Probability Models and Cancer

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Editors

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PROBABILITY MODELS AND CANCER

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edited by

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Jerzy Neyman

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1894-1981

In the late Spring 1981, Professor Neyman approached us with the idea that there should be an interdisciplinary conference for an exchange of ideas between statisticians and biologists working on Cancer. Furthermore, he wanted that conference to take place forthwith, or at the latest in early July. In the short time available, organization of such a meeting appeared difficult to impossible, but Neyman went at it with his usual energy and enthusiasm and there was a conference.

Neyman is well known for his fundamental contributions to the very foundations of the science of Statistics. He is also well known for his contributions to applications of Statistics to various domains, extending from Astronomy to Weather Modifications. His involvement in the subject of Cancer dates back to the late fifties when he spent three months at N.I.H. in Bethesda. This involvement led to over 20 years of research activity on the subject. At first Neyman was interested in the design of experiments that would distinguish between the one stage and multiple stage theories of carcinogenesis. He arranged for such experiments to be performed. Some of the history is recounted in his own paper in the present volume. Later on Neyman became interested in the action of radiation on organisms and on single cells. His efforts with P. S. Puri, led to elaboration of complex stochastic models and of a search for data that would either corroborate such models or show their deficiencies. The search for data was at first fruitless. However we learned, from Dr. Hackett and Dr. Ainsworth, that Dr. Yang was developing precisely such experimental data in a laboratory within walking distance from our own offices. At this point Neyman determined that it was imperative that we meet and exchange ideas with at least some of the people working on carcinogenesis, mutagenesis and related

subjects. Hence the conference whose Proceedings are in the present volume.

As already mentioned, the organizational task appeared difficult to impossible. In order to insure some impact on other workers in the field, Proceedings should be prepared and published. There was no time to secure Federal funds and our University dragged its administrative feet. Neyman proceeded along, with vigor, and made from his personal funds a grant to cover all expenses. The conference turned out to be an unqualified success. However shortly thereafter, Neyman was stricken and, after a short hospitalization, passed away. As was characteristic of him, he worked in the hospital to the very last hour before his demise.

He has left us with a monumental scientific heritage. His death marks the end of a remarkable era in the subject of statistics itself, an era marked by the names of Neyman, Pearson, Fisher, and Wald, whose contributions constitute the very basis of our science and methodology. But Neyman's legacy extends far beyond ordinary statistical methodology. He always insisted on the construction of stochastic models of natural phenomena, based on the available knowledge in the field. This meant delving into the subject itself and coming up with formulas with at least some semblance of relation to reality. In all of this he was great and was an inspiration to many.

We regret that he did not live to see the publication of the present Proceedings. However we would like, fondly and respectfully, to dedicate them to his memory.

Introduction

This is a collection of papers presented at a short Cancer Study Conference organized by J. Neyman and L. Le Cam in July 1981. The purpose of the conference was to improve communication between statisticians and scientists studying cancer in the laboratory, or in real life. The former group is often asked for advice on particular matters. Some of its members also have a genuine interest in the subject itself. They can propose mathematical models that should aid in understanding what happens in the laboratory and in life. However, some knowledge of the facts and some understanding of their relationships are indispensable, if the models are to be at all realistic. The conference itself provided a forum for interaction between several groups. It is our hope that the papers collected here will further such interest and cooperation.

The papers on the "substance" of the subject were kindly presented by their authors at a level accessible to statisticians. They cover many different aspects of the field. Dr. Hackett tells us about cell cultures maintained in her laboratory at the Peralta Cancer Research Institute. They have many uses in studying the structure of normal and abnormal cells and their reactions to various stimuli. It appears that tumors of the same generic name differ, but that even within a given tumor there is a surprisingly large variability that should be taken into account in the design of a drug cocktail appropriate to the chemotherapy of that tumor.

The paper by V. S. Byers *et al.* deals with the curious properties of monoclonal antibodies directed against osteosarcoma tumors. They do not bind to normal cells, but do recognize a number of other tumors, including several carcinomas. They can, and will be, used as "magic bullets" that stick to abnormal cells and inject them with toxins. They are most valuable in studies of antigen expression in normal and transformed cells.

Every one of us lives in a sea of mutagens. Joyce McCann and Renae Magaw tell us about the statistical problems involved in calibrating the various tests for mutagenicity and in the development of a suitable scale for mutagenic potency.

The paper by J. Ainsworth is a short treatise on the mutagenic, carcinogenic and other deleterious properties of radiation. It covers much of the current knowledge on dose-rate, dose fractionation effects, and comparison of "biological efficiency" of various forms of radiation.

There are two other papers on the effects of radiation. It turns out that J. Neyman and P. S. Puri had proposed a mathematical model of the effect of radiation on isolated cells in culture. It happens also that Tracy Yang and his colleagues were finding out experimentally what occurs if one irradiates cells in culture. Whether the mathematics and the laboratory results fit together is not yet known, but shall be in a few months. The Neyman-Puri equations include a time variable absent in previous models, even deterministic ones. Special experiments may be needed to verify that time does indeed play a role of the kind implied by the equations.

A very interesting development in cancer studies has been the discovery that genes responsible for the damage done in cases of transformation by viruses may be some of our own genes, which perform useful functions under normal conditions but are made overeager by viral action or other stimuli. The story is told very briefly by H. Oppermann.

Professor H. Rubin reminds us that an organism is more than just a congregation of separate cells. In his challenging view, the organization of cells in a tissue is a most important aspect, often neglected in the literature. By forcing malignant cells to "organize" themselves in close proximity, he can make them forget their malignant dispositions for a few generations. The mathematical problem of formulating models in which such organization is accounted for appears formidable.

On mathematical models, we have presentations by Bühler, Bartoszyński, Clifford, Le Cam, and Puri (mentioned earlier). P. Clifford shows that very different mathematical models may well be

indistinguishable, no matter how many observations are made. That creates real difficulties because, within the limits of non-identifiability, different models may suggest different predictions, policies, and therapies.

Neyman's paper deplores the fact that even with "serial sacrifices", lack of identifiability remains. Many important biological parameters cannot be estimated. He suggests the development of "non invasive" procedures to monitor the laboratory animals' health.

Although it was not planned that way, the papers by Bühler, Bartoszyński and Le Cam encountered a common theme: some of the most often used mathematical models of tumor growth or metastasis simply do not fit the observable facts.

Prehn's theory of carcinogenesis through clonal selection says that chemical carcinogens act, not by transforming cells, but by damaging normal cells more severely than some that already had undergone some transformation. Bühler shows that a model built on this assumption does not fit the facts.

The paper by Bartoszyński *et al.* and the paper by Le Cam point out that a very commonly used model, implicit in simplified form in much of the medical literature on tumor growth, just does not fit, and in fact is off by factors of 10^5. The two groups of authors differ strongly on the interpretation of the lack of fit and on how to fix it.

R. Bohrer considers a different problem: what statistical tests should be used if you are trying out various chemicals and their combinations for mutagenicity or carcinogenicity? The problem of optimal selection of the statistical procedures does not have a clear-cut answer.

E. L. Scott reports a series of detailed statistical analyses on the effect of ultraviolet irradiation in mice. The effects are complex, depending on the UV wave lengths, dose rates fractionation, etc. The human epidemiological studies on skin cancer do seem to bear out a possible extrapolation from mice to men.

We hope that the papers printed here will give the reader an inkling of present knowledge and spur him or her to try to improve the state of

the art.

Publication of the papers was made possible by the services of North Holland Publishing Company. Preparation of the camera-ready copies involved many of our associates. Particular thanks are due to Monica Jackson, Richard Eskow, Marilyn Hill, and, for the technically difficult parts of the process, to Richard Haney.

I wish to extend thanks also to my students and colleagues who proofed manuscripts at various stages of the process. The responsibility for the flaws that remain are not theirs, but mine.

July 13, 1982

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Opening Address

Jerzy Neyman
University of California, Berkeley

It gives me a great pleasure to open this conference intended to promote the interdisciplinary effort to study carcinogenesis.

I like to think of the present conference as the fourth of a sequence that started in 1977. The first conference of the sequence was organized by the Institute for Energy Analysis, Oak Ridge Associated Universities. It was a highly interdisciplinary conference. The participants included a substantial number of hosts, somehow connected with the institute, and about an equal number of statisticians from several centers in this country and a few from abroad. I attended this conference and have very pleasant memories. I learned at the Oak Ridge Conference many details of radiation related experiments on carcinogenesis that altered my perspective on the relative importance of certain statistical studies. The proceedings of the conference were published in 1978.

The second conference of the sequence occurred in 1979. It was also held at the Oak Ridge Institute for Energy Analysis, reflecting the conviction of the leading scholars there (Dr. Peter Groer) that the success of research in this particular domain depends on cross- fertilization.

As far as I know, the proceedings of the second Oak Ridge conference are not published, so that the ideas discussed do not reach research workers who did not attend the conference.

However, the two interdisciplinary conferences organized by "substantive" scholars at Oak Ridge inspired some statisticians. This inspiration is documented by a special session at the last summer's meeting of the Institute of Mathematical Statistics held on the Davis Campus of our

University. The session was labeled "Interdisciplinary Study of Carcinogenesis". The participants included Dr. J. M. Holland from Oak Ridge, whose ideas are very inspiring to me.

No attempt was made to publish the proceedings of the special session of Davis, which I consider as the third item of the sequence initiated in 1977 at Oak Ridge. Contrary to this, in organizing the present Cancer Study Conference a strong effort was made to have our Proceedings published. My hope is that they will appear *soon*!"

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The Cellular Biology of Mammary Cancer: Potential Resource for Biostatisticians

Hackett, A. J.

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1. The Cellular Biology of Mammary Cancer: Potential Resource for Biostatisticians

Mammary cancer is a highly variable disease and the basis for the variability is thought to be the cell of origin. Although most breast cancers are intraductal, they vary widely in morphological, behavioral and prognostic characteristics probably as a reflection of the stage in the differentiation process as well as the stage in malignant progression. In addition, the inductive basis for cancer may influence the nature of the disease.

There is epidemiological evidence that cancer in humans results from an interaction of multiple factors and that there is a reversible stage in the induction of cancer (1). While there are several multifactorial and multistage model systems of cancer induction in experimental animals that have provided information about these and other phenomena associated with carcinogenesis (2, 3), extrapolation from animal models to human cancer has been difficult. One difficulty in studies on the cellular biology of human cancer stems from the heterogeneity of the human population and