

**VITAMINS
AND HORMONES
VOLUME 22**

VITAMINS AND HORMONES

ADVANCES IN RESEARCH AND APPLICATIONS

Edited by

ROBERT S. HARRIS

*Massachusetts Institute of Technology
Cambridge, Massachusetts*

IRA G. WOOL

*The University of Chicago
Chicago, Illinois*

JOHN A. LORAINÉ

*Clinical Endocrinology Research Unit
Medical Research Council
The University
Edinburgh, Scotland*

Consulting Editors

G. F. MARRIAN

*The Imperial Cancer Research
Fund Laboratories
London, England*

KENNETH V. THIMANN

*Harvard University
Cambridge, Massachusetts*

Volume 22

1964



ACADEMIC PRESS, New York and London

COPYRIGHT © 1964, BY ACADEMIC PRESS INC.

ALL RIGHTS RESERVED.

NO PART OF THIS BOOK MAY BE REPRODUCED IN ANY FORM,
BY PHOTOSTAT, MICROFILM, OR ANY OTHER MEANS, WITHOUT
WRITTEN PERMISSION FROM THE PUBLISHERS.

ACADEMIC PRESS INC.

111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS INC. (LONDON) LTD.
Berkeley Square House, London W.1

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 43-10535

PRINTED IN THE UNITED STATES OF AMERICA

Contributors to Volume 22

Numbers in parentheses indicate the pages on which the authors' contributions begin.

A. E. AXELROD, *Biochemistry Department, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania* (591).

E. M. BOGDANOVE, *Department of Anatomy and Physiology and Combined Degree Program in Medicine, Indiana University, Bloomington, Indiana* (205).

HENRY BORSOOK, *Kerckhoff Biological Laboratories, California Institute of Technology, Pasadena, California* (855).

ALEXANDER E. BRAUNSTEIN, *Institute of Radiobiology and Physico-Chemical Biology, Academy of Sciences of the U. S. S. R., Moscow, U. S. S. R.* (451).

DAVID BAIRD COURSIN, *Research Institute, St. Joseph Hospital, Lancaster, Pennsylvania* (755).

K. DAKSHINAMURTI,* *Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, Massachusetts* (1).

GLADYS A. EMERSON, *School of Public Health, University of California, Los Angeles, California* (643, 655).

HONOR B. FELL, *Strangeways Research Laboratory, Cambridge, England* (81).

EDMOND H. FISCHER, *Department of Biochemistry, University of Washington School of Medicine, Seattle, Washington* (399).

K. FOTHERBY, *Postgraduate Medical School, London, England* (153).

HENRY L. FULLER, *Poultry Department, College of Agriculture, The University of Georgia, Athens, Georgia* (659).

CARL GEMZELL, *Akademiska Sjukhuset, Uppsala, Sweden* (129).

STANLEY N. GERSHOFF, *Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts* (581).

* Present address: Research Institute, St. Joseph Hospital, Lancaster, Pennsylvania.

- LOUIS D. GREENBERG, *Department of Pathology, University of California School of Medicine, San Francisco, California (677).*
- PAUL GYÖRGY, *Professor Emeritus of Pediatrics, University of Pennsylvania, Philadelphia, Pennsylvania (361, 885).*
- JOHN W. HARRIS, *Department of Medicine, Western Reserve University School of Medicine at Cleveland Metropolitan General Hospital, and Crile Veterans Administration Hospital, Cleveland, Ohio (721).*
- J. N. HAWTHORNE, *Department of Medical Biochemistry and Pharmacology, University of Birmingham, Birmingham, England (57).*
- ROBERT W. HILLMAN, *Department of Environmental Medicine and Community Health, State University College of Medicine, Downstate Medical Center, Brooklyn, New York (695).*
- DANIEL L. HERRIGAN, *University Hospitals of Cleveland, and Crile Veterans Administration Hospital, Cleveland, Ohio (721).*
- HIROE S. KISHI, *School of Public Health, University of California, Los Angeles, California (643).*
- EDWIN G. KREBS, *Department of Biochemistry, University of Washington School of Medicine, Seattle, Washington (399).*
- LINDA M. LIVINGSTON, *The Medical Research Center, Brookhaven National Laboratory, Upton, New York (261).*
- ENRICO MIHICH, *Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York (609).*
- S. P. MISTRY, *Division of Animal Nutrition, University of Illinois, Urbana, Illinois (1).*
- YOSHIMASA MORINO,* *Department of Biochemistry, Medical School, Osaka University, Osaka, Japan (411).*
- BOBBIE J. MORRILL, *School of Public Health, University of California, Los Angeles, California (643).*
- JOHN F. MUELLER,† *Department of Medicine, University of Colorado Medical Center and the Veterans Administration Hospital, Denver, Colorado (787).*

* Present address: Department of Biochemistry, University of California, Berkeley, California.

† Present address: Brooklyn-Cumberland Medical Center, Brooklyn, New York.

- CHARLES A. NICHOL, *Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York (609).*
- J. M. OSBOND, *Research Laboratories, Roche Products Limited, Welwyn Garden City, England (367).*
- JEAN MCLEOD PETERS, *Nutrition Research Laboratory, Oregon State University, Corvallis, Oregon (833).*
- MARILYN MACARTHUR POLANSKY, *Human Nutrition Research Division, Agricultural Research Service, U. S. Department of Agriculture, Beltsville, Maryland (825).*
- EUGENE ROBERTS, *Department of Biochemistry, City of Hope Medical Center, Duarte, California (503).*
- FRED ROSEN, *Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York (609).*
- H. E. SAUBERLICH, *U. S. Army Medical Research and Nutrition Laboratory, Denver, Colorado (807).*
- IRVING L. SCHWARTZ, *Department of Physiology, University of Cincinnati College of Medicine, Cincinnati, Ohio (261).*
- W. H. SEBRELL, JR., *Institute of Nutrition Sciences, Columbia University, New York, New York (875).*
- DAISY G. SIMONSEN, *Department of Biochemistry, City of Hope Medical Center, Duarte, California (503).*
- ESMOND E. SNELL, *Department of Biochemistry, University of California, Berkeley, California (485).*
- JAMES W. SNIPES, *School of Public Health, University of California, Los Angeles, California (643).*
- CLARA A. STORVICK, *Nutrition Research Laboratory, Oregon State University, Corvallis, Oregon (833).*
- EDWARD W. TOEPFER, *Human Nutrition Research Division, Agricultural Research Service, U. S. Department of Agriculture, Beltsville, Maryland (825).*
- ANTHONY C. TRAKATELLIS, *Biochemistry Department, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania (591).*
- SIDNEY UDENFRIEND, *Laboratory of Clinical Biochemistry, National Heart Institute, Bethesda, Maryland (445).*

RICHARD W. VILTER, *Department of Internal Medicine, University of Cincinnati, Cincinnati General Hospital, Cincinnati, Ohio (797).*

MAX WACHSTEIN, *The Division of Laboratories, Beth Israel Hospital, Passaic, New Jersey (705).*

HIROSHI WADA, *Department of Biochemistry, Medical School, Osaka University, Osaka, Japan (411).*

JANE B. WALKER, *School of Public Health, University of California, Los Angeles, California (643).*

FRITZ WEBER, *Department of Vitamin and Nutrition Research, F. Hoffmann-LaRoche & Co. Ltd., Basle, Switzerland (495).*

JOHN WEIN, *Department of Biochemistry, City of Hope Medical Center, Duarte, California (503).*

MARY ANN WILLIAMS, *Department of Nutritional Sciences, University of California, Berkeley, California (561).*

OSWALD WISS, *Department of Vitamin and Nutrition Research, F. Hoffmann-LaRoche & Co. Ltd., Basle, Switzerland (495).*

Preface

The Editors take much pleasure in presenting the twenty-second volume of *Vitamins and Hormones*. This volume contains seven regular articles and twenty-nine articles which represent the communications delivered at an International Symposium on Vitamin B₆ held in New York City on July 23 and 24, 1964. This symposium was held in honor of Professor Paul György on the thirtieth anniversary of the discovery of Vitamin B₆. This symposium is a sequel to those on Vitamin A and Vitamin E which were published in Volumes 18 and 20, respectively, of this series. It is especially gratifying to the Editors that publication of the proceedings of the Vitamin B₆ Symposium has been so rapid.

Of the regular articles, four are devoted entirely to hormones, two to vitamins, and one to both vitamins and hormones. Of the seven regular contributions to this volume one emanates from Sweden, three from the United Kingdom, and three from the United States.

The review articles in Volume 22 follow the pattern traditionally associated with *Vitamins and Hormones*. They are critical in content and personal in outlook. For the authors they represent a great investment both of effort and of time, for which the Editors are profoundly grateful.

October, 1964

ROBERT S. HARRIS
I. G. WOOL
JOHN A. LORAINÉ

VITAMINS AND HORMONES

Volume 22

ADVANCES IN RESEARCH AND APPLICATIONS

Edited by Robert S. Harris, Ira G. Wool, and John A. Loraine

ERRATA

Page 836, line 6, pyrodoxine should read: "pyridoxine"

Page 845, line 23, μg should read: " $\text{m}\mu\text{g}$ "

Page 847, line 28, delete: "catalyzed degradation of tryptophan to indole, pyruvic acid, and ammonia"

Page 854, line 8, *Univ. Texas Publ.* 4137, 22-26 should read *Univ. Texas Publ.* 4137, "24-26"

Contents

CONTRIBUTORS TO VOLUME 22	v
PREFACE	ix

Biochemistry of Biotin

S. P. MISTRY AND K. DAKSHINAMURTI

I. Introduction	1
II. Biogenesis of Biotin and Biotin Holoenzymes	2
III. Tissue Distribution and Metabolism of Biotin	4
IV. Structure and Specificity of Biotin	6
V. Biotin Enzymes	8
VI. Mechanism of Action of Enzyme-Bound Biotin	13
VII. Indirect Effects of Biotin Deficiency	20
References	49

The Biochemistry of the Inositol Lipids

J. N. HAWTHORNE

I. Introduction	57
II. Chemical Structure	58
III. Distribution of Inositol Lipids	61
IV. Biosynthesis	62
V. Enzymatic Hydrolysis of Phosphoinositides	66
VI. Possible Physiological Roles of Phosphoinositides	67
References	77

The Role of Organ Cultures in the Study of Vitamins and Hormones

HONOR B. FELL

I. Introduction	81
II. Vitamins	84
III. Hormones	96
IV. Conclusion	123
References	124

Therapy of Gynecological Disorders with Human Gonadotropin

CARL GEMZELL

I. Introduction	129
II. Human Chorionic Gonadotropin (HCG)	130
III. Human Pituitary Gonadotropin (HPFSH)	134
IV. Human Menopausal Gonadotropin (HMG)	146
V. Concluding Remarks	148
References	149

The Biochemistry of Progesterone

K. FOTHERBY

I. Introduction	153
II. Production and Metabolism of Progesterone	154
III. Progesterone-Gonadotropin Interrelationships	167
IV. Metabolic Effects of Progesterone	176
V. Biochemical Effects of Progesterone on the Uterus	181
VI. Effect of Progesterone on Enzyme Systems <i>in Vitro</i>	193
VII. Concluding Remarks	196
References	197

The Role of the Brain in the Regulation of Pituitary Gonadotropin Secretion

E. M. BOGDANOVE

I. Introduction	206
II. Dependence of GTH Secretion on Hypothalamic Neurohumors	206
III. Direct Evidence about Neurohumors Which Influence GTH Secretion	210
IV. Gonadal Steroid Feedback	216
V. The Role of the Brain in the Control of Ovulation	234
VI. Summary	251
References	254

Cellular and Molecular Aspects of the Antidiuretic Action of Vasopressins and Related Peptides

IRVING L. SCHWARTZ AND LINDA M. LIVINGSTON

I. Introduction	261
II. Nomenclature	266

III. Assay and Standardization	268
IV. Structure-Activity Relationships of the Neurohypophyseal Hormones	270
V. Mechanism of Antidiuresis: Facts and Theories	342
References	349

International Symposium on Vitamin B₆ in Honor of Professor Paul György

The History of Vitamin B₆. Introductory Remarks

PAUL GYÖRGY

Text	361
References	365

Synthesis and Labeling of the Vitamin B₆ Group

J. M. OSBOND

I. Introduction	367
II. Syntheses of Pyridoxine	369
III. C ¹⁴ -Labeled Pyridoxine	386
IV. Pyridoxine 5-Phosphate	387
V. Pyridoxal	388
VI. Pyridoxal 5-Phosphate (Codecarboxylase)	389
VII. Pyridoxamine	391
VIII. N ¹⁵ -Labeled Pyridoxamine	392
IX. Pyridoxamine 5-Phosphate	393
X. Summary	393
References	393

Phosphorylase and Related Enzymes of Glycogen Metabolism

EDWIN G. KREBS AND EDMOND H. FISCHER

I. Introduction	399
II. Pathways of Glycogenesis and Glycogenolysis	400
III. Interconversion of the Two Forms of Glycogen Phosphorylase	401
IV. The Structure and Properties of Glycogen Phosphorylase	402
V. Vitamin B ₆ Deficiency and Carbohydrate Metabolism	405
VI. Muscle Phosphorylase as a Repository for Vitamin B ₆ in the Animal	407
References	409

Comparative Studies on Glutamic-Oxalacetic Transaminases from the Mitochondrial and Soluble Fractions of Mammalian Tissues

HIROSHI WADA AND YOSHIMASA MORINO

I. Introduction	411
II. Pyridoxamine Transaminase	412
III. Identity of Pyridoxamine-Oxalacetic Transaminase with the Apoprotein of Glutamic-Oxalacetic Transaminase	414
IV. Glutamic-Oxalacetic Transaminases from Mitochondrial and Soluble Fractions of Mammalian Tissues	419
V. Concluding Remarks	441
References	443

Amino Acid Decarboxylation Steps in the Biosynthesis of Norepinephrine, Serotonin, and Histamine

SIDNEY UDENFRIEND

I. Introduction	445
II. Norepinephrine	445
III. Serotonin	447
IV. Histamine	448
V. Summary	449
References	449

Binding and Reactions of the Vitamin B₆ Coenzyme in the Catalytic Center of Aspartate Transaminase

ALEXANDER E. BRAUNSTEIN

I. Introduction	451
II. The Linkage of Coenzyme and Apoenzyme in the Catalytic Center of Aspartate Transaminase	452
III. Reactions of Substrates and Inhibitors with the Coenzyme in the Catalytic Center	457
IV. Spectropolarimetric Investigation of Aspartate Transaminase	468
V. Concluding Remarks	479
References	481
Addenda	482

Summary of Session I and Some Notes on the Metabolism of Vitamin B₆

ESMOND E. SNELL

I. Observations Relevant to the Preceding Papers	485
II. Pyridoxal Kinase in Vitamin B ₆ Metabolism	490

III. Concluding Remarks	493
References	493

Biochemical Pathology of Vitamin B₆ Deficiency

OSWALD WISS AND FRITZ WEBER

I. Introduction	495
II. Activities of Pyridoxal Phosphate Enzymes in Progressive Vitamin B ₆ Deficiency	495
III. Metabolic Alterations in the Vitamin B ₆ Deficiency State	497
IV. Summary	500
References	500

γ -Aminobutyric Acid (γ ABA), Vitamin B₆, and Neuronal Function—A Speculative Synthesis

EUGENE ROBERTS, JOHN WEIN, AND DAISY G. SIMONSEN

I. Introduction	504
II. The Synapse as a Common Ground for Chemist and Biologist	505
III. γ ABA Shows Some of the Properties Expected of the Hypothetical Synaptic Negative Feedback Transmitter	513
IV. Relations between Apoenzymes (or Nonenzymatic Proteins) and Vitamin B ₆	519
V. Some Carbonyl Reagents Can Produce Conclusive Seizures and Defects in Collagen Structure	544
VI. Correlations with the Proposed Synaptic Model	546
VII. Comment	555
References	556

Vitamin B₆ and Amino Acids—Recent Research in Animals

MARY ANN WILLIAMS

I. Introduction	561
II. Vitamin B ₆ Intake and Amino Acid Metabolism	562
III. Vitamin B ₆ and Amino Acid Transport	568
IV. Adaptive Changes in Levels of Activity of Vitamin B ₆ Enzymes	570
V. Summary	576
References	576

Vitamin B₆ and Oxalate Metabolism

STANLEY N. GERSHOFF

I. Introduction	581
II. Amino Studies	582

III. Metabolic Studies	585
IV. Human Studies	587
V. Summary	588
References	589

Relationship of Pyridoxine to Immunological Phenomena

A. E. AXELROD AND ANTHONY C. TRAKATELLIS

I. Introduction	591
II. Relationship of Pyridoxine to Immune Processes	591
III. Mechanism of Action of Pyridoxine	602
IV. Summary	606
References	607

Selective Metabolic and Chemotherapeutic Effects of Vitamin B₆ Antimetabolites

FRED ROSEN, ENRICO MIHICH, AND CHARLES A. NICHOL

I. Introduction	609
II. Inhibition of Growth of Experimental Tumors	610
III. Vitamin B ₆ Deficiency and Cancer in Man	616
IV. Selective Effects of Pyridoxine Deficiency	617
V. Means of Interfering with Pyridoxine Metabolism	628
VI. Concluding Remarks	636
References	638

Effects of Low Intakes of Vitamin B₆ upon Diabetic and Control Rats

GLADYS A. EMERSON, HIROE S. KISHI, BOBBIE J. MORRILL,
JAMES W. SNIPES, AND JANE B. WALKER

I. Introduction	643
II. Experimental	646
III. Results	647
IV. Summary	652
References	653

Summary and Comment on Tissue Changes in Vitamin B₆ Deficiency

GLADYS A. EMERSON

Text	655
----------------	-----

Vitamin B₆ in Farm Animal Nutrition and Pets

HENRY L. FULLER

I. Introduction	659
II. Poultry	660
III. Swine	667
IV. Dogs	669
V. Other Animals	670
VI. Practical Considerations	672
References	674

Arteriosclerotic, Dental, and Hepatic Lesions in Pyridoxine-Deficient Monkeys

LOUIS D. GREENBERG

I. Introduction	677
II. Arteriosclerotic Lesions	678
III. Dental Lesions	683
IV. Hepatic Lesions	689
V. Summary	693
References	693

Effect of Vitamin B₆ on Dental Caries in Man

ROBERT W. HILLMAN

I. Introduction	695
II. The Oral Environment	696
III. Epidemiological Observations	698
IV. Clinical Studies	700
V. Summary and Conclusions	701
References	703

Evidence for a Relative Vitamin B₆ Deficiency in Pregnancy and Some Disease States

MAX WACHSTEIN

I. Introduction	705
II. Abnormal Tryptophan Metabolism	706
III. Determination of Transaminases in Circulating Blood	712
IV. Urinary Estimation of 4-Pyridoxine Acid	713
V. Vitamin B ₆ Content of the Circulating Blood	714

VI. B ₆ Content of Tissues during Pregnancy	715
VII. Concluding Remarks	715
References	716

**Pyridoxine-Responsive Anemia—Prototype and Variations
on the Theme**

JOHN W. HARRIS AND DANIEL L. HARRIGAN

I. Introduction	722
II. The Prototype	723
III. Signs, Symptoms, and Laboratory Findings in Pyridoxine-Responsive Anemia: Variations Documented among 72 Acceptable Cases	736
IV. Etiology and Pathogenesis	746
V. Summary	749
References	750

Vitamin B₆ Metabolism in Infants and Children

DAVID BAIRD COURSIN

I. Introduction	756
II. Vitamin B ₆ Deficiency	756
III. Vitamin B ₆ Dependency	758
IV. Other Central Nervous System Disorders in Which B ₆ May Have a Role V. Anemia as a Symptom of Abnormal Vitamin B ₆ Metabolism	769
VI. Inhibitors of Vitamin B ₆ Activity	772
VII. Diagnostic Tests for Derangements of Vitamin B ₆ Function	773
VIII. Nutritional Requirements	774
IX. Possible Mechanisms Affecting the Function of Vitamin B ₆ at the Subcellular Level	776
X. Selected Critical Biochemical Roles of Vitamin B ₆ Affecting Physiologic Function	778
XI. Summary	782
References	783

Vitamin B₆ in Fat Metabolism

JOHN F. MUELLER

I. Introduction	787
II. Animal Studies	788
III. Human Studies	793
IV. Summation	794
References	795