In 1913, McCollum and Davis (1) published a paper entitled “The Necessity of Certain Lipins in the Diet During Growth” in which they showed that ether extractable organic compounds present in butter or eggs were required for maintaining the normal growth of rats. This effect on growth could not be obtained simply by feeding lard or olive oil. This was taken by McCollum and Davis to indicate that dietary fat alone was not responsible for their findings. These early investigators went on to conclude “…that there are certain accessory articles in certain food-stuffs which are essential for normal growth for extended periods.” This paper from a century ago is generally considered to be the first to provide evidence for the existence of fat-soluble vitamins. We now understand that there are four distinct fat-soluble vitamins that are required to maintain the good health of higher organisms, vitamins A, D, E, and K. We also now understand, at the molecular level, much regarding how these vitamins act to maintain good health. Each vitamin has its own distinct metabolism and distinct mechanism(s) of action. These four fat-soluble vitamins will be the focus of a new Journal of Lipid Research Thematic Review Series that will be published in four separate issues. This is the first installment of the Thematic Review Series and will have as its focus recent advances in the area of vitamin A biology and biochemistry. Subsequent Journal of Lipid Research issues will consider each of the other fat-soluble vitamins.

VITAMIN A BACKGROUND

By definition, vitamin A is all-trans-retinol. In the mid-1970s, Sporn coined the term retinoid to refer to all compounds, both natural and synthetic, which bear a structural resemblance to all-trans-retinol, with or without the biological activity of vitamin A (2). The term retinoid is now generally used interchangeably with the term vitamin A, although vitamin A is more frequently used when referring to nutritional interventions or nutritional studies. Retinoid is more frequently used when the focus of the research is on molecular mechanisms or processes. To be consistent with the terminology used for vitamins D, E and K, I will use the term vitamin A rather than retinoid in this Introduction.

Although vitamin A has been the focus of scientific investigation for almost 100 years, considerable research interest remains focused on this essential micronutrient. This broad research interest can be divided into three smaller, more focused research areas. Nutritional deficiency of vitamin A remains a major public health concern in many parts of the Third World. It was very recently estimated that vitamin A deficiency in the developing world is responsible for a million or more instances of unnecessary death or blindness each year (3). Consequently, there is a large amount of public health research aimed at identifying populations that are at risk of vitamin A-deficiency and eliminating this risk. This research interest has spawned much sophisticated molecular research aimed at developing fortified (with provitamin A β-carotene) plant food sources, including golden rice and other fortified food staples (4, 5). A second area of research interest focused on vitamin A concerns its potential role in the prevention and/or causation of human disease. This research is primarily epidemiologic in nature and is aimed at understanding both whether dietary vitamin A intake and/or blood levels of vitamin A are associated with disease incidence or development. There is a clear strong rationale for this research interest given that many disease states involve abnormal cell proliferation and differentiation and vitamin A is a very potent regulator of these cellular processes (6, 7). It should be noted that the epidemiologic literature at times refers to vitamin A as an “antioxidant vitamin” (8). This is incorrect for vitamin A. There is no credible evidence in the literature going back over 30 years that vitamin A per se acts within the body as an antioxidant. The third and final focus of vitamin A research activity involves investigations aimed at gaining new insights into the molecular actions of vitamin A and the molecular processes involved in its metabolism. This includes interest in elucidating the molecular events central to understanding how and why vitamin A can act in the prevention and/or
treatment of human disease states. The articles on vitamin A in this Thematic Review Series are firmly grounded in this final research area.

THE VITAMIN A THEMATIC REVIEWS

Four review articles, each covering different aspects of vitamin A biochemistry, molecular biology, and physiology, accompany this Introduction.

Since the time of its identification as fat-soluble A, now vitamin A, the central question regarding this micronutrient has concerned how it acts at the molecular level to promote normal health and prevent disease. The early research addressing this issue focused on vitamin A actions in vision. This culminated in the award in 1967 of the Nobel Prize in Physiology and Medicine to George Wald for his work establishing the role of 11-cis-retinaldehyde as the visual chromophore (9). However, a great deal of early research had also demonstrated that vitamin A is required to maintain the good health of many tissues outside of the eye and it was understood early on that these actions of vitamin A did not involve 11-cis-retinaldehyde. Many hypotheses explaining the observed physiological effects of vitamin A were proposed in the early literature but none of these satisfactorily explained vitamin A actions. It was not until the seminal, simultaneous work of the Chambon and Evans laboratories, first published in 1987, that it became clear that the vitamin A metabolite retinoic acid modulates genomic expression acting through its cognate ligand-dependent transcription factors, the retinoic acid receptors (RARs) (10, 11). There is now a very detailed understanding at the molecular level of retinoic acid and RAR actions in regulating transcription. The review by Rochette-Egly and colleagues (12) in this issue entitled “Vitamin A and retinoid signaling: genomic and nongenomic effects” considers the current state of this knowledge. In addition, Rochette-Egly and colleagues provide insights into recent advances that have been made in identifying and explaining nongenomic effects of vitamin A in the body. These nongenomic actions of vitamin A are the focus of much contemporary research and it is becoming increasingly clear that vitamin A acts both genomically and nongenomically to regulate cellular processes.

The knowledge that retinoic acid is the transcriptionally active, and consequently the functionally significant form of vitamin A, led investigators to question how retinoic acid is formed from its much more abundant retinol precursor and how retinoic acid is catabolized and eliminated from cells and tissues. Early investigations established that retinoic acid is formed through a two-step process involving the enzymatic oxidation of retinol, through a retinaldehyde intermediate (13). This early work showed that soluble medium chain alcohol dehydrogenases isolated from mammalian liver could catalyze retinaldehyde formation from retinol, although it is no longer thought that this family of dehydrogenases is physiologically important for catalyzing this reaction. Early work also showed that aldehyde dehydrogenases present within tissues could catalyze retinaldehyde oxidation to retinoic acid. During the same period, there were published reports demonstrating that retinoic acid could be oxidized through the actions of a number of different cytochrome P450 (CYP) enzymes. The molecular identities of physiologically significant dehydrogenases and CYPs are now established and their biochemical properties are generally understood. Our current understanding of these and related enzymatic processes is summarized in this issue in the review by Kedishvili (14) entitled “Enzymology of retinoic acid biosynthesis and degradation”.

Early investigations established that tissues, primarily liver but also others including the eyes and adipose tissue, accumulate vitamin A stores as retinyl esters when the organism is maintained continuously on a diet that contains sufficient vitamin A. These retinyl ester stores were proposed to buffer against the adverse pathological outcomes observed when animals were fed a vitamin A-deficient diet. Indeed, the ability to store an essential micronutrient like vitamin A provides a very substantial selective advantage to the organism by relieving it from the obligate need to acquire vitamin A regularly from the diet. The mechanisms that have evolved to facilitate vitamin A storage and the mobilization of these stores are unique to vitamin A and involve a number of specific vitamin A-binding proteins and enzymes. The current state of understanding regarding vitamin A storage and the mobilization of these stores is discussed in the accompanying review from O’Byrne and Blaner (15) entitled “Retinol and retinyl esters: biochemistry and physiology”.

Ultimately, all vitamin A present in higher organisms must be derived from dietary provitamin A carotenoids such as β-carotene, because no higher animal species can synthesize vitamin A de novo. Most higher animals express the sole enzyme, β-carotene-15,15'-monooxygenase (BCMO1), that cleaves provitamin A carotenoids centrally at the 15,15'-double bond to form vitamin A. Alternatively, higher organisms can acquire vitamin A that had been formed from provitamin A carotenoids by animals lower on the food chain. A second enzyme, a close homolog of BCMO1, β-carotene-9',10'-dioxygenase (BCDO2) catalyzes asymmetric cleavage of provitamin A and nonprovitamin A carotenoids about the 9’10’-double bond to form compounds which, along with other carotenoid metabolites, are collectively known as apocarotenoids. For a long period, spanning the early 1960s through the early 2000s, there was controversy in the literature as to whether both the central and asymmetric cleavage pathways or simply the central cleavage pathway was responsible for vitamin A synthesis form provitamin A carotenoids. Similarly, although it was known for many decades that apocarotenoid products could be formed by higher organisms, it was never understood whether these nonvitamin A carotenoid metabolites had independent physiological actions within tissues. Research carried out over the last decade has provided many new insights into questions related to carotenoid conversion to vitamin A and carotenoid metabolism to apocarotenoids. The review entitled “Carotenoid metabolism in mammals including man: formation, occurrence and
function of apocarotenoids” from Eroglu and Harrison (16) in this issue will consider new research findings in these areas, as well as other new findings related to carotenoid actions and metabolism in higher animals.

As noted above, the current research interest in vitamin A is very broad. The four reviews on vitamin A in this Thematic Review Series are focused on recent advances in our understanding of the biochemical and molecular processes responsible for mediating vitamin A actions and metabolism in higher organisms. Necessarily, owing to the breadth of this research field, many topics of potential interest to the Journal of Lipid Research readers may have received only brief or possibly no coverage in these articles on vitamin A. Our aim is to provide readers with a broad overview of the current state of this research field.

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