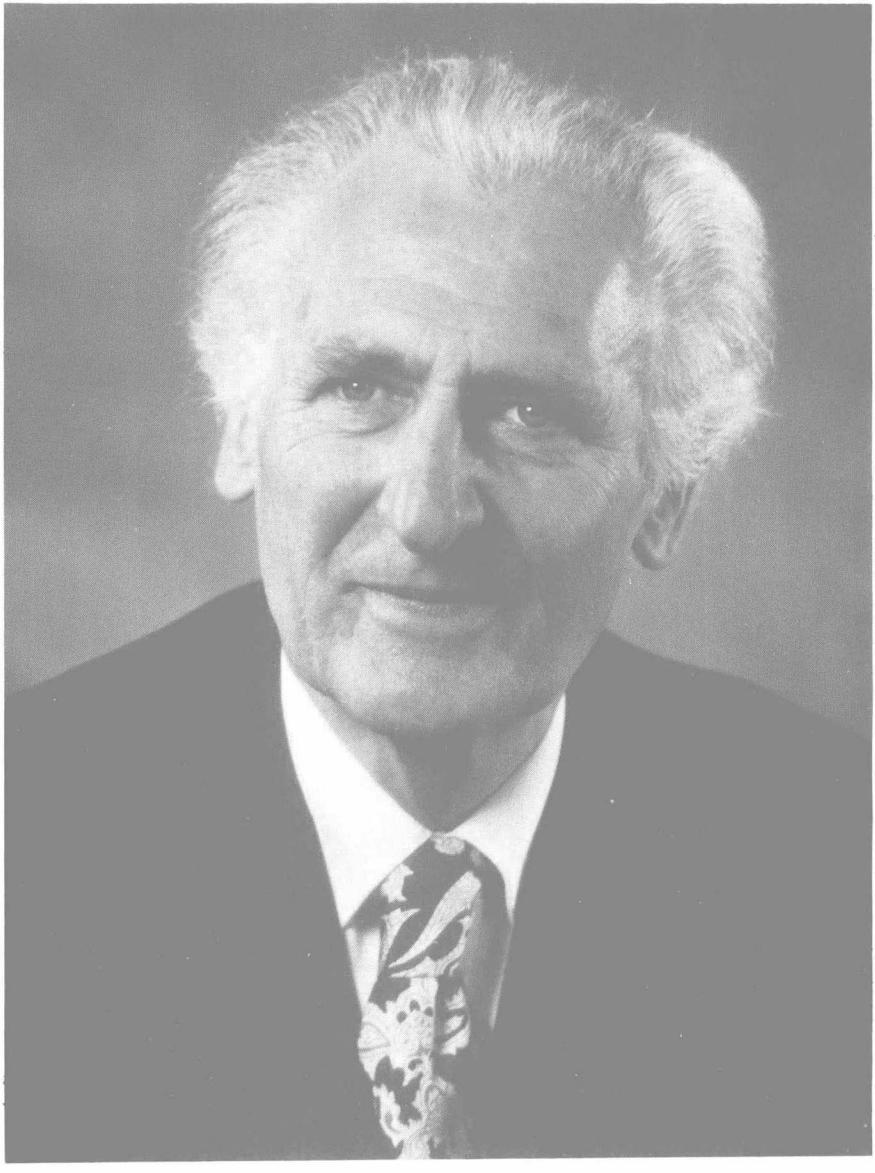

Sir Richard Doll

Preface

This series of essays was collected in honour of Richard and Joan Doll, on the occasion of Richard's retirement as Warden of Green College. The term 'retirement' with its connotations of rest and relaxation seems inappropriate: Richard's previous 'retirement' from the Regius Professorship of Medicine was followed by one of the busiest and most productive periods of his life during which he was responsible for establishing Green College. This retirement was in practice a transition from one occupation to another. Similarly Richard's 'retirement' from Green College is another transition, on this occasion to full-time cancer research. He still somehow finds time to listen to the theories of the youngest research workers with sincere interest, and is easily accessible in his office at Green College, or in the lunch-time bustle of the Radcliffe Infirmary canteen.

This *Festschrift*, therefore, is not in the British tradition, to mark the end of a distinguished career, but more in the tradition of Germany, where a *Festschrift* is often issued to honour someone on his birthday, looking both backwards and forwards. For this reason we chose to concentrate on cancer risks and cancer prevention, not only to cover a subject in which Richard has been pre-eminent but also to review a field in which he will continue to be a leader now that his change of occupation, following his second retirement, allows him once more to concentrate on research.

The contributors to this book constitute only a sample of the many people whose work has been influenced by Richard and the subjects covered comprise only a sample of the health problems which he studied during his career. The book is not intended to be a comprehensive text on cancer epidemiology and prevention; the topics have been selected to demonstrate some of the areas in which Richard's work has increased our knowledge about the aetiology of cancer and its prevention. The book does not, however, pay sufficient tribute to the other main impact of his epidemiological expertise: the influence his work has had on medical education and on the practice of medicine. The epidemiological approach is now employed in all areas of medicine and the mathemetical techniques that were once the preserve of the statistician now form one of the foundations of clinical research and thus clinical practice.

Neither does the book directly pay tribute to the kindness that Richard and Joan have shown to so many students and colleagues. Our gratitude to

them is best expressed, not in the compliments they deserve, but in the following discussion of one of the subjects they have done so much to advance – cancer risks and cancer prevention.

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Foreword

Sir Austin Bradford Hill, CBE, DSc, FRS,
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In 1945, at the end of the Second World War, I returned to the London School of Hygiene and Tropical Medicine. In succession to Professor Major Greenwood, I had been appointed Professor of Medical Statistics and Honorary Director of the group of statisticians on the staff of the Medical Research Council who had worked under him in the department. It was obvious that, in both teaching and research, a heavy load of work lay ahead.

On the academic side, many medical men and women released from war duties were anxious to be trained for work in the field of public health. The demand was so great that, for some time, the School had to run two parallel classes in the course for the University Diploma of Public Health. On the research side, I was, almost immediately, to be heavily involved in the Medical Research Council's trial of streptomycin in tuberculosis. This was the first randomized trial but with the rapid introduction of new drugs at that date it was clearly the precursor of many clinical trials. Running parallel were the large-scale trials of vaccines. Whooping cough was already on the doorstep; BCG and poliomyelitis were looming round the corner. Clinical and preventive medicine were changing and it was an exciting time.

To meet these requirements I had to rebuild my Department of Medical Statistics and Epidemiology and, hopefully, to develop the Medical Research Council group into a unit that could undertake its own researches and also give the statistical and epidemiological advice and collaboration that was likely to be called for on a growing scale.

In the later part of the war I had been working in the Medical Directorate of the Royal Air Force, ruled over by its vigorous and invigorating Director General of Medical Services, Sir Harold Whittingham. To work under my direction he had brought in a station medical officer from some distant aerodrome, Squadron-Leader Donald Reid. Reid had been doing some original work in measuring the stresses to which aircrew were subjected and their resulting health problems. The nature of this work and the interests it aroused in him led him, on demobilization, to consider specializing in psychiatric medicine. I was, however, able to attract him to epidemiology and he joined me at the London School of Hygiene

and Tropical Medicine as a lecturer in my department. Somewhat later Peter Armitage, an accomplished statistician, joined my Medical Research Council staff. With these accessions the immediate pressures were reduced and I was able to give more time to a course of teaching (set up before the war) in which I took great interest. This was a brief course in statistical ideas and methods (on two days a week for three months). Non-medically qualified students were accepted along with the medically qualified. The former were usually statisticians (for example, Dr Austin Heady and Dr Peter Oldham) who sought to make their careers in the medical field. The object was to introduce them to examples of the types of problem they would meet, the methods needed to solve them, the nature of medical statistics, and the kind of medical know-how they should seek to be able to use them intelligently. With the medically qualified students the object was to give them a similar knowledge of the simple statistical methods they would find useful in research work but – still more – to make them *think* numerically and experimentally, e.g. of the problems of collecting and interpreting data, of presenting them, of avoiding and detecting bias, of sampling, and so on; in short, arithmetic, logic, and common sense.

To this course, in 1947, came Richard Doll and his wife-to-be Dr Joan Faulkner, who was then, and for many more years, a distinguished member of the Medical Research Council's Headquarters' Administrative Staff. I was already acquainted with Richard through his work on the aetiology of peptic ulcer. The Medical Research Council had set up a committee to supervise this study under the chairmanship of Professor John Ryle; and I was a member of this committee. I do know that Richard came to consult me, but nearly 40 years, and some 40 committees, later I cannot claim to have any reliable memory of this 'supervision'. But at least it must have been close enough to impress me with his grasp of the statistical aspects of the job and with his skills and persistence in carrying it out – to achieve, for instance, a response rate of nearly 100 per cent in some required group. Already he had clearly, perhaps intuitively, at heart my subsequent teaching that all the standard errors and chi-square tests in the world could not compensate for incomplete, imperfect, or biased data.

During his attendance at the short course at the London School of Hygiene and Tropical Medicine I had the opportunity to get to know Richard well. The numbers attending the course were usually in single figures, and much of the interest, on my side, lay in the close contact that I had with the younger medicos of the day who were thus showing an interest in 'sums'. What was their work? What were their aims?

It was this close contact and my judgement of his character that led me to invite Richard to join my staff, to investigate with me the aetiology of cancer of the lung. There had been, in 1947, a Medical Research Council conference to discuss the increased, and increasing, mortality from the

disease, to which attention had been repeatedly drawn in the annual reports of the Registrar-General of England and Wales by that fine statistician Dr Percy Stocks, the Chief Medical Officer at the General Register Office. From the mortality returns – for town and country, and men and women – Stocks had argued effectively that the more accurate diagnosis of this cause of death was unlikely to be more than a contributory factor. An environmental cause was, therefore, to be sought and, initially, the obvious candidates were increasing air pollution (from the internal combustion engine) and the smoking of tobacco (with, in particular, the great increase in the smoking of cigarettes). Given funds and a medically qualified assistant, I was glad to accept the Council's invitation to undertake this research – with some initial aid and advice in its setting-up from Dr Percy Stocks and Sir Ernest Kennaway.

It was essential that my partner in the work should be *medically* qualified. There would be much organization involving hospitals, there would be much correspondence with doctors concerning their patients, over questions of diagnoses and the evidence upon which they were based. Owing to the First World War I had myself been unable to qualify in medicine and I had to seek someone willing to give medical support to an unqualified practitioner! I was, indeed, fortunate to have at hand Richard Doll and that he consented to play the role.

The inquiry, following the classical methods of epidemiology, was to be retrospective – in short, what were the characteristics and habits of patients with cancer of the lung in comparison with those of patients with other diseases? Smoking was only one fact. Deliberately, I widened the investigation. We sought information on many other personal features that might conceivably have a bearing on the problem – such as social class, occupational history, places of residence, specific or possible exposures to air pollution, forms of domestic heating in the home, and so on. All were brought into the final analysis. I decided also to include patients with cancer of some other sites, and their possible aetiological factors, in the hope that if we failed on the swings we might pick up a profit on the roundabouts.

On a grant from the Medical Research Council, Richard joined me at the beginning of 1948, and I soon realized how wise I had been in my choice. From twenty London hospitals we had a continuous flow of notifications of patients with cancer of the lung (and other selected sites); we had our own almoners visiting and interviewing these patients and also other patients whom they were instructed to choose (on closely defined rules) to serve as our 'controls'; we checked, after the discharge of each patient, the diagnosis of cancer and its basis – and we succeeded in doing so in 99.6 per cent – characteristic of Richard's persistent search for perfection and his capacity to persuade a host of doctors to respond to his

requests; a monument to his administrative skills. Finally, he put the returns in order and, step by step, we jointly built up the statistical analysis of the data. We concluded that 'smoking is a factor, and an important factor, in the production of cancer of the lung'. This we published in the *British Medical Journal* in 1950.

Such a conclusion led, naturally, to a great deal of scientific controversy. Also, with important vested interests concerned, we were subject to much ill-informed and tendentious criticisms in the lay press. Coming of a legal family (downwards from an Attorney-General and a Judge of the High Court) I would send these on to my elder brother marked 'Query libellous?', but the invariable answer was 'No, vulgar abuse'.

Richard was clearly unmoved by all this, for in 1950 he became a whole-time member of my Statistical Research Unit. In other words, at this point he elected to make his career in medical statistics and epidemiology. At the same time he maintained his clinical attachment to the Central Middlesex Hospital. Of this I was strongly in favour as I believed that, whatever other interests he might have, nothing could keep the 'doctor' so happy as to have some patients in his care. It would also, as time was to show, allow him to develop his own clinical trials of treatments in gastroenterology. (But this is the province of Sir Francis Avery Jones and I must not trespass.)

Returning to cancer of the lung, we had embarked upon an extension of the retrospective inquiry. This had been confined to the London area. With certain modifications, we had extended it to some large provincial towns. Richard continued with the enormously heavy organizational task and the continual checking and thoughtful watching as the data flowed in. I was thus free of all fears that some data might be lacking in quantity or quality; and he had a remarkable capacity for working long hours at the most exacting tasks. When finally we called a halt we had the results of interviews with nearly 5000 patients, including nearly 1500 with cancer of the lung.

The results of our analysis of all this material confirmed those of our earlier paper, but with larger numbers, we were able to extend the analysis to the other features we had recorded. For instance, we were unable to implicate atmospheric pollution in itself as a cause of lung cancer (though conceivably it could act in conjunction with smoking). This second paper we published in the *British Medical Journal* in 1952.

While the work on this paper was in progress – I think it was in early 1951 – I suffered an attack of influenza. While I was convalescent, and had an unusual freedom from academic duties, I had time to think. And my thoughts were of a *prospective* inquiry. My choice of a population fell on the medical profession. This was based upon three beliefs: (1) that knowing the importance of the subject, medically qualified men and women

would be sympathetic to such an inquiry; (2) that they would, therefore, be likely to reply on their smoking habits and history so long as the form was made short and simple; (3) that it would be possible to identify their subsequent deaths with the aid of the Registrars-General of the UK, since the medical qualification was likely to appear upon the death certificate.

On my return to the School I propounded this scheme to Richard and, at his suggestion, and as good experimentalists, we immediately put it to a preliminary test. We drew up a short and simple form and sent it to a small group of doctors drawn randomly from the medical register. The response was encouraging and so, in October 1951, we launched the full study. To this, we had finally some 40 000 responses and, as ever, Richard had their ordering and tabulating under full control.

I can remember opening many of those envelopes myself – not because we were short of clerical labour but because of my belief (which I still hold) that in such an investigation one should always get close to at least some of the original data if one is not to be misled subsequently by neat tabulations made by an assistant or, in these days, a computer.

We reported the results of this prospective inquiry in a brief paper in 1954 and more fully 2 years later, when a total of 1854 deaths from all causes had been reported to, or discovered by, us. They came not only from the returns made to us by the Registrars-General but from the General Medical Council and the British Medical Association and many other minor sources. In this Richard had again applied his customary assiduous search to ensure a complete record. For every one of the 88 deaths attributed to cancer of the lung he had sought confirmation, and the basis of the diagnosis, from doctor, consultant, or hospital. We accepted 84 as established. Once more, step by step, we jointly analysed these data and built up the statistical picture.

This is no place in which to discuss the results in detail and I shall confine myself to one paragraph from the summary to the paper (*British Medical Journal* 1956).

> From the retrospective studies . . . we concluded that if large groups of persons of different smoking habits were observed for a number of years they would reveal distinct differences in their rates of mortality from lung cancer. They would show, we believed, (1) a higher mortality in smokers than in non-smokers, (2) a higher mortality in heavy smokers than in light smokers, (3) a higher mortality in cigarette smokers than in pipe smokers, and (4) a higher mortality in those who continued to smoke than in those who gave it up. In each case the expected result has appeared in this prospective inquiry.

During these five years of the inquiry while we had to wait patiently (or impatiently) for the deaths to occur, Richard occupied himself with much other research (including his continued work on peptic ulcers). He examined the causes of death among gas workers with special reference to cancer of the lung. He made a similar study of asbestos workers. He collaborated with Peter Armitage in a study of the age distribution of

human cancers and a multistage theory of carcinogenesis to explain it. He began his very fruitful association with Dr Court Brown, who was subsequently the Director of the Medical Research Council's Unit on Clinical and Population Cytogenetics. Together they studied the hazards of radiation and, in particular, the incidence of leukaemia in certain circumstances, e.g. in patients treated by irradiation for ankylosing spondylitis, in British radiologists, in geographical areas with varying levels of background radiation, in infants *in utero* whose mothers had been X-rayed during pregnancy.

In those five years 1951–55, while scoring up the deaths of British doctors, Richard published (alone or as a co-author) 26 papers – 9 dealing with gastroenterology, 13 with cancer, and 4 with miscellaneous subjects. Hardly time to squeeze in a dull moment! Equally I do not think we experienced many dull moments in the 10 years of continuous inquiry that we had now made into one subject – the aetiology of cancer of the lung. The intrinsic interest and the social importance of the subject were such that we were determined, throughout, to secure accurate data on a very large scale and covering every possible aetiological agent, to analyse them comprehensively and rigidly and, finally, to present them simply and clearly. Of course, we had long discussions on the analysis, and we made, no doubt, many adjustments in the ways of presentation to meet our individual viewpoints. But ultimately, as I recall, we never, over the whole 10 years, had a serious difference of opinion.

A few years later (1961) I decided to retire. To succeed me Donald Reid became Head of the Department of Medical Statistics and Epidemiology, Peter Armitage was appointed to the University Chair of Medical Statistics, and Richard, to my pleasure and great content, was appointed Director of the Statistical Research Unit. With him he took the prospective inquiry; with Malcolm Pike and Richard Peto, he continued it for a further 20 years. During this time he moved the unit to Oxford, on becoming the Regius Professor of Medicine. Though our paths occasionally crossed, e.g. in the work on the Committee on Safety of Medicines, in the main I could now only rejoice and admire from afar.

A recent major publication (with Richard Peto) was completed in 1981, not long before his own retirement. It was entitled *The causes of cancer*. He sent me a copy and this he had kindly inscribed: 'With continuing admiration and gratitude for your teaching, much of which is reflected in this book, and your friendship'.

In one's old age it is pleasant to have flattery and an assurance of the continued friendship which doubtless gives rise to it. Both serve to remind me of my good fortune – that a great many years ago I was in a position to initiate the distinguished career to which this present publication is a tribute.

Foreword

Sir Francis Avery Jones, CBE, MD, FRCP,
Consulting Physician, Central Middlesex Hospital, London;
Consulting Gastroenterologist, St. Mark's Hospital,
London.

Professor Richard Doll has become the leading epidemiologist of our time, contributing new concepts of Man's relationship with his environment and opening up new fields for scientific study. He has made numerous oustanding research contributions and at the same time encouraged and stimulated many around him in their own researches. One of the secrets of his success has been his great ability to organize both his own time and other peoples'. His research has covered a wide spectrum including smoking, radiation, drugs, diet, and infection in relation to cancer. He has defined a programme for prevention, particularly in relation to cancer and cardiovascular disease and signposted the way forward for scientists, educationalists and politicians. His has been a medical contribution of Harveian proportions.

In these two Forewords, Bradford Hill and I describe the foundations on which Richard's scientific career has been built. It was my good fortune to pave the way for his first major epidemiological study soon after the war, supported by the Medical Research Council and based at the Department of Gastroenterology at the Central Middlesex Hospital. Throughout the war I had been working as a physician and Deputy Medical Director under the direction of the Central Medical War Committee.

Being surrounded by a large industrial zone, and serving 300 000 people, the hospital had a busy and eventful war. At the beginning of the war, medical students from the Middlesex Hospital lived in the 'Central', where they continued their clinical training, and this was an important step in building up the Central Middlesex as the first District General Hospital to play a full role in undergraduate and postgraduate teaching and in research.

With the encouragement of the dynamic Medical Director, Dr Horace Joules, I was able to begin to establish a Department of Gastroenterology. Most of the patients admitted with peptic ulcer and its complications, together with the other main diseases affecting the gut, were cared for in my wards. Fortunately, having a tireless Czech assistant, Dr H. Pollak, it was possible for me to keep good records, particularly relating to gastric

and duodenal ulcer and especially on patients who had bled. Links with the Invalid Kitchens of London, the forerunners of Meals on Wheels, enabled local factories to be stimulated to take a special interest in their dyspeptic workers. This brought me in touch with these cases, and a survey was arranged at the neighbouring Heinz factory to determine the prevalence of indigestion among their staff. The memorable figure of 57 per 1000 who had had or still had ulcer symptoms was recorded.

In the early post-war years plans were evolved to extend this work and an application was made to the Medical Research Council for support for a wide-scale study of occupational factors in the causation of gastric and duodenal ulcer. This project was accepted and sponsored by the Industrial Health Research Board of the Medical Research Council with a co-ordinating committee with Professor J.A. Ryle as Chairman, and Richard Doll was appointed to carry out the work. After a period of careful and detailed planning Richard tackled the field studies with great energy, covering a number of different occupations; a total of 6047 people were interviewed and assessed. The work took Richard to different parts of the country interviewing people at their places of work; his persistence knew no limits – he was prepared to climb to the top of a haystack if that was where a recalcitrant agricultural worker was to be found! It was a measure of his enthusiasm and good planning that as few as 1.6 per cent of those he wished to interview failed to come, a lapse rate remarkably small for this type of field inquiry.

The results of the survey were of great interest; among Londoners between the ages of 15 and 64 the prevalence of peptic ulcer was found to be 5.8 per cent for men and 1.9 per cent for women. This implied that over England and Wales the number of people with a peptic ulcer history was of the order of one and a half million and the number of men who had symptoms each year was over half a million. Foremen and others in positions of special responsibility in industry were found to be particualrly prone to peptic ulcer and agricultural workers particularly free from it. No confirmation was obtained of the widespread belief that bus drivers were especially liable to be sufferers. Anxiety at work, but not irregularity of meals or shift work, appeared to be aetiologically significant. Striking differences were observed between gastric and duodenal ulcers, notably in their social-class incidence, the former being more frequent among the labouring classes and rare among the professional, whereas duodenal ulcer was equally prevalent in all social classes.

Thanks to Richard's equally exhaustive library work and his skill in drafing, the Medical Research Council Report, Special Series No. 276 *Occupational factors in the aetiology of gastric and duodenal ulcer: with an estimate of their incidence in the general population* was published in 1951. This remains a classic study and proved to be an important guide for later