Paget's Disease of Bone

**Clinical Assessment,
Present and Future
Therapy**

Design on preceding page: In 1877 Sir James Paget published his classic paper “On a form of chronic inflammation of the bones (osteitis deformans).”

Microscopic sketches of the bone pathology were prepared by Mr. H.T. Butlin and published in this paper. This design was adapted from Figure 10 drawn by Mr. Butlin. The black represents bone with a scalloped border. The lined adjacent space represents the bone marrow. The multinucleated cell is an osteoclast, which has produced the resorbed surface of the bone. Thus this is a depiction of the earliest event in Paget’s disease: increased bone resorption.

Paget's Disease of Bone

Clinical Assessment, Present and Future Therapy

Proceedings of the Symposium on the Treatment of Paget's
Disease of Bone, held October 20, 1989 in New York City

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Preface

Paget's disease is an old disease historically, but a new disease therapeutically. Human remains unearthed in Lancashire, England, dating from approximately 900 AD, show clear evidence of the affliction. However, it was not until the 1800s that physicians rediscovered the condition, and a little more than 100 years ago that Sir James Paget published a perceptive and accurate description of the disease from the clinical and pathologic points of view. He felt the disease represented an inflammatory condition of the skeleton and hence named it osteitis deformans. The condition again lapsed into anonymity for several decades afterwards, and therapeutic approaches did not evolve until after World War II when several groups, located mainly in the Boston area, began using a variety of agents, including corticosteroids for treatment of this condition. These early attempts at therapy were unsuccessful and the condition remained essentially untreatable until the development of the calcitonins and the bisphosphonates in the 1970s.

In 1978, the Paget's Disease Foundation, a private nonprofit voluntary health agency, was founded to assist individuals afflicted by Paget's disease of bone, to provide education regarding this condition to the medical community, and to encourage research efforts to better understand and treat the condition. An international conference was organized under the aegis of the Paget's Disease Foundation and was held in New York City in October, 1989, ten years after the founding of the Paget's Disease Foundation. The purpose of the conference was to discuss the progress, within the previous ten years, of the clinical assessment of Paget's disease and to place in perspective the status of present therapy and the prospects for future therapy. This book is based on this international

conference and details the latest information concerning the diagnosis and treatment of Paget's disease.

Fourteen internationally known authorities on Paget's disease participated in the conference and in the preparation of this unique volume. Dr. Stephen Krane, from Harvard Medical School, reviewed the biology and biochemistry of the condition and the biochemical parameters that can be used to characterize disease activity. Dr. Stephen Teitelbaum of Washington University School of Medicine reviewed the pathologic features of Paget's disease and discussed both the cellular and structural abnormalities characteristic of the disorder. Dr. Ethel Siris of Columbia University College of Physicians and Surgeons discussed the clinical signs and symptoms and indications for treatment, paying special attention to the management of bone pain, intercurrent orthopedic surgery, and complications such as hearing loss, disturbed mineral metabolism, and the deleterious effects of immobilization. Dr. Alex Norman of New York Medical College outlined the radiologic features, the use of radiologic techniques in diagnosis, and the radiologic features of Paget's disease complications, including fractures and secondary tumorigenesis. Dr. Stephen Krane also discussed arthritis management in Paget's disease. Dr. Frederick Kaplan of the University of Pennsylvania School of Medicine discussed the role of orthopedic surgery in the management of patients with complications.

The remainder of the conference was devoted to medical therapies presently available and those projected for future utilization. Dr. Stanley Wallach of the University of South Florida College of Medicine summarized prior experience using porcine calcitonin and the present use of salmon calcitonin. Dr. John Haddad of the University of Pennsylvania School of Medicine provided similar discussion with regard to the use of human calcitonin. Dr. Charles Nagant de Deuxchaisnes of the Catholic University of Louvain, Belgium discussed European experience with new dose forms of calcitonin, especially the nasal spray form that avoids the need for injections. Dr. Frederick Singer of the University of California School of Medicine at Los Angeles discussed the emergence of resistance to calcitonin and the role of antibody formation in the resistant patient.

Several discussants dealt with the use of oral and intravenous bisphosphonates, which are in common use as effective alternatives to calcitonin. Dr. Pierre Meunier of the Faculté Alexis Carrel of the Medical School in Lyon, France discussed his experience with etidronate disodium, the first bisphosphonate to be used as therapy for Paget's disease and the only bisphosphonate available in the United States at present. Dr. Olav Bijvoet of the Medical School at the University of Leiden in The Netherlands discussed his experience using disodium pamidronate, a second generation bisphosphonate. Dr. Peter Burckhardt of Chuv University, Switzerland

discussed the use of short-term disodium pamidronate treatment and the results to be expected with this newest way of using the bisphosphonates. Dr. John Kanis of the University of Sheffield, England discussed several third generation bisphosphonates undergoing clinical trials in Europe at present.

Finally, Dr. Will Ryan of Rush Presbyterian St. Lukes Medical School in Chicago discussed the present status of plicamycin treatment, a potent antipagetic agent which can be used when neither the calcitonins nor the bisphosphonates are feasible. He also alluded to the newest agent presently in development, gallium nitrate, which was not formally discussed.

This volume and the conference on which it is based have brought the outstanding progress of the last 20 years in treating Paget's disease into present perspective. It also provided much new material that will assist the reader in understanding and applying present research efforts to future therapies. The joint efforts of basic and clinical investigators, the pharmaceutical industry, governmental and voluntary agencies, and of treating physicians are to be recognized for the successes of the past two decades in addressing this previously untreatable disease.

Frederick R. Singer, MD
Stanley Wallach, MD

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The editors of this volume wish to extend their sincere thanks to the Paget's Disease Foundation for undertaking the development and management of this fruitful conference, and to the following sponsors for their support of the Symposium: Ciba Geigy Pharmaceuticals, Fujisawa USA-Lyphomed, Merck Sharp and Dohme Research Laboratories, Norwich Eaton Pharmaceuticals, Rhône-Poulenc Rorer, Sandoz Pharmaceuticals, Sanofi Pharmaceuticals, Inc.

The authors are especially indebted to the President of the Board of Directors of the Paget's Disease Foundation, Mr. John B. Johnson, who has been the guiding spirit of the foundation since its inception, and to Mrs. Charlene Waldman, the Executive Director of the Paget's Disease Foundation, who has labored untiringly in the development and management of the conference and has worked yet harder in making this volume a reality.

Special thanks are also due to a number of individuals who were of great importance to the success of the Symposium and this volume. It was the idea of Mr. Walter Oberstebrink, past Chairman of the Paget's Disease Foundation, to sponsor a meeting about the advances in the evaluation and treatment of Paget's disease. Valuable assistance with the preparation of the manuscript was provided by Foundation staff Pamela Campbell

xiv ACKNOWLEDGMENTS

and Barbra Schulman and William Dracos, a Duke University student, who served as a summer intern for the Foundation in 1990.

Finally the herculean efforts of my Co-Editor, Dr. Stanley Wallach, in the editing of many of the chapters of this volume, should be publicly recognized.

Frederick R. Singer, MD

Foreword to the Annotated Bibliography

On behalf of the National Arthritis and Musculoskeletal and Skin Diseases Information Clearinghouse (NAMSIC), I am pleased to present a reprint of our publication, *Paget's Disease: An Annotated Bibliography*.

This annotated bibliography contains 190 citations to patient and professional education materials; most have been published since 1984. Its purpose is to provide information sources for physicians, nurses, other health professionals, and patients and their families regarding the diagnosis, treatment, symptoms, and complications of Paget's disease.

I thank the following individuals for their review of this bibliography: Robert Canfield, MD, Columbia University, New York, New York; Stephen Gordon, PhD, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, Maryland; Stephen M. Krane, MD, Massachusetts General Hospital, Boston, Massachusetts; Reva C. Lawrence, MPH, National Institutes of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, Maryland; Frederick R. Singer, MD, Cedars-Sinai Medical Center, Los Angeles, California; Ethel S. Siris, MD, Columbia Presbyterian Hospital, New York, New York; Stanley Wallach, MD, University of South Florida College of Medicine, Tampa, Florida; and especially to Ms. Charlene Waldman, Executive Director, Paget's Disease Foundation, Brooklyn, New York.

The bibliography was prepared by Cheryl Harris, NAMSIC staff, and produced for the Institute under contract No. NO1-DK-2290.

The Clearinghouse selects, acquires, and processes documents and other materials in the areas of patient education, public education, profes-

sional education, community demonstration programs, and federally funded programs in rheumatic, musculoskeletal, and skin diseases. These materials are available to the public through the Combined Health Information Database (CHID), which can be accessed through the services of a medical librarian or through BRS Information Technology, an online database vendor.

The Clearinghouse also provides a wide range of information dissemination services related to arthritis and musculoskeletal and skin diseases, including responding to public inquiries; publishing a news bulletin, *MEMO*, which is sent to over 9,000 people on the Clearinghouse mailing list; developing bibliographies, fact sheets, and other materials of interest to health professionals and their patients; and distributing professional and patient education materials.

For more information about NAMSIC and our services, please write or call:

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Again, I am honored to be able to contribute to this important text.

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