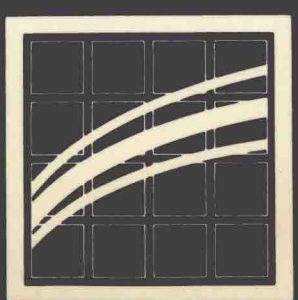
RICKETS

EDITED BY
FRANCIS H. GLORIEUX

Nestlé Nutrition
Workshop Series
Volume 21



NESTLÉ NUTRITION

RAVEN PRESS

Rickets

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Nestle Nutrition
Workshop Series
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RAVEN PRESS ■ NEW YORK

Nestec Ltd., Avenue Nestlé 55, CH-1800 Vevey, Switzerland
Raven Press, Ltd., 1185 Avenue of the Americas, New York, New York 10036

Made in the United States of America

Library of Congress Cataloging-in-Publication Data

Rickets / editor, Francis H. Glorieux.
p. cm. — (Nestlé Nutrition workshop series ; v. 21)
Based on the papers presented at the 21st Nestlé Nutrition Workshop, held in Buenos Aires, Argentina, Dec. 5–8, 1988.
Includes bibliographical references and index.
ISBN 0-88167-809-0
1. Rickets—Congresses. I. Glorieux, Francis H. II. Nestlé Nutrition S.A. Workshop (21st : 1988 : Buenos Aires, Argentina) III. Series.
RJ396.R44 1991
616.3'95—dc20 91-11849

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9 8 7 6 5 4 3 2 1

RICKETS

The 21st Nestlé Nutrition Workshop, Rickets, *was held in Buenos Aires, Argentina, December 5–8, 1988.*

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Preface

The term *rickets* may sound like a headline in the history of medicine but, in fact, it is very much a current problem for today's physicians. Early in this century, vitamin D deficiency was recognized as an environmental hazard, and the ensuing enrichment of food products, especially milk, with vitamin D has greatly decreased the prevalence of rickets in many countries. There are parts of the world, however, where it remains a public health problem. There are also several genetically-determined forms of rickets for which precise diagnosis and management have considerably improved over the last fifteen years. The practicing physician must remain aware of the various forms of the disease and keep abreast of the continuing efforts at prevention, differential diagnosis, and long-term treatment of rickets.

Rickets in the strict sense of the term is the disease caused by any interference with the process of endochondral bone formation, the cascade of events normally taking place in the epiphyseal growthplates and resulting in gain in length of long bones. However, this is not the only calcifying structure in the growing individual. Bone remodeling and increase in thickness by periosteal bone apposition are also active in growth and an alteration at those levels will result in osteomalacia, leading to excessive accumulation of osteoid tissue throughout the skeleton. The skeleton will thus be affected in its two main functions as the mechanical support for the other organs and the major mineral reservoir to serve a large array of physiologic functions.

Rickets and osteomalacia are anatomically distinct conditions arising from the common event of mineral insufficiency. As bone mineral is mostly made of calcium and phosphate, rickets and osteomalacia may arise from either primary calcipenia or primary phosphopenia (Fig. 1). Chapters on primary calcipenia will specifically address dietary calcium deficiency, vitamin D deficiency in children and neonates, and the major forms of pseudo-deficiency. Chapters on primary phosphopenia will focus on the neonatal period and on the heritable forms of hypophosphatemic rickets.

To provide current background information for the discussions of calcipenia and phosphopenia, several chapters discuss the biochemistry and physiology of vitamin D and parathyroid hormone and the intricacies of calcium and phosphorus homeostasis. A detailed description of the growthplate is also included that underlines the complexity of the cell-matrix interactions during the growing process. Chapters demonstrating the use of bone cell culture for studying specific pathophysiologic mechanisms, and underlining the role of the placenta in the transfer of minerals from the mother to the fetus will introduce the reader to a basic approach to unsolved clinical questions. Finally, chapters detailing rickets as a public health problem permit a comparison of data gathered on four continents. To further aid the reader, there is also an extensive list of references in the chapters as well as in discussion sections.

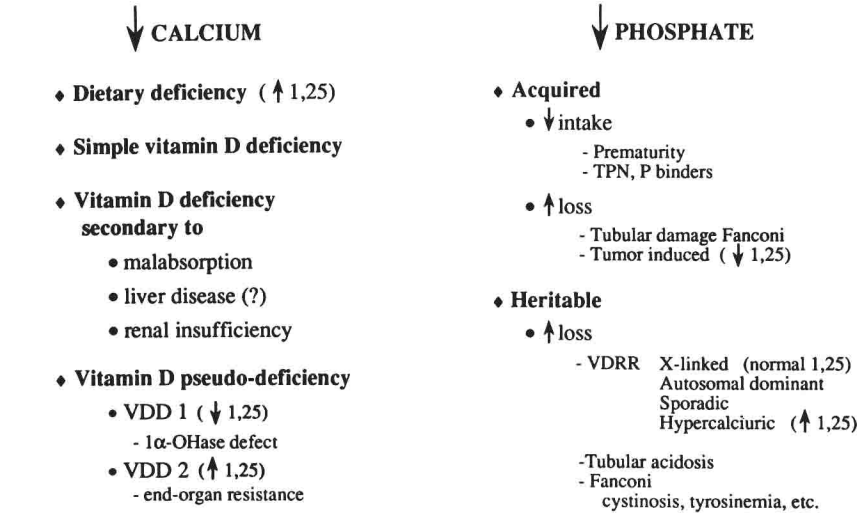

FIG. 1. Rickets and osteomalacia are best characterized by the deficiency of a major mineral component of the bone matrix (calcium or phosphate) because of insufficient intake or excessive loss. In the calcipenic state secondary hyperparathyroidism and its consequences on skeletal and renal functions are seen. In phosphopenic circumstances, calcium homeostasis is not significantly affected. [1,25: increased (↑) or decreased (↓) serum $1,25(OH)_2D$ levels.]

This will stand as a rich and concise source of information on the control of bone mineralization and skeletal development in the growing child and on the various forms of acquired and heritable rickets that still present a challenge to modern medicine.

FRANCIS H. GLORIEUX, M.D., Ph.D.

Foreword

Within the last twenty years the word *rickets* has become rather unfashionable in industrialized countries. With one exception, France, infant formulas and ordinary cow's milk are fortified with a level of vitamin D that is sufficient to prevent rickets.

The term, rickets, is now frequently misused by specialists such as neonatologists, who often label the hypophosphatemic osteopenia of the premature baby as rickets. Nephrologists often call rickets renal osteodystrophy, which is partly due to the defect of one hydroxylation of the 25(OH) vitamin D by the kidney, but also due to the hyperparathyroidism related to the hyperphosphatemia.

In industrialized countries rickets, which was so frequent at the turn of the century and was still seen up to the start of World War II, is now a very rare disease. The few cases seen today are in children who are breast-fed until the age of twelve to eighteen months, whose complementary food is not enriched with vitamin D and who have received insufficient exposure to the sun.

However, rickets remains a very prevalent disease in developing countries. It is found especially in Muslim countries where the cultural habit of pregnant and lactating women, as well as for infants, is to avoid sun exposure. Because there is a large infant population in developing countries, the number of babies suffering from rickets is very great, placing it among the five most prevalent diseases. Preventing or curing this common vitamin-sensitive disease is easy. It is only a problem of organization and money.

Besides the most frequent type of rickets there are other types. Vitamino-resistant rickets are rare but are good models for studying the metabolism of vitamin D and its activity on the various cells or organs (not only on cartilage) on which 1-25 dihydroxycholecalciferol acts as a hormone. This explains why rickets research in cell and molecular biology is still very active in many industrialized countries.

In this workshop on rickets we were fortunate to bring together the most prestigious researchers on the biology of vitamin D, pediatricians from developing countries who frequently see and treat common rickets, and specialists in the most unusual forms of vitamino-resistant rickets.

The discussions were very vivid and rich, and we hope that this feeling has been captured in this volume to make it one of the most interesting updates on the subject.

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Nestlé Nutrition Workshop Series, Vol. 21.
Nestec Ltd., Vevey/Raven Press, Ltd.,
New York © 1991.

Photosynthesis, Metabolism, and Biologic Actions of Vitamin D

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HISTORICAL INTRODUCTION

Vitamin D is a most interesting seco-sterol that has its origin dating back at least 0.5 billion years ago when it was produced in ocean-dwelling plankton (1). Although it is not known what its physiologic function was in these lower life forms, it appears that vitamin D became extremely important in the evolution of animals with ossified endoskeletons. In terms of human history, the role of sunlight and vitamin D became important at the beginning of the industrial revolution. As people began to congregate into cities and their children played in crowded, sunless alleyways (Fig. 1), the children developed a severe bone disease that was first appreciated in the mid-seventeenth century by Whistler, Glisson, and DeBoot (Fig. 2) (2,3). The incidence of this debilitating bone disease increased dramatically during the industrial revolution especially in Northern Europe and North America and by the latter part of the nineteenth century, autopsy studies done in Leiden (The Netherlands), suggested that approximately 90% of the children raised in this crowded and polluted city had the disease. This disease had devastating consequences for young women who often had a deformed pelvis that resulted in very high incidences of infant and maternal morbitity and mortality. It was this single factor that led to the increased use of cesarean sectioning for delivery of children from rachitic mothers.

As early as 1822, Sniadecki observed that children living in Warsaw had a much higher incidence of the disease compared to children living in rural areas. These observations prompted him to conclude that exposure to sunlight was the most important factor in the prevention and cure of rickets (4). Almost 70 years later Palm (5) reported his epidemiologic survey that included clinical observations from a number of physicians throughout the British Empire and the Orient. Based on his observation that rickets was rare in children who lived in squalor in the cities of Japan, China, and India whereas children of the middle class and poor who lived in industrialized cities in the British Isles had a high incidence of this disease, he concluded that the common denominator was sunlight. He urged the systematic use of sunbathing to prevent and cure rickets (5). However, it was inconceivable at that time

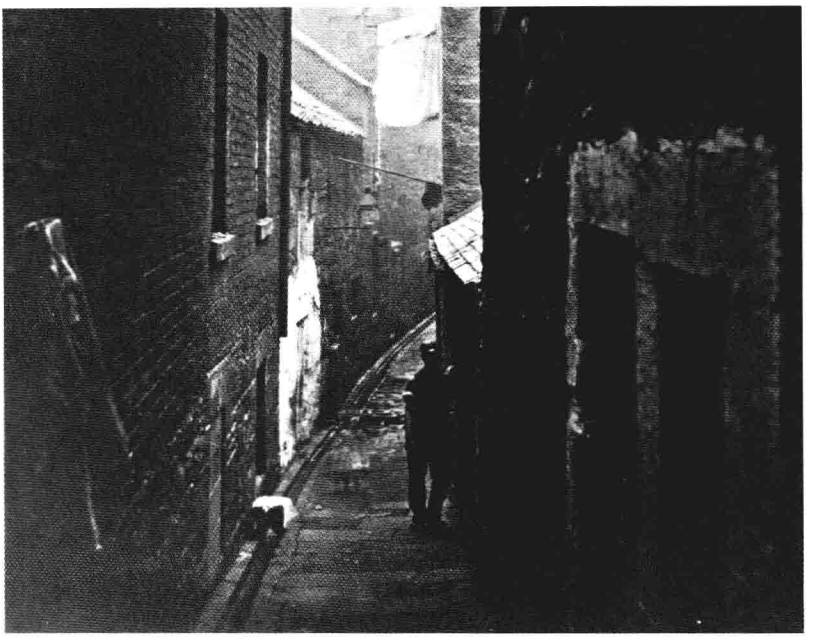

FIG. 1. A typical scene in Glasgow in the mid-1800's as captured by this photograph taken by Thomas Annan. From Annan T (63), with permission.

for scientists and physicians to accept such a simple remedy for such a devastating bone disease. As a result, another 30 years would pass before Huldshinsky unequivocally demonstrated that exposure to radiation from a mercury arc lamp could cure rickets (6). Two years later Hess and Unger exposed seven rachitic children on a roof of a New York City hospital to varying periods of sunshine and reported that x-ray examination showed marked improvement of rickets in each child as evidenced by calcification of the epiphyses (7).

Simultaneously, Mellanby reported that he could produce rickets in dogs by feeding them oatmeal and could cure the disease by adding cod-liver to their diet (8). Indeed, it was a common folklore practice on the coast lines of the British Isles and the Scandinavian countries to use fish liver oils to prevent and cure this bone deforming disease. At first it was thought that the antirachitic activity in cod-liver oil was due to vitamin A. However, when the vitamin A activity was destroyed by heat and oxidation the cod-liver oil continued to have antirachitic activity (9). As a result of these observations, it was concluded that there was a new fat-soluble vitamin that was called vitamin D.

Now that it was known that the antirachitic factor could be generated in the skin after exposure to sunlight or could be obtained from cod-liver oil, it became confusing as to whether there was more than one antirachitic factor. This issue was resolved