

Technical Reports

Erstmalige Verleihung des Helmut Horten Forschungspreises an Richard Doll und Richard Peto

Am 29. November 1991 wurde in Lugano im Rahmen eines feierlichen Aktes erstmals der Helmut Horten Forschungspreis an die beiden englischen Wissenschaftler Prof. Sir Richard Doll und Dr. Richard Peto verliehen. Die Preissumme betrug eine Million Schweizer Franken. Weil es das erste Mal ist, dass Wissenschaftler, die nicht Grundlagenforschung betreiben, mit einem derart prestigeträchtigen Preis – der von der finanziellen Dotierung her einen Vergleich mit dem Nobelpreis durchaus aushält – ausgezeichnet wurden, soll nachstehend etwas ausführlicher auf dieses bemerkenswerte Ereignis eingegangen werden.

Kurzportrait der Helmut Horten Stiftung

Helmut Horten, der Gründer der gleichnamigen Stiftung, hat in den fünfziger und sechziger Jahren in der Bundesrepublik Deutschland den gleichnamigen Warenhauskonzern auf- und ausgebaut. Nach seinem Rückzug aus dem wirtschaftlichen Leben und der Übersiedelung nach Croglio im Kanton Tessin schuf er 1971 die Stiftung „Villalta“, die nach seinem Ableben den Namen „Helmut Horten Stiftung“ erhielt. Durch Legat wurde das Stiftungskapital auf derzeit 60 Millionen Schweizer Franken aufgestockt.

Die Stiftung bezweckt „die Förderung des Gesundheitswesens durch Zuwendungen an medizinische Forschungsstätten, Spitäler und sonstige Institutionen der Krankenpflege sowie an Personen, die im medizinischen Sinne bedürftig sind. Unterstützt werden können alle Massnahmen, die die Gesundheit des Menschen schützen wollen“.

Die Tätigkeit der Stiftung war bisher vor allem ausgerichtet auf die Finanzierung medizinisch-biologischer Forschungsvorhaben, auf die Ausrichtung von Spenden für die Beschaffung von Apparaturen, Geräten und Spezialausstattungen, auf die Durchführung von Therapien, auf die Förderung spezialisierter Ärzte zur Weitergabe an die Schweizer Kollegen sowie auf Präventivaktionen und Aufklärungen.

Im Sommer 1989 hat der Stiftungsrat beschlossen, im ehrenden Andenken an den 1987 verstorbenen Helmut Horten den Helmut Horten Forschungspreis und den Helmut Horten Förderpreis zu schaffen. Der Forschungspreis wird für hervorragende Leistungen auf dem Gebiet der Medizin und der Biologie verliehen, „die geeignet sind, massgeb-

lich zur Förderung der menschlichen Gesundheit beizutragen“. Der Preis wird vorläufig alle zwei Jahre verliehen.

Anspruchsvolle Arbeit für das Preiskomitee

Ein Preiskomitee unter dem Vorsitz von Professor Dr. Georg Martz, emeritierter Professor für Onkologie an der Universität Zürich, musste aus insgesamt 153 vorgeschlagenen Wissenschaftlern beziehungsweise Forschungsteams aufgrund strenger Auswahlkriterien die Preisträger ermitteln.

Mit Professor Sir Richard Doll und Dr. Richard Peto von der Universität Oxford wurden zwei englische Wissenschaftler ausgezeichnet für ihre herausragenden Leistungen auf den Gebieten der theoretischen und der angewandten medizinischen Statistik mit denen sie in der Gesundheitsvorsorge und der Behandlung chronischer Krankheiten, insbesondere bei der Bekämpfung von Krebs- und Herzkrankheiten, bahnbrechende Ergebnisse erzielt haben. Nachfolgend findet sich eine englischsprachige Würdigung der wissenschaftlichen Leistungen der beiden preisgekrönten Forscher, verfasst durch Professor Carlo La Vecchia, Lausanne/Milano.

In seiner ebenfalls hier wiedergegebenen Laudatio würdigt Prof. Sir Colin Dollery das Werk der beiden Preisträger, das auch stark beeinflusst wurde vom bereits verstorbenen Sir Austin Bradford Hill. Professor Sir Richard Doll und Dr. Richard Peto haben die medizinische Statistik weiterentwickelt und zu einem Instrument ausgebaut, welches wichtige Zusammenhänge aufzeigt zwischen Verhaltensweise im Alltag und späterer Todesursache. Durch statistische Erfassung über Jahre hinweg und stetige Verfeinerung der mathematischen Methoden ist ihnen der Nachweis gelungen, dass beispielsweise das Rauchen nicht nur Lungenkrebs begünstigt, sondern auch andere Krebs- und Krankheitsarten fördert. Diese Erkenntnisse aufgrund mehrjähriger Beobachtungsreihen sind nicht nur wichtig für die Behandlung von Krankheiten, sondern vor allem auch für die Prävention. Sie leisten damit einen bedeutenden Beitrag zur Volksgesundheit. Schliesslich ist auch, gleichsam als Schlusswort, die kurze Dankesrede des Preisträgers Sir Richard Doll abgedruckt.

Prof. Felix Gutzwiller, Zürich

Sir Richard Doll

Sir Richard Doll has been, over the last four decades, one of the leading personalities in medical research, being involved and responsible of some of the most important achievements in the field of epidemiology, public health and clinical experimentation.

His most important single contribution is probably the 1950 case-control study of smoking and carcinoma of the lung with Professor Bradford Hill, which already included most of the current knowledge in terms of dose- and duration-risk relationships, as well as population attributable risk. That study provided the framework on which the subsequent cohort study of British doctors was planned, and which contributed to establish and quantify the relationship between tobacco smoking and several other neoplasms, chronic lung disease, cardiovascular diseases etc., as well as to provide a comprehensive framework for interpreting the smoking-lung cancer relationship.

The definition and quantification of the health consequences of smoking are, however, only one of the major contributions by Sir Richard Doll. Among several others, there are:

1. Definition and application of clinical trial methodology, starting from earlier studies of peptic ulcer.
2. Studies of radiation and cancer risk.
3. Several major issues of occupational carcinogenesis, from asbestos and lung cancer, to gas-coal workers, to lung and nasal sinuses cancers in nickel workers.
4. Major theoretical contributions, such as the formal development of the multistage theory of carcinogenesis, and of subsequent mathematical models for the age distribution of cancer in man.
5. Oral contraceptives, including myocardial infarction and other health consequences of their utilization.
6. Other aspects of drug epidemiology, including therapies of asthma, gastric ulcer, benzodiazepines, immunosuppressive treatments.
7. Descriptive epidemiology, particularly as the main editor of the first issues of *Cancer Incidence in Five Continents*.
8. Overview and risk assessment papers, such as the widely quoted 1981 paper with Richard Peto on the "Causes of Cancer".

Thus, Sir Richard Doll has covered a uniquely wide range of areas which have consistently been in the center of the scientific debate, and in all of these areas has proved his excellence since the beginning of his scientific career. He has certainly been, over the last few decades, the leading European figure in epidemiology, and one of the most outstanding personalities of the world scientific community. The impact of these achievements on human health

are consequently invaluable. Indeed, the reduction of smoking prevalence in some developed countries and, consequently, the waning of the tobacco-related epidemic in these countries which is a direct consequence of Sir Richard Doll's research has no comparison, in terms of public health impact, on a worldwide scale.

Prof. Carlo La Vecchia, Lausanne

Mr. Richard Peto

Richard Peto has been reader in cancer studies at the University of Oxford since 1975. He has produced a number of outstanding contributions towards our understanding of the process of carcinogenesis in animals and of the causes of cancer in humans. His major achievements have spanned over a number of other fields, including:

1. Theoretical medical statistics, with a number of important original contributions, including the development of the logrank test for the analysis of the results of clinical trials and animal experiments, and important review papers on the design and analysis of randomized clinical trials.
2. Applied statistics to animal and human data, with several important and original contributions to the development of the multistage theory of carcinogenesis, and problems of extrapolation and low dose estimation.
3. Studies on the natural history of chronic bronchitis and emphysema.
4. Meta-analysis applied to important clinical problems, such as the treatment of ischaemic heart disease and breast cancer.
5. Large-scale clinical trials of the treatment of myocardial infarction, particularly those based on the coordination of the ISIS study group.
6. A number of studies of tobacco, cholesterol, lung, gastric cancer and other major diseases in the Chinese population.
7. A long standing attention towards tobacco and the tobacco-related epidemic, particularly in the developing world.
8. Overview and risk assessment papers, such as the widely quoted 1981 paper with Richard Doll on the "Causes of Cancer".

In all these areas, Mr. Peto's achievements are of unique originality and substantial importance, and it is difficult to identify any other scientist of his generation with such a wide range of interests and outstanding level of achievements in any of the areas considered.

In terms of impact of Mr. Peto's work on human health, his contributions towards a better definition of treatment for important diseases such as breast cancer and cardiovascular disease would represent, by themselves, outstanding achievements. Even more important, on a worldwide scale, are his con-

tributions for a better understanding of the process of (tobacco-related) carcinogenesis, and his continuous involvement in major health policy issues, such as the control of tobacco and major health problems in developing countries.

Prof. Carlo La Vecchia, Lausanne

Laudatio

During their pre-clinical training medical students are trained as scientists and understand that correct conclusions can only be reached by carefully designed and properly controlled experiments of adequate size. In the clinical years the emphasis is on the patient as a unique individual and patient management decisions are often based on opinions, impressions and poorly validated consensus. Many doctors have found it hard to accept that conclusions about the aetiology of disease and its response to treatment should be based upon similar scientific and mathematical principles to those applied in experimental laboratory science. An early rebel against the system was a 4th year medical student at St. Thomas's Hospital in London, one of our most traditional medical schools. The young Richard Doll wrote an article on the importance of Medical Statistics in the St. Thomas' Hospital Gazette in 1936.

Perhaps the greatest contribution to changing that way of thinking was made by Sir Austin Bradford Hill who died earlier this year. For it was Bradford Hill, a non-medical statistician with a deep understanding of clinical problems, who established the statistical basis of the randomised controlled clinical trial which has become the standard means of assessing the worth of new forms of medical treatment.

There are experiments of man, when we deliberately administer drugs or carry out surgical procedures, and there are experiments of nature when humans by their habits or their environment expose themselves to toxic substances. Chief among these is tobacco. The most important early papers in the long battle against tobacco-induced cancer of the lung were written by Richard Doll and Bradford Hill between 1950 and 1956 where they clearly set out the greatly enhanced risk of lung cancer in smokers. But these conclusions were by no means universally accepted at the time and the tobacco companies mounted a strong defence, aided by a famous statistician of the day who cast doubt on the conclusions. More data, better data and, particularly prospective data was needed. Richard Doll initiated the famous study on British doctors in which their smoking habits were correlated prospectively with certified cause of death. Year by year and inexorably the evidence piled up. This study not only demonstrated in a most convincing manner the

greatly increased risk of lung cancer in smokers but it added a whole list of other smoking related cancers from the point of entry of the carcinogen at the lip and tongue to its exit in the bladder and urethra. It did more, it showed a great increase in deaths from bronchitis and emphysema and a whole range of cardiovascular diseases, particularly from coronary disease.

There is of course much else besides for Sir Richard's work has included seminal contributions in many fields ranging from the safety of the contraceptive pill and deaths from asthma to the hazards of ionising radiation. But Sir Richard's contribution in exposing the health hazards of tobacco smoking dwarfs these other achievements. The decline in smoking amongst the better informed and educated throughout the western world and the evidence of a downward trend in tobacco related disease is an achievement which owes more to his work than to any other factor. It is an achievement in benefiting human health that very few other doctors have made.

If Bradford Hill is the grandfather and Richard Doll the father then Richard Peto is the son (some might say the enfant terrible) in this distinguished lineage of statisticians and epidemiologists. Richard Peto is a brilliant mathematician who has raised the interpretation of clinical trials to a higher plane of art. It started from the simple proposition that most clinical trials, even if they include thousands of patients, are too small to permit robust conclusions and important benefits (and hazards) might be missed because they were insufficient of those events in any one trial to reach statistical significance. Indeed, it is quite common for clinical trials to be contradictory even if the majority point one way. Before Peto such disagreements often lead to confusion and paralysis of decision. The answer, Peto reasoned, was to do what any sensible citizen would do which is to look at the totality of the evidence. His particular contribution was to devise a formal mathematical technique for pooling the evidence derived from many trials for a particular class of therapeutic agents or in a particular disease entity. This technique, known as meta-analysis, proved to be remarkably powerful. Besides giving a much more accurate assessment of overall benefit it also disclosed new information. For example meta-analysis of the hypertension trials by Peto and his colleagues showed that there was a small but definite reduction of coronary events besides the well established reduction of stroke. Meta-analyses of the breast cancer trials have yielded valuable new information supporting the value of supplemental chemotherapy. Peto's other great contribution has been to emphasise the value of large simple clinical trials versus small complex ones. His influence can clearly be discerned in a whole range of cardiovascular trials with thrombolytic agents (e. g. streptokinase tpa) and in cancer trials.

Richard Doll, long nominally retired is still at his desk in Richard Peto's unit. They still publish together and have inspired a whole new generation of recruits to medical statistics and epidemiology. They have put forward challenging evidence concerning the environmental basis of many human cancers based on international comparisons. Few other investigators can claim that their sample size is equal to the human population of the world.

It is a particular pleasure for me as clinician to commend these two remarkable people to you for through their work in studying morbidity and mortality in large groups of people they have contributed greatly, not just to the health of nations, but to the care of individuals afflicted by diseases ranging from heart disease to cancer. By their contributions through the methods of epidemiology and statistics Richard Doll and Richard Peto have attained the highest level of medical science and made an enormous and direct contribution to public health. They are worthy winners of this, the first, international prize of the Helmut Horten Foundation.

Sir Colin Dollery, London

Speech of Sir Richard Doll, joint winner of the Research Award

Epidemiology, the branch of medical science in which I have been working since 1946 and in which Richard Peto has been working since we started our collaboration in 1967, has the tremendous advantage that its findings are often directly applicable to the prevention or cure of disease. Initially, as the origin of the term implies, it was concerned only with the epidemics of what subsequently proved to be diseases spread by infection with microorganisms or parasites. Later it came to be concerned also with all other diseases that varied in incidence with time and place or, within populations, with human behaviour and which occurred, in truth, in epidemics but in epidemics with broader time scales and less easily visible geographical or social boundaries. Now, we also use the term to include not only observational studies of the correlates of particular diseases, but also experimental studies in which efforts are made to evaluate methods for both the prevention and treatment of disease by randomised controlled trials.

I was personally particularly fortunate when, seeking an opportunity for the conduct of medical research shortly after the end of the second world

war, I was offered an appointment by Professor Bradford Hill, for he was just then beginning to define the requirements for productive epidemiological research into the causes of chronic diseases and he shortly afterwards introduced the concept of randomisation into the conduct of clinical trials. I was, moreover, doubly fortunate, as I had the opportunity of applying these techniques with him to epidemiological problems that were ripe for solution, and with Dr. Avery Jones to the separation of effective and ineffective remedies for gastric and duodenal ulcers.

Epidemiological research has not contributed much to the understanding of the mechanism by which chronic disease is produced (though it has contributed something), and it has not been good at detecting small effects of the hundreds of chemicals that may have been shown to cause cancer in laboratory animals and to which workers have been exposed in small amounts in industry or to which the public has been exposed in the environment. To criticize it for this, however, is to criticize it for failing to achieve aims that it does not have. Epidemiology starts not with the 10,000 chemicals that may be found to pollute a particular area but with the 10,000 deaths that occur annually in an area and it tries to determine the major causes of these actual deaths. It is certainly more likely to overlook many small effects of chemicals than laboratory studies might do: but it is much less likely to overlook the large determinants of contemporary mortality rates from common conditions like cancer, ischaemic heart disease, hypertension, and emphysema – determinants such as smoking and blood cholesterol levels that have been found by epidemiological research to be each responsible for premature deaths in more than 10 percent of the populations in many developed countries.

It was the direct human relevance of epidemiology that attracted both Richard Peto and me to it as a scientific discipline and we have tried to use it in our research and in our writings to assess major hazards and to help society develop a sense of proportion about the major and minor risks of daily life. It was, therefore, with delight that we learnt that the trustees of the Helmut Horten Stiftung had a similar concern. That they should have made the first award to us is, perhaps, because they believe as strongly as we do in the benefits of random allocation. We are nevertheless immensely grateful for it and look forward to putting the award to good practical use.

Sir Richard Doll, Oxford