

Epicenter

Department of Epidemiology Newsletter

Special Edition



Sir David Cox

Honorary Fellow

Nuffield College, Oxford, UK

165th Cutter Lecture on Preventive Medicine

Statistical Science: A Grammar For Research

May 3, 2017



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Special Edition

165th Cutter Lecture

Lecturer: Sir David Cox

Cutter Lecture on Preventive Medicine

Since 1912, the Cutter Lecture on Preventive Medicine has been one of the most respected presentations, especially in the field of epidemiology. The lectures are administered by the Department of Epidemiology at the Harvard T.H. Chan School of Public Health according to the bequest from John Clarence Cutter, MD (1851-1909), a graduate of the Harvard Medical School. He specified that the lectures be delivered in Boston, free of charge to medical professionals and the press. Covering a range of public health topics, the lectures remain dedicated to enhancing the physical and social welfare of the world's population.



Sir David Cox

Sir David Cox graduated in mathematics from the University of Cambridge. He worked in government sponsored industrial research for six years before returning to University of Cambridge's Statistical Laboratory. After five years he spent one year at Princeton, Chapel Hill and Berkeley before holding posts at Birkbeck College, London and for 20 years at Imperial College, London. He then spent six years at Warden, Nuffield College, Oxford before retiring in 1994. Dr. Cox's research interests have combined theoretical and substantive issues, over recent years often with an epidemiological or medical focus. He has made pioneering and important contributions to numerous areas of statistics and applied probability, of which the best known is perhaps the proportional hazards model, which is widely used in the analysis of survival data.

He holds a number of honorary degrees, notably one from Harvard, and was knighted by Queen Elizabeth II in 1985. He is a Fellow of the Royal Society, Foreign Associate of the National Academy of Sciences and Fellow of the Royal Society of Canada. David Cox is the recipient of many awards including in 1990 Kettering Prize and Gold Medal for Cancer Research, in 2010 Copley Medal of the Royal Society, and is the first ever recipient of the International Prize in Statistics. From 1966 to 1991 he was the editor of *Biometrika*. He has written or co-authored 300 papers and books.

His books include *The Planning of Experiments* (1958), *Queues* (1961), *The Theory of Stochastic Processes* (1965), *Analysis of binary data* (1969), *Applied statistics, principles and examples* (1981), *Analysis of survival data* (1984), *Asymptotic techniques for use in statistics* (1989), *Multivariate dependencies, models, analysis and interpretation* (1995), and *Principles of Statistical Inference* (2006).

Statistical Science: A Grammar for Research

On May 3, 2017, the Harvard T.H. Chan School of Public Health hosted the first-ever live-stream transatlantic Cutter Lecture, delivered by Sir David Cox from his home in Oxford, England. Cox began by outlining the primary purposes of statistical thinking as it relates to scientific research, particularly in the field of preventive medicine. One role is to present a series of unified ideas regarding a topic; the other intent involves systematic methodologies for analyzing situations involving variability and uncertainty. Cox cautioned that in order to be fruitful, statistical concepts must emerge seamlessly from the subject matter at hand. This is often a challenge since some scientists reactively add statistics to a research project, primarily to satisfy regulatory authorities. He urged the audience to refute this temptation and understand that there is a far more significant and constructive purpose for statistical thinking. Overemphasis on formalities can distract us from the underlying value statistics bring to designing and drawing meaningful conclusions from research studies.

Designing an Effective Investigation

The first steps in a research study center on formulating focused and answerable questions, and determining which individuals you will observe. Other aspects include metrology (measurement), data collection, analysis, conclusions, and, lastly, interpretation of results to influence medical policies and practices. When devising questions, Cox suggested it may be best to keep things simple and begin with a single focused question in studies that involve topics with minimal existing literature. Conversely, in a field that has already been broadly analyzed, it may be more efficient and insightful to ask a battery of interlocking questions that can be studied simultaneously.

Reinforcing the importance of simplicity, Cox cited a colleague who conducted a small trial comparing treatment and control among his arthritis patients by asking one simple question: “Could you put your shoes and socks on unaided today?” The yes or no answers he received provided sufficient data to assess the effectiveness of intervention.

A natural, unobtrusive question is more likely to elicit truthful answers than multi-dimensional questionnaires, which are difficult to administer once, impractical to process multiple times, and perhaps intrinsically unreliable in certain situations.

After summarizing a nutritional experiment that examined the impact of milk on the height and weight of 20,000 children in Lanarkshire, Scotland, in 1930, Cox pointed out that a little mathematics can go a long way in providing critical insight for effective study design. The validity and potential for meaningful interpretation of the milk study were destroyed when basic premises and calculations were overlooked, directing milk to the most disadvantaged children rather than adhering to the randomization criteria required for relevant research conclusions.

Randomized Versus Observational Studies

Comparisons between randomized clinical trials and observational studies can be misleading, warned Cox. A more telling contrast involves interventionist studies in which treatment allocation is determined by a defined algorithm specified by the investigator. In an observational study, we know who experiences a particular exposure, but we do not know why or how, whereas in an interventionist study, we know the details of the procedure, including the reasons behind treatment allocation. In some cases, such as when there is subjective allocation or potential bias involved—as in the Lanarkshire milk experiment—it is absolutely crucial that allocation involve randomization. However, there are two situations when randomization is a bad idea.

In some cases, the complexity of the lab situation demands abandoning randomization in favor of systematic order. Cox pointed to his experience with a large investigation that involved eight specimens, each of which required a different lab procedure. In this scenario, randomization could have led to confusion and specimens receiving the wrong treatment, resulting in errors during the interpretation phase of the research study.

The second instance when formal randomization may reflect poor study design is when only a small number of units are involved, such as a small-scope intervention trial involving a few communities. There is nothing to be gained by randomization. It is better to look at all the possibilities here, examining the differences between communities and systematically choosing the best treatment allocation approach.

When R.A. Fisher, the statistician who invented the randomization technique, was asked what one should do if the approach results in an undesirable experiment design, he replied: “Throw it away and start again, of course.”

Special Edition - 165th Cutter Lecture: Sir David Cox



Check out all of the photos from the event [here](#).



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Analysis and Interpretation: Discovering What Is Most Significant

Cox stressed the importance of planning the analysis stage of an investigation. “Collecting data without knowing how you will analyze it is a recipe for disaster,” he noted. However, this does not mean that an investigator must stick rigidly to the plan. The data may actually dictate a different direction, especially when anomalies are discovered, or a long time has elapsed between the study planning and data gathering stages of an experiment.

Cox went on to summarize several types of scientific study. First, he asked listeners to assume a small number of explanatory variables (intrinsic properties of subjects, exposures, and treatments, for example) and a modest number of individuals. In this case, the scientist may safely use standard regression methods but should check for abnormalities, critically examining the scenario even though it is relatively straightforward. In this situation, it is likely that a simple table will suffice to summarize data; no elaborate analysis is required.

In another example, the audience was presented with a scenario featuring an enormous number of explanatory variables and a small number of individuals—a genomics study, for example, where you may have 10,000 or more variables and only 100 patients. How are you going to study the dependencies associated with outcomes when there are so many more variables than subjects? In 1996, Robert Tibshirani, a Stamford University scientist, suggested a concept called the “lasso,” in which an investigator enforces an economical model that requires selection of a limited number of explanatory variables. This drives discovery of the specific variables contributing to outcomes.

Cox and colleague Dr. Heather Battey of Imperial College (London) are currently engaged in a related study involving large numbers of variables. In their exploration, each variable is tested numerous times under a variety of conditions, always in conjunction with other variables. Some variables “always win,” appearing frequently, while others show up only once or twice. The scientists are able to reduce the number of selected variables from 10,000 to about 1000 and then repeat the process until only a very small number of significant variables remain. This is the data that provides meaningful explanation and the basis for insightful interpretation. Statistics can take you no further, Cox explained. The goal is not one single answer; it is rather an attempt to specify several reasonable alternative explanations.

Next, Cox addressed challenges faced during the interpretation phase of investigation. Imagine a simple randomization study, comparing a treatment with a control, in a pharmaceutical context, for example. Researchers find that treatment is significantly better than control. In aggregate, if all the patients in the study receive treatment, the outcome will be better than if all were in the control group, all other things being equal. But there are some patients for whom the proposed treatment is a decidedly bad idea. What do we do about that? This raises the issue of generalization and specificity. The challenge involves the ability to provide a general recommendation for a majority population of patients while at the same time delivering tactical advice to clinicians tasked with tailoring approaches for specific patients—treatment based on variables.

Go Forth... With Courage and Caution

In closing, Cox reiterated that the main limitation of statistical thinking likely derives from an emphasis on formality in investigations that encourages some scientists to obsess with instruments like significance tests and competence intervals. Instead, the focus should be on designing studies that produce sound and justified conclusions.

One prevailing notion of disease causality centers on exposure variables leading to different outcomes (the foundation of randomized experiments), but Cox prefers reliance on a deeper hypothesis that points to evidence of underlying (i.e., biological) mechanisms. Particularly in a public health context, conclusions should be reached via subject matter interpretation and independent justification that can explain the onset and timing of various effects. Citing a common example of misguided causal inference, Cox mentioned the rash, often unsubstantiated dietary recommendations typically touted by the press, which damage the public image of medical science and produce skepticism. The most powerful scientific conclusions arise from synthesizing evidence from many different sources. Statistical arguments can establish the viability of individual components.

Cox urged researchers to be courageous as well as cautious in their research endeavors. Science simultaneously requires consistent bravery, insightful interpretation, and precise communication. Statistical thinking has much to contribute to the cause.



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