HENRY FORD HOSPITAL

International Symposium

Bone Biodynamics

COPYRIGHT © 1964 BY LITTLE, BROWN AND COMPANY (INC.)

ALL RIGHTS RESERVED. NO PART OF THIS BOOK MAY BE REPRO-DUCED IN ANY FORM WITHOUT PERMISSION IN WRITING FROM THE PUBLISHER, EXCEPT BY PARTICIPANTS IN THE SYMPOSIUM WHO MAY USE ANY FIGURES IN THEIR OWN PAPERS WITHOUT FURTHER PERMISSION, PROVIDED PROPER CREDIT IS GIVEN.

LIBRARY OF CONGRESS CATALOG CARD NO. 64-22983

FIRST EDITION

Previously Published Henry Ford Hospital International Symposia

- 1. The Dynamics of Virus and Rickettsial Infections
- 2. The Hypophyseal Growth Hormone, Nature and Actions
- 3. Cardiovascular Surgery: Recent Studies in Physiology, Diagnosis, and Techniques
- 4. Enzymes: Units of Biological Structure and Function
- 5. The Leukemias: Etiology, Pathophysiology, and Treatment
- 6. Hepatitis Frontiers
- 7. Reticular Formation of the Brain
- 8. Mechanisms of Hypersensitivity
- 9. Biology of Pyelonephritis 10. Blood Platelets
- 11. Otosclerosis
- 12. Biological Interactions in Normal and Neoplastic Growth
- 13. The Etiology of Myocardial Infarction

October, 1953 October, 1954

March, 1955 November, 1955 March, 1956 October, 1956 March, 1957 March, 1958 October, 1959 March, 1960 November, 1960 May, 1961 November, 1961

Published in Great Britain by J. & A. Churchill Ltd., London

Bone Biodynamics

Editor

HAROLD M. FROST, M.D.

Director, Orthopaedic Research Laboratory Associate Surgeon, Department of Orthopaedic Surgery Henry Ford Hospital



LITTLE, BROWN AND COMPANY
Boston, Massachusetts

Contributors

CHARLES H. BACHMAN, Ph.D.

Professor of Physics, Syracuse University, Syracuse, New York.

C. ANDREW BASSETT, M.D.

Director, Orthopedic Research, College of Physicians and Surgeons, Columbia University, New York, New York.

GÖRAN C. H. BAUER, M.D.

Director of Research, Hospital for Special Surgery; Professor of Orthopaedic Surgery, New York Hospital-Cornell University Medical College, New York, New York.

ROBERT D. BECKER, M.D.

Assistant Professor of Orthopaedic Surgery, State University of New York, Upstate Medical Center in Syracuse, Syracuse, New York.

DAVID A. CAMERON, M.D., Ph.D.

Associate Professor of Pathology, University of Sydney, Sydney, Australia.

D. HAROLD COPP, M.D.

Professor of Physiology, University of British Columbia, Vancouver, Canada.

JAMES F. DANIELLI, Ph.D.

Professor of Medicinal Chemistry, State University of New York at Buffalo, Buffalo, New York.

HONOR B. FELL, D.Sc., Ph.D., F.R.S.

Director, Strangeways Research Laboratory, Cambridge, England.

SYLVIA FITTON-JACKSON, M.D.

Strangeways Research Laboratory, Cambridge, England.

BOY FRAME, M.D.

Associate, Department of Medicine, Henry Ford Hospital, Detroit, Michigan.

HAROLD M. FROST, M.D.

Director, Orthopaedic Research Laboratory; Associate Surgeon, Department of Orthopaedic Surgery, Henry Ford Hospital, Detroit, Michigan.

C. HOWARD HATCHER, M.D.

Professor of Orthopedic Surgery, Stanford University School of Medicine, Palo Alto, California.

WEBSTER S. S. JEE, Ph.D.

Bone Group Leader, Department of Anatomy, University of Utah College of Medicine, Salt Lake City, Utah.

LENT C. JOHNSON, M.D.

Department of Pathology, Armed Forces Institute of Pathology, Washington, D.C.

JENIFER JOWSEY, Ph.D.

Albert Einstein Medical Center, Philadelphia, Pennsylvania.

J. LEE KAVANAU, Ph.D.

Associate Professor of Zoology, University of California, Los Angeles, California.

JAMES MACGREGOR, M.Sc.

Gardiner Institute, Glasgow, Scotland.

FRANKLIN C. McLEAN, M.D.

Emeritus Professor of Physiology, Department of Physiology, University of Chicago, Chicago, Illinois.

C. LESLIE MITCHELL, M.D.

Chairman, Department of Orthopaedic Surgery, Henry Ford Hospital, Detroit, Michigan.

WILLIAM F. NEUMAN, Ph.D.

Professor of Radiation Biology, University of Rochester School of Medicine and Dentistry, Rochester, New York.

B. E. CHRISTOPHER NORDIN, M.D., M.R.C.P., Ph.D.

Department of Medicine, Gardiner Institute, Glasgow, Scotlano.

HOMER A. PASCHALL, M.D.

Fellow, Orthopedic Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland.

ROBERT D. RAY, M.D., Ph.D.

Professor of Orthopaedic Surgery, Department of Orthopaedic Surgery, University of Illinois College of Medicine, Chicago, Illinois.

JOHN M. REINER, PH.D.

Associate Professor of Microbiology, School of Medicine, Emory University, Atlanta, Georgia.

ROBERT A. ROBINSON, M.D.

Professor of Orthopaedic Surgery, Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland.

ALFRED S. ROMER, Ph.D.

Alexander Agassiz Professor of Zoology, Museum of Comparative Zoology, Harvard University, Cambridge, Massachusetts.

ROBERT E. ROWLAND, Ph.D.

Senior Technical Associate in Radiation Biology, Department of Radiobiology, University of Rochester School of Medicine and Dentistry, Rochester, New York.

TAWFIK Y. SABET, Ph.D.

Research Associate in Orthopaedic Surgery, Department of Orthopaedic Surgery, University of Illinois College of Medicine, Chicago, Illinois.

ELIAS D. SEDLIN, M.D.

Department of Orthopaedic Surgery, Henry Ford Hospital, Detroit, Michigan; Postdoctoral Fellow of the National Institutes of Health.

RICHMOND SMITH, M.D.

Chairman, Division of Endocrinology, Henry Ford Hospital, Detroit, Michigan.

JOSEPH TRUETA, M.D.

Professor of Orthopaedic Surgery, Nuffield Orthopaedic Center, Oxford, England.

MARSHALL R. URIST, M.D.

Clinical Professor of Orthopaedic Surgery, Department of Surgery, University of California, Los Angeles, California.

CHARLES L. WADKINS, Ph.D.

Associate Professor of Physiological Chemistry, Johns Hopkins University School of Medicine, Baltimore, Maryland.

MACKENZIE WALSER, M.D.

Associate Professor of Pharmacology and Experimental Therapeutics, Department of Pharmacology and Experimental Therapeutics, Johns Hopkins University School of Medicine, Baltimore, Maryland.

PAUL WEISS, Ph.D.

Professor of Biology, Rockefeller Institute, New York, New York.

IRA G. WOOL, M.D., Ph.D.

Associate Professor of Physiology, Department of Physiology, University of Chicago, Chicago, Illinois.

RICHARD W. YOUNG, Ph.D.

Assistant Professor of Anatomy, Department of Anatomy, University of California, Los Angeles, California.

Discussants

Andrew C. Bassett New York, New York Göran C. H. Bauer New York, New York Robert O. Becker Syracuse, New York L. Bélanger Ottawa, Canada David A. Cameron Sydney, Australia I. Cameron Madison, Wisconsin Harold Copp Vancouver, Canada P. Craig Philadelphia, Pennsylvania P. H. Curtiss Cleveland, Ohio James F. Danielli Buffalo, New York A. Fahmy Atlanta, Georgia Honor B. Fell Cambridge, England J. W. Fielding New York, New York F. Fischer Detroit, Michigan Sylvia Fitton-Jackson Cambridge, England

Harold M. Frost

Detroit, Michigan

N. R. Greville Gainesville, Florida Howard C. Hatcher Palo Alto, California R. Heaney Omaha, Nebraska G. W. Hyatt Washington, D.C.Lent C. Johnson Washington, D.C. Jenifer Jowsey Philadelphia, Pennsylvania Lee J. Kavanau Los Angeles, California I. B. Kulka Boston, Massachusetts M. B. Mathews Chicago, Illinois Franklin C. McLean Chicago, Illinois William F. Neuman Rochester, New York B. E. Christopher Nordin Glasgow, Scotland Maureen Owen Upton, New York R. Ramsey Dearborn, Michigan John M. Reiner Atlanta, Georgia Robert A. Robinson Baltimore, Maryland

Discussants

Alfred Romer
Cambridge, Massachusetts
Robert E. Rowland
Rochester, New York

Tawfik Y. Sabet Chicago, Illinois

J. Samachson Hines, Illinois

Elias D. Sedlin
Detroit, Michigan

B. Sherman
Brooklyn, New York

M. Silberberg
St. Louis, Missouri
Joseph Trueta

Joseph Trueta
Oxford, England

Marshall R. Urist

Los Angeles, California

Charles L. Wadkins
Baltimore, Maryland

S. Wallach Brooklyn, New York

Mackenzie Walser Baltimore, Maryland

Paul Weiss New York, New York

Ira G. Wool
Chicago, Illinois

Richard W. Young
Los Angeles, California

Preface

The purpose of the Bone Biodynamics Symposium was to stimulate a greater diversity and volume of research in the orthopaedic basic sciences, in part by bringing together representatives of a number of disciplines who, in composite, had a broad biological interest. The structure of the program and the material in it were arranged on a biological and dynamic basis instead of being oriented toward a single disease or group. Some of the participants and persons attending had worked with bone previously and some had not.

The field of biology is at present undergoing a major upheaval in its methods of study, in its concepts and language, in methods of approaching problems, and in the motivation and philosophy underlying the activities of biologists.

Since bone is a part of biology, its study is similarly affected. Being somewhat aside from the mainstream of biological investigation, the newer modalities and philosophical orientation to the study of bone have not been applied to the fullest extent possible.

There is a great need for expanded and more diversified research activity in the fields of bone, which include physiology, pathology, genetics, tissue repair, tissue regeneration, growth, and other aspects of physiology in its broad sense.

The program participants were asked to provide the audience—and, through this text, the reader—with examples of philosophy, methodology, interpretation of the meaning of data, and relation of studies to problems of clinical or conceptual interest and importance.

When this symposium was first planned, an integral part of the concept was publication of its papers in a book which would extend the reach of the symposium's objectives as far as possible. The orthopaedic basic science field needs more investigators willing to leave the classic approaches in order to cope with the still pupal molecular biology so rewarding in many other divisions of biology and medicine. It needs more thinkers, men willing to concoct a new (and therefore in some quarters automatically and hopelessly wrong) concept or theory but at the same time willing and able to put it to the test, to distinguish fact from thought. As Dr. Danielli said during the symposium, our problem is not that we need more data;

xii

there is a data surplus of awesome magnitude now. Rather, we need better theories and concepts in the light of which this data can be sorted, organized, and understood.

The young investigator should find much food for thought in these pages, as well as useful information and insight. There are ample examples of theorizing, model building, experimental design, interpretation of data, methodology, and the actual digging out of data from the raw stuff: tissue. There are ample examples of unsolved—or uninvestigated—problems.

The book begins with a summary or précis of the symposium which is intended to orient the specialist who may not be acquainted with the details of some of the participants' work. The précis should help to fit the various pieces into context, to show why the participants were following their chosen paths.

It is my feeling that the participants achieved more success in executing the objectives of the symposium than reasonably could be expected through the medium employed. It is my pleasure here to submit to the reader a truly impressive collection of papers, arranged on a skeleton which progresses from the molecule at the bottom, through time, through ultrastructure and microstructure, through problems involving regulation and mineral kinetics to practical clinical problems at the head.

It is deeply regretted that the valuable contributions of Sylvia Fitton-Jackson, M.D., and Howard Hatcher, M.D., were not available in manuscript form at the time this material went to press.

H. M. F.

Detroit

Contents

Contributors	v
Discussants	ix
Preface	хi
I. ORIENTATION	
Chairman, HAROLD M. FROST	
1. The Bone Biodynamics Symposium: A Précis Harold M. Frost	3
2. Bone in Early Vertebrates Alfred S. Romer	13
General Discussion: Frost, Romer, Urist, Wool	38
II. MOLECULAR AND CYTOLOGICAL PHYSIOLOGY Chairmen, William F. Neuman and Franklin C. McLean	
3. Introduction to the Living Cell Paul Weiss	43
4. The Dynamic Function of Cellular and Intracellular Membranes James F. Danielli	51
5. Enzyme Kinetics and Tissue Dynamics John M. Reiner	59
6. The Immune Mechanism of Transplantation and Possible Role of DNA and RNA Tawfik Y. Sabet and Robert D. Ray	71
General Discussion: Frost, Weiss, Kulka, Neuman, Wool, Danielli, Reiner	84
Panel Discussion: Sherman, Sabet, Weiss, Hyatt, Danielli, Robinson, Wadkins	87
7. The Ultrastructure of Bone Cells David A. Cameron, Homer A. Paschall, and Robert A. Robinson	91

xiv Contents

8.	Mechanisms Concerned with Intracellular Energy Transduction Charles L. Wadkins	105
9.	Specialization of Bone Cells Richard W. Young	117
	General Discussion: McLean, D. A. Cameron, Wool, Young, Sabet, Mathews, Fitton-Jackson, Owen	140
	Panel Discussion: Frost, Young, J. Cameron, D. A. Cameron, Trueta, Silberberg, Fitton-Jackson, Bassett, Fell, Bélanger	143
	III. PROBLEMS INVOLVED IN CELL REGULATION	
	Chairman, C. Andrew Bassett	
10.	Further Observations Bearing on the Bone-Body Fluid Continuum: Composition of the Skeleton and Serums of Cyclostomes, Elasmobranchs, and Bony Vertebrates Marshall R. Urist	151
11.	Remarks on Calcium in Physiological Solutions Mackenzie Walser	181
12.	Some Factors in the Regulation of Cell Physiology in Skeletal Tissues Honor B. Fell	189
13.	Bioelectric Factors Controlling Bone Structure Robert O. Becker, C. Andrew Bassett, and Charles H. Bachman	209
14.	Environmental and Cellular Factors Regulating Osteogenesis C. Andrew Bassett	233
15.	The Dynamics of Bone Circulation Joseph Trueta	245
16.	The Influence of Reduced Local Vascularity on the Rate of Internal Reconstruction in Adult Long Bone Cortex Webster S. S. Jee	259
	Panel Discussion: Romer, Urist, Frost, Becker, D. A. Cameron, Fell, Young, Bassett, Trueta, Silberberg, Samachson, Mathews Ramsey	278

	Contents	xv
17.	Theoretical Endocrinology Ira G. Wool	285
18.	Dynamics of Bone Remodeling Harold M. Frost	315
19.	Resorption and Bone Physiology Robert E. Rowland	335
20.	A Model of Growth and Growth Control in Mathematical Terms—Compensatory Organ Growth in the Immature Animal J. Lee Kavanau	353
	General Discussion: McLean, Frost, Fielding, Baner, Trueta, Heaney, Rowland, Fahmy, Fischer, Wool, Greville, Urist, Danielli, Kavanau, Johnson, D. A. Cameron, Owen, Bélanger, Curtiss, Young, Sabet	375
	IV. BONE MINERAL DYNAMICS	
	Chairman, ROBERT A. ROBINSON	
21.	Blood-Bone Exchange William F. Neuman	393
22.	Blood-Bone Equilibrium James MacGregor	409
23.	Observations Regarding Compartments for Tracer Calcium in the Body Robert A. Robinson	423
24.	The Hormones of the Parathyroid Glands and Calcium Homeostasis Harold Copp	441
25.	Variations in Bone Mineralization with Age and Disease Jenifer Jowsey	461
26.	Some Observations on the Measurement of Bone Formation Rate with Bone-seeking Isotopes R. F. Christopher Nordin	481

	٠
WIT	1
AV.	

27. Kinetics of Bone Disease

Contents

489

Göran C. H. Bauer	107
General Discussion: Walser, Neuman, Robinson, Jowsey, Nordin, Urist, Bauer, Heaney, Frost, Bélanger, Copp, Wallach	508
V. APPLICATION OF BASIC SCIENCES TO CLINICAL PROBLEMS	
Chairman, C. Leslie Mitchell	
28. The Application of Basic Science to Osteoporosis B. E. Christopher Nordin	521
29. Morphologic Analysis in Pathology: The Kinetics of Disease and General Biology of Bone Lent C. Johnson	543
30. Uses of Bone as a Model System in the Study of Aging Elias D. Sedlin	655
General Discussion: Frost, Hatcher, Robinson	667
Panel Discussion: D. A. Cameron, Nordin, Frost, Johnson, Hatcher, Fahmy, Craig, Sedlin	669
Index	675

Orientation

Chairman: HAROLD M. FROST, M.D. (Detroit, Michigan)



I

The Bone Biodynamics Symposium: A Précis

HAROLD M. FROST, M.D.

(Detroit, Michigan)

Evolution

It used to be thought that skeletal evolution began with the development of hyaline cartilage, followed in order by the development of calcified cartilage, replacement of this with fibrous or woven bone, replacement of this with circumferential lamellar bone, and, last, the appearance of Haversian remodeling of bone.

Certain aspects of the fossil record have led paleontologists to question this view and to propose in its place a scheme in which lamellar bone appeared first, to be followed in time by the development of woven bone and then cartilage. Certainly the first known exoskeletons were lamellar

bone, and endoskeletons appeared later.

Significantly, the first mineralized skeletons did not reveal evidence of accompanying resorptive capability, cell-mediated resorption of calcified tissues appearing afterward. The first animals could form but not destroy, and so they could not remodel. The appearance of calcified skeletons was presumably accompanied by changes in internal osmoregulation, and the ability to resorb calcified skeletal material was presumably accompanied by changes in internal regulation of plasma calcium and phosphate ion concentrations, especially by the kidney.

Curiously enough, in present day animals with bony skeletons, resorption usually precedes the formation of bone. On two counts then-"devolution" of the skeleton and primacy of resorption over formation-the inference is suggested that ontogeny and cytodynamic activity can be the

reverse of phylogeny.

Cytophysiology

Time-lapse motion pictures of cell cultures, taken during various modifications of the medium embedding the cells, dramatically show that cells