The Retinoids

VOLUME 1

Edited by

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Preface

This two-volume treatise, the collected effort of 19 authors, represents the first comprehensive survey of the chemistry and biology of the retinoids. Profound advances in organic chemistry, analytical methodology, cell biology, and biochemistry, as well as in clinical applications, have occurred since the topic of vitamin A was last reviewed in 1967 in a multi-authored volume ("The Vitamins," 2nd ed., W. H. Sebrell, Jr. and R. S. Harris, eds., Academic Press). There is now an entire domain of new substances, representing analogs of retinol, retinaldehyde, and retinoic acid, which were scarcely known in 1967; the entire set of molecules, including the naturally occurring parent compounds as well as their synthetic derivatives, have collectively been termed retinoids. The introductory chapter provides a brief overview of the impact that the retinoids have had on both basic and clinical investigations in the past 10 years. It is our intention that this treatise should be of interest to both basic scientists and clinicians.

The two volumes are organized to begin with basic chemistry and progress toward biological and then clinical considerations. The first chapters in Volume 1 deal with new advances in organic chemistry and tracer chemistry, followed by surveys of chemical and biological methods for analysis and assay of retinoids; the first volume concludes with a comprehensive survey of vitamin A in animal and human nutrition. Volume 2 begins with several chapters that review the biochemistry and metabolism of the retinoids and of specific retinoid-binding proteins that are found in plasma and in cells. These chapters deal with the biosynthesis and metabolism of retinol, with plasma retinol-binding protein, with intracellular retinoid-binding proteins, and with the metabolism and role of retinoids in the eye. Following a chapter on the metabolism of retinoic acid and synthetic retinoids, current knowledge of the cellular and molecular mechanisms of action of the retinoids is reviewed at length. The final four chapters deal with the applied biology of the retinoids and include reviews of toxicology and teratology, immunology, and applications of retinoids in the fields of cancer and dermatology. An Appendix showing the chemical structures which are referred

to in the text appears in each volume and should be of major help to the reader. Since the chemistry and biology of carotenoids have been comprehensively reviewed elsewhere, the present volumes devote relatively little attention to these topics.

We would like to acknowledge the assistance of the many colleagues who have contributed to the reviews of the manuscripts of the various chapters. In particular, we wish to thank David Bridges, Gerald Chader, Frank Chytil, Marcia Dawson, Peter Elias, Fritz Frickel, Charles Frolik, William Lennarz, Reuben Lotan, Robert McIntire, James Olson, Gary Peck, and Barbara Underwood for their editorial help. We are indebted to Fritz Frickel and colleagues at BASF Aktiengesellschaft for assistance with the Appendix, and to the National Eye Institute and Hoffmann–La Roche Inc. for help with the color illustrations. We would like to express our sorrow at the untimely death in July 1983 of one of the authors, Hans Kaegi. Dr. Kaegi was one of the leading tracer chemists in his field, and at the time of his death was attempting to synthesize new retinoidal benzoic acid derivatives of extremely high specific activity. Finally, we would like to express our appreciation to the staff of Academic Press, for all of their efforts in bringing this treatise to publication.

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Contents of Volume 2

Contents

1

Introduction

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These two volumes represent the first attempt to provide a comprehensive treatise on the retinoids, the family of molecules comprising retinol, retinaldehyde, retinoic acid, and their synthetic analogs. Although numerous books and reviews on the topic of vitamin A have been published over the years, this is the first time that the chemistry and biology of the entire domain of substances related to vitamin A have been reviewed in a comprehensive manner. Although the important original discoveries in this field were in the areas of nutrition and vision, the chemistry and biology of retinoids now pertain to a much broader area of biological and medical investigation, and the retinoids have become important substances for the basic cell biologist as well as for the practicing and investigative physician. Although the retinoids remain of paramount importance in the fields of nutrition and vision, the new surge of interest in these substances reflects their applications, both practical and theoretical, to the study of many other problems. The retinoids are now seen as fundamental mediators of cell differentiation and cell proliferation, and the implications of this viewpoint suggest that they ultimately may play as important a role in clinical medicine as their relatives, the steroids.

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I. HISTORICAL BACKGROUND

Night blindness was a recognized disease entity in ancient Egypt. Moreover, it has been suggested since ancient times that there might be a substance in the diet necessary for night vision. In 1913 McCollum and Davis (1913) reported the existence in certain foods of an essential lipid-soluble substance, capable of promoting growth in rats. They subsequently called this substance "Fat Soluble A" to distinguish it from essential water-soluble nutrients, which they called "Water Soluble B." During the subsequent decade, further information about the existence and properties of this soluble essential nutrient was obtained from the work of a number of investigators, including McCollum and his associates, Osborne and Mendel, Stepp, Steenbock, Moore, and others. It was shown that "Fat Soluble A" (later named vitamin A) not only maintained growth in rats but was capable of preventing xerophthalmia and night blindness. Subsequently, the relationship between vitamin A in animals and the provitamin carotene in plants was also clarified, particularly after Karrer and his associates (Karrer *et al.*, 1930) determined the chemical structure of β-carotene in 1930 and of retinol in 1931 (Karrer *et al.*, 1931).

In 1937 Holmes and Corbet (1937) were able to crystallize pure retinol from fish liver. A decade later, Arens and Van Dorp (1946) and Isler and his associates (Isler *et al.*, 1947) succeeded in achieving the chemical synthesis of pure retinoic acid and retinol. Shortly thereafter, the total synthesis of β-carotene was also reported (Karrer and Eugster, 1950).

Many studies were conducted in the first half of this century dealing with various aspects of the physiology and metabolism of vitamin A. Particularly noteworthy was the identification by Wald (1934) and by Morton (1944) of the chromophore of the visual pigment as retinaldehyde. These various studies provided considerable information about the role of vitamin A in vision (Wald, 1968) and about the pathology and pathophysiology of vitamin A deficiency.

In this introduction, we do not provide a more detailed review of the "classical" discoveries in the field of vitamin A research. As already discussed in part, these classical discoveries included the original description of fat-soluble A and the introduction of the term "vitamin A"; the recognition of retinol as a substance distinct from its carotenoid precursors; the development of quantitative chemical methods for the analysis and assay of retinol and related substances; the elucidation of the chemical structure and then the total synthesis of retinol, retinyl esters, and retinoic acid; the description of the unique pathology of both hypovitaminosis A and hypervitaminosis A in experimental animals and man; the elucidation of the fundamental role of retinaldehyde in vision; the determination of human and animal needs for retinol or its precursors for adequate nutrition; and the development of practical syntheses for the commercial production of retinyl esters to meet those nutritional needs. This historical story has been

eloquently told many times before, in several instances by scientists who participated directly in the great early discoveries in this field (Karrer and Jucker, 1950; Sebrell and Harris, 1954, 1967; Moore, 1957; McCollum, 1957; Wald, 1968; Isler, 1971; Pommer, 1977; Wolf, 1980). The reader interested in a more detailed historical narrative should consult these references.

II. NOMENCLATURE

Vitamin A-active substances are compounds, other than carotenoids, that exhibit qualitatively the biological activities of retinol. The term, "retinoid" is a general term that includes both the naturally occurring compounds with vitamin A activity and synthetic analogs, with or without biological activity, of retinol. In a report of the IUPAC–IUB Joint Commission on Biochemical Nomenclature (1982) it was stated that, "Retinoids are a class of compounds consisting of four isoprenoid units joined in a head-to-tail manner. All retinoids may be formally derived from a monocylic parent compound containing five carbon–carbon double bonds and a functional group at the terminus of the acyclic portion. To avoid confusion with previously used names in this field no parent hydrocarbon is named." It was recommended that, "The term vitamin A should be used as the generic descriptor for retinoids exhibiting qualitatively the biological activity of retinol. This term should be used in derived terms such as vitamin A activity, vitamin A deficiency, vitamin A antagonist."

III. GOAL OF THIS TREATISE

These two volumes are meant to be a modern treatise that broadly reflects the contemporary interest and excitement in current retinoid research. They include detailed discussions of the continuing themes of the roles of retinoids in nutrition and in vision. These topics have been under investigation for decades, yet remain scientifically and clinically timely and important. Indeed, in the area of public health, the widespread occurrence of vitamin A deficiency is still one of the world's major nutritional problems, and the chapter on nutritional aspects of vitamin A is one of the most extensive in these two volumes. Similarly, the biochemistry of retinoids in vision is still an issue of major scientific importance, and an extensive review of this topic is also presented here.

However, in many respects this treatise represents a significant departure from the review of the field which was presented when the field of "Vitamins A and Carotene" was summarized in "The Vitamins, Second Edition" (Sebrell and Harris, 1967). There have been major advances in synthetic organic chemistry, particularly with the application of the Wittig reaction (Pommer, 1977), resulting

in the synthesis of well over a thousand new retinoids. Some of the new chemistry has resulted in the synthesis of compounds that superficially bear little resemblance to retinol or retinoic acid but nevertheless retain many of the biological activities of these substances. Advances in tracer chemistry now allow the synthesis of almost any desired retinoid in radioactively labeled form. New methods have been developed for the chemical separation and analysis of retinoids; the development of high-performance liquid chromatography has revolutionized the problem of isolation and characterization of retinoids and their metabolites. A whole array of new *in vitro* bioassay systems has been developed, some of which are even more sensitive than the chemical detection methods. The net result of these new developments in chemical and biological assay is that many of the classical techniques for measurement of retinoids are now almost totally obsolete. Since 1967, major advances have occurred in understanding the intermediary metabolism as well as the transport systems, both extracellular and intracellular, for retinoids. Although the problem of the molecular mechanism of action of retinoids in control of cell differentiation and proliferation remains unsolved, it has become the subject of an immense experimental literature. There has been a striking thrust in the development of the new retinoids for prevention or treatment of disease, particularly in the areas of oncology and dermatology, and as ancillary issues to these two fields, there has been a major increase in the investigation of the toxicology of retinoids and their interactions with the immune system. All of these topics are extensively reviewed in the present treatise.

The domain of retinoid research thus has moved well beyond its classical roots in the study of nutrition and vision, and in doing so it has created a great deal of excitement in the biomedical community. The development of cell culture techniques has facilitated study of the effects of retinoids at the level of the single cell. Fundamental to these new studies is the realization that retinoids are highly potent agents for control of cell differentiation and cell proliferation. The retinoids have become valuable tools for the investigator to study one of the most basic problems in all of biology, namely the control of cell differentiation; in this regard, they have had a particularly striking role in helping to illuminate the problem of malignant cell differentiation. Out of these new studies has come a profusion of new findings that are leading to a reevaluation of concepts at the molecular, cellular, and clinical levels. The synthesis of new structures that are much more active than either retinol or retinoic acid in a variety of biological systems has led to a fundamental reevaluation of what in meant by the word "retinoid" and to a new generation of substances that were undreamed of in 1967. The ability of retinoids to arrest the progression of premalignant cells or to induce terminal differentiation of malignant cells has had a powerful influence in the field of cancer research and has raised hopes that new modalities of prevention and treatment of cancer will be found in the near future that will lessen the need to treat the cancer patient with highly cytotoxic drugs. The clinical success

of retinoids in treating both rare and common skin diseases that have previously been refractory to therapy has had major impact on the practice of dermatology.

These two volumes, then, seek to provide a summary of the current chemical and biological knowledge in the field of retinoids, which should be the foundation for further advances in clinical medicine. The progress that has been made in the past decade has been indeed great, and we anticipate that major advances concerning the chemistry, the biology, and the potential clinical roles of the retinoids will continue to be made in the years to come. We hope that these volumes will be of value to those who wish to understand these recent developments and will help scientists and clinicians in the further pursuit and application of new knowledge in this field.

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