BIOSTATISTICS:

Statistics in Biomedical,
Public Health and
Environmental Sciences

The Bernard G. Greenberg Volume

Edited by P. K. Sen

NORTH-HOLLAND

BIOSTATISTICS:
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edited by

Pranab K. SEN

Department of Biostatistics
University of North Carolina
Chapel Hill, NC
U.S.A.

Dedicated to Professor Bernard George Greenberg

PREFACE

This set of essays in a broad spectrum of Biostatistics is dedicated to our highly esteemed colleague, Bernard George Greenberg, Kenan Professor of Biostatistics and former Dean, School of Public Health, University of North Carolina, Chapel Hill. Professor Greenberg attained his sixty-fifth birthday on October 4, 1984, and this commemorative monograph is in honor of this occasion. It is a measure of the esteem and affection with which he is held, and reflects the tributes of his colleagues and students. For more than three decades, Dr. Greenberg has played a key role in the development of Biostatistics program in North Carolina (as well as in a national cum international setup), broadening the traditional corners of Biometry to include Public Health, Environmental and Biomedical Sciences. It is indeed by virtue of fruitful interaction of statistical methodology planning and the real world problems arising in Demography, Epidemiology, Clinical Trials, Occupational Health and Environmental Sciences, Health Administration and Education, Delivery of Health Services and a variety of Biomedical (including Neurological) Sciences that Biostatistics has emerged as a discipline on its own with significant academic as well as professional utility. The art of Biostatistics lies in the harmonious blending of the delicate art of understanding the salient features of the basic problems in experimental sciences, transmitting them to statistically meaningful and interpretable forms and drawing valid and reliable statistical inferences from them. The Department of Biostatistics, University of North Carolina, Chapel Hill represents an exemplary example of such interaction, and this is largely due to the outstanding leadership of Professor Greenberg and his contributions to both theoretical and applied Biostatistics.

There is hardly any area within the wide spectrum of Biostatistics that has not been enriched by the contributions of Professor Greenberg. An article in appreciation of his varied contributions, written by his younger son, Dr. Raymond S. Greenberg, included in this volume, depicts this picture clearly. A complete list of published work of Professor Greenberg is also included in this volume for a comprehensive account of his long career as a biostatistician academician. It is within this broad realm of Biostatistics, we have attempted to have contributions to this volume along with the hope that it would match his visions in spirit. It was very difficult to have an exhaustive set of contributions in this respect, and because of obvious limitations, we had to limit ourselves. We apologize if any areas has been left out inadvertently or any important contribution has been omitted.

I feel it a great honor and privilege to edit this volume. In the development of my professional career, Professor Greenberg has been the most influential person, and, on a personal level too, he has always been like my own elder brother. The task of editing this volume has been made easier by the warm and most friendly support I have received from most of my colleagues in this department as well as from the school. In particular, Dr. James E. Grizzle's consistent help and encouragement have always been very helpful. Most of the administrative work relating to this volume has been carreid out by Ms. Roberta Clark, and the whole monograph has been typed by Ms. Jennie Capparella, to both of whom I am deeply indebted for their able assistance. I would also like to record here the encouragement and support from Dr. Gerard Wanrooy of North Holland Publishing Company towards to the planning and preparation of this monograph. Finally, all the articles in this volume have been reviewed, mostly by other contributors and sometimes by other colleagues acknowledged at the end of some of the papers. To all of them, we express our sincere thanks for this whole hearted cooperation and professional work.

Professor Bernard G. Greenberg is planning for retirement by the end of June 1985. We all wish him a very happy and long life after retirement.

Chapel Hill, NC
November 13, 1984

P.K. Sen

CONTRIBUTORS

[Numbers in parentheses relate to the initial page numbers of the articles contributed.]

M.G. Akritas, *Institute of Statistics, Texas A&M University, College Station, TX 77843 (221).*

Ingrid Amara, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (357).*

S.I. Bangdiwala, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (13).*

V.P. Bhapkar, *Department of Biostatistics, University of Michigan, Ann Arbor, MI 48109 (237).*

George E. Bonney, *Department of Biometry, Louisiana State University Medical Center, New Orleans, LA 70112 (437).*

N.E. Breslow, *Department of Biostatistics, University of Washington, Seattle, WA 98195 (55).*

Erica Brittain, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (31).*

Edward Bryant, *Ortho Pharmaceuticals, Raritan, NJ 08869 (251).*

Shoutir Kishore Chatterjee, *Department of Statistics, Calcutta University, Calcutta 700019, India (283).*

Prithwis Das Gupta, *Population Division, U.S. Bureau of the Census, Washington, DC 20233 (75).*

H.A. David, *Department of Statistics, Iowa State University, Ames, IA 50011 (305).*

C.E. Davis, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (31).*

Jeremy E. Dawson, *Department of Physiology, J.C.S.M.R., Australian National University, Canberra, A.C.T. 2601, Australia (345).*

N.E. Day, *University of Washington, Department of Biostatistics SC-32, Seattle, WA 98195 (55).*

Victor De Gruttola, *Department of Biostatistics, Harvard University School of Public Health, Boston, MA 02215 (421).*

Donald L. Doerfler, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (195).*

Neil Dubin, *Institute of Environmental Medicine, New York University Medical Center, 550 First Avenue, New York, NY 10016 (165).*

Regina C. Elandt-Johnson, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (109).*

Robert C. Elston, *Department of Biometry, Louisiana State University Medical Center, New Orleans, LA 70112 (437).*

K. Ruben Gabriel, *Department of Statistics and Division of Biostatistics, University of Rochester, Rochester, NY 14642 (315).*

Edmund A. Gehan, *Department of Biomathematics, University of Texas System Cancer Center, Houston, TX 77030 (39).*

Dennis Gillings, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (251).*

Raymond S. Greenberg, *Atlanta Cancer Surveillance Center, Emory University School of Medicine, Decatur, GA 30030 (1).*

Muhammad K. Habib, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (511).*

Frank Harrell, *Division of Biometry, Department of Community and Family Medicine, Duke University Medical Center, Durham, NC 27710 (333).*

Sherman A. James, *Department of Epidemiology, University of North Carolina, Chapel Hill, NC 27514 (179).*

Norman L. Johnson, *Department of Statistics, University of North Carolina, Chapel Hill, NC 27514 (345).*

Ellen B. Kaplan, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (455).*

Azza R. Karmous, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (121).*

David G. Kleinbaum, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (179).*

Gary G. Koch, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (357).*

Lawrence L. Kupper, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (179).*

Peter A. Lachenbruch, *Department of Preventive Medicine and Environmental Health, University of Iowa, Iowa City, IA 52240 (389).*

Kerry L. Lee, *Division of Biometry, Department of Community and Family Medicine, Duke University Medical Center, Durham, NC 27710 (333).*

Nripes Kuman Mandal, *Department of Statistics, Calcutta University, Calcutta 700019, India (283).*

Nathan Mantel, *Department of Mathematics, Statistics and Computer Science, The American University, Bethesda, MD 20814 (399).*

Kadambari K. Namboodiri, *Cancer Control Consortium of Ohio, 101A Hamilton Hall, 1645 Neil Avenue, Columbus, OH 43210 (455).*

El-Sayed Nour, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (143).*

Charles L. Odoroff, *Department of Statistics and Division of Biostatistics, University of Rochester, Rochester, NY 14642 (315).*

Bernard S. Pasternack, *Institute of Environmental Medicine, New York University Medical Center, 550 First Avenue, New York, NY 10016 (165).*

Ibrahim A. Salama, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (413).*

Sara H. Salama, *Department of Geography, University of North Carolina, Chapel Hill, NC 27514 (121).*

A.K.Md.E. Saleh, *Department of Mathematics & Statistics, Carleton University, Ottawa, Canada K1S 5B6 (221).*

A.E. Sarhan, *Institute of Statistical Research, Cairo University, Giza, Egypt (413).*

P.K. Sen, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (13, 221, 511).*

Julio M. Singer, *Departmento de Estatistica, Universidade de Sao Paulo, Brazil (357).*

C.M. Suchindran, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (143).*

Chung-Yi Suen, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (179).*

Michael Symons, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (195).*

K.W. Teoh, *Department of Statistics, University of Kentucky, Lexington, KY 40506 (237).*

James H. Ware, *Department of Biostatistics, Harvard University School of Public Health, Boston, MA 02215 (421).*

Robert F. Woolson, *Department of Preventive Medicine and Environmental Health, University of Iowa, Iowa City, IA 52242 (389).*

Yang C. Yuan, *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27514 (195).*

CONTENTS

IN APPRECIATION OF BERNARD G. GREENBERG

Raymond S. Greenberg

Atlanta Cancer Surveillance Center
Emory University School of Medicine
Decatur, Georgia 30030

This book is dedicated to Bernard George Greenberg, Kenan Professor of Bio-
statistics at the University of North Carolina. The broad range of topics
presented in this volume is a fitting tribute to Greenberg's contributions in
both theoretical and applied biostatistics.

Bernard Greenberg was born on October 4, 1919 in New York City. He was educated
in the public school system, followed by undergraduate studies at the City
College of New York. At 19 years of age, Greenberg was elected to Phi Beta Kappa
and graduated with a Bachelor of Science degree in mathematics.

After college, Greenberg was employed briefly as a Junior Statistician for the
United States Bureau of the Census. In 1940, he accepted a position as an
Assistant Statistician at the New York State Department of Health. This first
exposure to the field of public health lasted only one year, but it played a
central role in his subsequent choice of careers. Greenberg learned the im-
portance of reliable data and field observations under the direction of a bright
young physician, David Rutstein. The friendship that Greenberg and Rutstein
developed in Albany remained intact throughout their long and distinguished
careers in public health.

In 1941, Greenberg was inducted into the United States Army where his leadership
skills were quickly recognized. He was selected as a candidate for the officer
training program and upon successful completion of the training, Greenberg was
appointed as an instructor. Later, he advanced to the rank of captain and com-
manded infantry troops in the European Theater.

Upon return to the United States, Greenberg married Ruth E. Marck, a Research
Assistant in physiological chemistry at Yale University. Following discharge
from military service, Greenberg returned temporarily to the New York State
Department of Health, but decided to obtain further academic training in
statistics. His fiancée arranged a meeting with Chester Bliss, a prominent
biometrician on the staff of the Connecticut Agricultural Experiment Station and
the faculty at Yale. Bliss suggested that the young couple should consider the
newly formed Institute of Statistics in Raleigh, North Carolina (1). Acting
upon this advice, the Greenbergs travelled to North Carolina in 1946 to attend a
Special Summer Session.

The Institute of Statistics, under the direction of Gertrude Cox, was developing rapidly during the postwar years. Miss Cox, the first woman professor on the faculty of North Carolina State University, recruited Harold Hotelling, who chaired the Department of Mathematical Statistics in Chapel Hill, and William C. Cochran, who provided the statistical and intellectual leadership of the Department of Experimental Statistics in Raleigh. Research conducted at the Institute was expanded beyond the traditional role in biological and social sciences to include research in mathematical, physical and industrial statistics. As financial support increased, new faculty were hired, including Henry ´Curly´ Lucas, Francis McVay, Richard Anderson, Paul Peach and Jackson Rigney (2).

During the Special Summer Session of 1946, in addition to Bliss, courses were offered by R.A. Fisher, George Snedecor, Jacob Wolfowitz, William Cochran and Gertrude Cox. Greenberg took the courses taught by Fisher and Snedecor for credit and he audited the courses taught by Wolfowitz and Cochran. It was a stimulating academic environment, but one lecturer stood out from the rest. In Greenberg's own words (1): "Before the end of the first week, I knew that Cochran was the person and teacher that I most wanted to emulate and applied immediately to become a regular graduate student that fall."

Greenberg was assigned to work with Curly Lucas, whose background in animal nutrition was the most closely related to public health. As a mentor, Lucas was unusually adept in several aspects of statistical analysis. First and foremost, Lucas was interested in the mathematical modeling of biological phenomena. Also, he played a prominent role in the application of analysis of variance to experimental and nonexperimental data.

As already indicated, Greenberg chose Cochran as a special role model. In later years, Greenberg commented that: "Bill Cochran was the greatest influence in my statistical career... (he) was the perfect gentleman and scholar with a superb sense of humor... In my eyes, he was the world's greatest experimental statistician."(1)

The special relationship that Cochran maintained with the graduate students is best illustrated by his approach to Ph.D. written examinations. Instead of contributing questions, Cochran would ask the student to referee a manuscript submitted to him for consideration of publication in the Journal of the American Statistical Association. In Greenberg's case, the first assigned paper was written by Johannes Ipsen, on the topic of estimating the mean and standard deviation of a truncated normal distribution. Two previous referees had recommended disapproval of the paper on the basis of its unconventional mathematics. However, Cochran suspected that Ipsen's method was reasonable, and Greenberg was assigned the task of comparing the performance of the new approach with other procedures. Simulation studies indicated that Ipsen's method worked as well or better than the

alternatives. Then, Greenberg and Cochran met together on almost a daily basis to reconstruct what the former thought should be the mathematics of the original paper. These private sessions offered a unique opportunity for Greenberg to observe Cochran's approach to solving a current research problem.

In 1949, Greenberg completed his doctoral dissertation in Experimental Statistics, as one of the first Ph.D. recipients in Statistics from North Carolina State College. On July 1 of that year, a Department of Biostatistics was established in the School of Public Health on the Chapel Hill campus. Greenberg was appointed as the chairman of this new department because of his background in public health and his strong ties to the Departments of Mathematical and Experimental Statistics. The role of the Department of Biostatistics was to provide basic instruction and consultation for students and faculty in public health and other allied disciplines. A training program for biostatisticians leading to the Master of Public Health degree was introduced in 1950. The curriculum was expanded to include courses in biological assay, quantitative epidemiology and the history and uses of vital statistics and demography.

C. Clark Cockerham was the second faculty member hired in Biostatistics and after a brief stay he was replaced by Harry Smith. At the time, Smith was a graduate student in Raleigh. Since the Department of Biostatistics did not have a doctoral program, a formal arrangement was established for doctoral students to specialize in Biostatistics while they fulfilled the degree requirements of one of the affiliated statistical departments. Under this arrangement, Smith was the first student to graduate, with Greenberg serving as the chair of his doctoral committee.

In 1953, the National Heart Institute awarded a grant to the University of North Carolina to facilitate the training of biostatisticians. This training grant provided funds for students, postdoctoral fellows, permanent and visiting faculty. Through this mechanism, the Department of Biostatistics was able to obtain the services of such prominent visiting professors as David R. Cox, J.O. Irwin, David B. Duncan, David J. Newell, Ahmed E. Sarhan, Herbert A. David, Robert C. Elston, K. Ruben Gabriel, Pranab K. Sen, and others, many of whom remained as tenured faculty.

Greenberg implemented a number of original programs during the 1950's. Master's degree students were encouraged to participate in field training under the supervision of advisors in various health agencies. These internships were intended to offer the students a practical experience in public health. The inspiration for this program may be traced to Greenberg's predoctoral work with the New York State Department of Health. The philosophy behind such field training can be found in an article written by Greenberg on this subject (3).

The Department of Biostatistics also contributed to the development of principles and methods for collaborative, multicenter, clinical trials. In 1955, the National Cancer Institute contracted with the Department to serve as the statistical coordinating center for the Southeastern Cooperative Cancer Chemotherapy Study Group. Through this collaborative group of about ten medical schools, research was conducted on the efficacy of new chemotherapeutic agents. A subsequent contract was signed with the Veterans Administration for the provision of statistical services for a multihospital study of the treatment of gastric ulcers. In 1959, Greenberg was the first investigator to publish a set of guidelines for the design and conduct of such collaborative medical trials (4).

With successful competition for federal research support, the Department of Biostatistics began to add new faculty at an unprecedented rate. The list of faculty associated with the Department is too long to be enumerated completely here. During Greenberg's tenure as chairman, he successfully recruited amongst others Harry Smith, Jr. (1953), Ahmed E. Sarhan and Edmund A. Gehan (1955), Thomas G. Donnelly (1956), Earl L. Diamond (1957), H. Bradley Wells and Roy R. Kuebler, Jr. (1958), Bernard S. Pasternack (1959), James E. Grizzle, Robert C. Elston and John Kosa (1960), Dana E.A. Quade and Khatab M. Hassanein (1962), Regina C. Elandt-Johnson, Herbert A. David and Jay J. Glasser (1964), James R. Abernathy, Elizabeth J. Coulter, Peter A. Lachenbruch and Pranab K. Sen (1965), Forrest E. Linder (1966), Gary G. Koch, Donna R. Brogan and Anthony F. Bartholomay (1967), Ronald W. Helms and Mindel C. Sheps (1968), Michael J. Symons (1969), O. Dale Williams, David G. Kleinbaum, Larry L. Kupper, Joan W. Lingner and J. Richard Stewart (1970), Dennis B. Gillings and Craig D. Turnbull (1971).

Under Greenberg's leadership, the Department of Biostatistics expanded its academic offerings. In 1965, a Ph.D. in Biostatistics was authorized by the Graduate School. That same year M.S.P.H. and Ph.D. programs in statistical aspects of demography and population studies were established. Also, a Ph.D. in statistical genetics was added in 1965. Later, masters and doctoral programs with emphases in mental health, environmental health, and health services research were established.

During two decades as chairman of the Department of Biostatistics, Greenberg continued to expand his research horizons. In collaboration with Ahmed E. Sarhan, he made fundamental contributions to order statistics (5) by means of a contract with the U.S. Army Office of Ordnance Research. With H. Bradley Wells and James R. Abernathy, Greenberg published seminal research on perinatal mortality (6,7). With A.E. Sarhan, he worked on approaches to matrix inversion (8). Later, he joined with several colleagues in advancing the theory and practice of the randomized response survey technique (9-11). Greenberg worked with Curtis G. Hames,

a general practitioner in Evans County, Georgia and John C. Cassel, chairman of the Department of Epidemiology at Chapel Hill, to establish a major prospective cohort study of atherosclerotic cardiovascular disease among white and black participants.

Greenberg's contributions to statistics and public health have been recognized by many honors, including fellowship in the American Statistical Association, the American Public Health Association, the Institute of Mathematical Statistics and the American College of Epidemiology. Also, he was nominated and elected to membership in the International Statistical Institute, the American Epidemiological Society and the Institute of Medicine. He served as chairman of the Statistics Section of the American Public Health Association (1958-60), and the Training Section of the American Statistical Association (1959-60), as well as the president of the Biometric Society (ENAR, 1971-72) and vice president of the Association of Schools of Public Health (1973-75). Greenberg was selected for the editorial boards of the Journal of Chronic Diseases, the Review of the International Statistical Institute, the American Journal of Obstetrics and Gynecology, and the Journal of Statistical Planning and Inference.

Greenberg was appointed to seven study sections in the National Institutes of Health, including chairmanship of the Nursing Research Study Section, the Special Review Committee on Therapeutic Agents for Cardiovascular Disease, the Special Project Committee of the National Heart Institute, and the Epidemiological Studies Review Committee of the National Institute of Mental Health. He served as chairman of the Publications Advisory Board of the National Center for Health Services Research and Development from 1969 through 1972. He completed a two year term with the newly created Committee on National Statistics of the National Academy of Sciences and a three year term with the U.S. National Committee on Vital and Health Statistics. Greenberg has been an active consultant to the National Institutes of Health, the Children's Bureau, the National Center for Health Statistics, the Veterans Administration and the World Health Organization.

In 1966, Greenberg received the Bronfman Award from the American Public Health Association for his many contributions to research and education in the health field. Three years later, he was named Kenan Professor of Biostatistics at the University of North Carolina. In 1972, Greenberg was appointed as Dean of the School of Public Health in Chapel Hill. During the decade of his deanship, the School expanded its student enrollment and faculty, with concomitant increases in its research and service activities. Through his creative leadership, an undergraduate program was introduced leading to the B.S.P.H. degree, and alternative sources of funding were located to support academic programs that were threatened by reduced federal capitation. Also, he was honored by the Minority Student Caucus

for his leadership of programs for black and native American students.

In 1983, Greenberg was inducted into the prestigious Order of the Golden Fleece for his service to the University of North Carolina. That same year he was the recipient of the O. Max Gardner Award for contributions to the welfare of the human race.

It is impossible to measure the full impact of Bernard Greenberg's career in bio-statistics. He nas been a visionary leader who inspired students and colleagues by his love of teaching, devoted service, hard work, and perseverance. Under his guidance, the Department of Biostatistics grew from a faculty of one in 1949 to its present size of over 30 regular full-time faculty. He bridged the gaps be-tween statistics and other disciplines such as demography, epidemiology, mental health, survey research, environmental sciences, health services research, and clinical medicine. His broad range of interests and clarity of expression have made him a highly valued consultant. As an administrator, he was renowned for this sensitivity to the needs of both students and faculty, and his creativity in solving problems.

The author of this biographical sketch would be remiss not to note his own debt of gratitude to Bernard Greenberg. As the youngest of his three children, I have been priviliged to know Bernard Greenberg as a public figure and also as a devoted family man. Just as he treasures his private tutorials with Cochran, I fondly recall my private sessions on long evening walks with Bernard Greenberg. He succeeded in nurturing "a burning yearning for learning" in many individuals, including this writer.

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SELECTED ANNOTATED PUBLICATIONS OF BERNARD G. GREENBERG

[1] Greenberg, B.G., Wright, J.J., Sheps, C.G.: A technique for analyzing some factors affecting the incidence of syphilis. J. Am. Stat. Assn. 45: 373-399, 1950.

The authors considered the general case of a series of rates that are classified by age and period of time. They proposed a logarithmic model with age and period as main effects and the interaction term representing a cohort effect. This was the first attempt made to quantify the cohort effect. Age, period and cohort models are currently undergoing a popular revival along these lines. The authors were able to estimate the parameters in this example by placing restrictions on the age and cohort factors.

[2] Greenberg, B.G.: Why randomize? Biometrics. 7: 309-322, 1951.

The author discussed the advantages of randomization as contrasted with systematic schemes of allocating treatments. Greenberg illustrated the potential hazards of systematic designs, with an example from experimental parasitology. Also, the statistical efficiencies of various randomized designs were compared.

[3] Greenberg, B.G.: The use of analysis of covariance and balancing in analytical surveys. Am. J. Pub. Health. 43: 692-699, 1953.

In this paper, Greenberg discussed the concept which epidemiologists would later refer to as 'confounding'. He used a cross-sectional study of the growth of school children to illustrate an analysis of the efficiency of balancing (matching), which foreshadowed conclusions reached by others almost two decades later.

[4] Peterson, O.L., Andres, L.P., Spain, R.S. and Greenberg, B.G.: An analytical study of North Carolina general practice 1953-1954. J. Med. Educ. 31: 1-165, 1956.

This work was a landmark investigation in the fields of medical sociology and health services research. From a stratified random sample of general practitioners in North Carolina, the authors concluded that inadequate