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SYMPOSIUM ON 'VITAMIN A IN NUTRITION AND DISEASE'

Historical introduction

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This paper provides a brief history of the events and discoveries leading to the present-day understanding of the chemistry, biochemistry, and role of vitamin A in nutrition and disease. Only the chief discoveries have been detailed, but the dates and authors of these have been included in the list of references for those who may wish to read further. Details of these main discoveries are provided in chronological order in Table 1.

Information in the early days leading to our knowledge of vitamin A stemmed from three main sources: defective dark vision, exterior eye abnormalities and a study of the nutritional value of fats.

Defective dark vision

The recognition that defective dark vision, or night-blindness, might be connected with poor nutrition can be traced back over many centuries. Thus an ancient Egyptian medical treatise of about 1500 BC, known as Eber's Papyrus, recommended that roast ox-liver might be used as a cure for those who were unable to see properly at night. Since those early days it has gradually become recognized that night-blindness is indeed due to poor diet, though the precise reason had to wait for a fuller understanding of the missing nutrient.

Exterior eye abnormalities

In 1816 Magendie gave dogs a restricted diet of wheat gluten, starch, sugar or olive oil as their sole food. When describing the symptoms of inanition that developed he mentioned that ulcers formed on the corneas of the animals so fed. In 1857 David Livingstone, the medical missionary in Africa, described the effects on his native porters when forced by circumstances to subsist for a time on sugarless coffee, manioc and meal (Livingstone, 1905). He stated 'the eyes became affected as in the case of animals fed on experiment on pure gluten or starch'. It is likely that he referred to the experiments of Magendie.

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Table 1. *Highlights in vitamin A history*

Date	Authors	Event
		Defective dark vision
1816	Magendie	Dogs on defective diet → eye abnormalities
1857	Livingstone	Native porters developed similar lesions
1917	McCollum & Simmonds	Xerophthalmia in rats
1921	Bloch	Relationships of xerophthalmia to deficiency
1906–12	Hopkins	Accessory food factors
1912	Funk	Name: 'vitamine'
1915	McCollum & Davis	'Fat soluble A'
1915	Osborne & Mendel	Activity of butter fat remained after heating
1919	Steenbock & Gross	Correlation with 'yellowness', but not always
1919	Palmer & Kempster	Birds would not grow on 'white' diet, but did on diet augmented with pig's liver
1925	Drummond *et al.*	Vitamin A in cod-liver oil is not carotene
1926	Carr & Price	$SbCl_3$ blue colour
1928	von Euler *et al.*	Carotene active with vitamin D
1929	Moore	Carotene → colourless vitamin A
1932	Karrer	Structural formula
1935	Wald	Role in retina
1944	Morton	Wald's retinene is vitamin A aldehyde (retinal)
1946	Milas	Synthesis
1947	Isler *et al.*	Synthesis
1947	Karrer	Synthesis
1946	van Dorp & Arens	Vitamin A acid
1948	Salah & Morton	Vitamin A_2
1949	Hume & Krebs	Vitamin A requirements of human adults
1957	Moore	Book: 'Vitamin A'
1960	American Chemical Society	Name: 'Retinol' (from Morton's 'retinal')
1968	Goodman and co-workers	Retinol-binding protein (RBP)
1975	Bjelke	Vitamin A and cancer

McCollum & Simmonds (1917) concluded that the lesions seen in some experimental rats were due specifically to vitamin A deficiency and not to general malnutrition. These workers described xerophthalmia in detail. In the following years Bloch (1921) made extensive studies on the relationship between xerophthalmia and a deficiency of vitamin A in the human.

Nutritive value of fats

Turning now to the studies made on the nutritive value of various fats we must first mention the pioneering work of Hopkins carried out at the University of Cambridge in the years 1906–12. Hopkins' experiments were carried out with much care and devotion and were planned in minute detail. From his studies, eventually published in 1912, he claimed that in addition to all the then known nutrients (protein, fats, carbohydrates and minerals) certain accessory food factors were necessary. He did all he could to emphasize the importance of these factors.

About the same time as Hopkins' results were published the Polish biochemist Funk (1912) suggested the name 'vitamine' for these factors, believing at the time they were amines. Later when it was realized they were not all amines the terminal 'e' was dropped at the instigation of Drummond (1920).

In 1915 McCollum & Davis made the first major step to separate the vitamins by postulating the existence of two factors, viz: 'fat-soluble A' and 'water-soluble B'. These workers had already shown that the fat-soluble factor resisted the action of alkali and could be recovered in the unsaponifiable fraction after the hydrolysis of active fats. Osborne & Mendel (1915) supplemented these findings by treating butter fat with steam for 2·5 h and showed that this had no effect on its growth-promoting property.

Confusion now followed because the roles of the preformed vitamin and of its precursor were not understood. As a result some conflicting results were found and these somewhat delayed a full understanding of the true position. However, in 1919 Steenbock & Gross showed a correlation between activity and 'yellowness', though this was not always the case. Palmer & Kempster (1919) demonstrated that birds did not grow on a 'white' diet but they did when the diet was augmented with pigs' liver (now known to contain the colourless form of vitamin A). By 1925 Drummond and co-workers had shown that the vitamin A in cod-liver oil was not carotene and an understanding of the two forms of the vitamin emerged.

Measurement of the vitamin and the role of carotene

Following the use by various workers of colour reactions with sulphuric acid and arsenic trichloride to detect vitamin A, Carr & Price (1926) improved detection by using a solution of antimony trichloride in chloroform. This reagent produces a bright blue colour with vitamin A enabling quantitative determinations to be made. In 1928 von Euler and co-workers conducted experiments with young rats in which both carotene and vitamin D were provided. These animals grew normally, thereby confirming the findings of Steenbock & Gross (1919) that carotene is indeed a source of vitamin A. The existence of the anti-ricketic vitamin D had previously been demonstrated and it had been noted that young rats kept indoors, away from direct sunlight, and deprived of this vitamin, developed abnormal bones and were stunted. Hence, von Euler and co-workers were successful in confirming the activity of carotene. However, it is now apparent that the reason why some carotene supplements were found to be inactive was because solutions, which had been made up to last for several weeks, had deteriorated. In 1929 Moore found that carotene is in fact provitamin A. He gave purified carotene to young rats depleted of vitamin A and later showed that the colourless form of the vitamin was present in the livers of these rats. This explained why Palmer & Kempster (1919) had succeeded with their chickens when pig liver, free from yellow pigments, was the only source of vitamin A. The pigs would have eaten carotene and converted it into the colourless form of the vitamin.

Chemistry of the vitamin and related compounds

A more thorough understanding of vitamin A chemistry followed the elucidation of the structural formula of the vitamin by Karrer in 1932. Methods for its synthesis were eventually evolved in 1946–47 by three different groups of workers

independently, viz Milas (1946), Isler *et al.* (1947) and Karrer (1947). Also in 1946, van Dorp & Arens synthesized vitamin A acid, a compound of considerable theoretical interest to those concerned with vitamin A metabolism because it has high biological activity without undergoing conversion to the vitamin itself. Two years later another compound, vitamin A_2, was isolated by Salah & Morton (1948) from the livers of fresh-water fish. This compound has vitamin A activity but differs from vitamin A in having an additional double bond in its ring structure.

During this period in which the chemistry of the vitamin was being developed, advances in its biochemistry were also proceeding. Thus Wald (1935) showed in detail how the vitamin functioned in vision and he gave the name 'retinene' to the form of the vitamin present in the retina. In 1944 Morton showed that Wald's 'retinene' is vitamin A aldehyde and gave it the name 'retinal'. Further extensive spectroscopic studies by Morton and his colleagues have since added greatly to our understanding of the physiology and metabolism of vitamin A.

Requirements and more recent advances

In 1949 Hume & Krebs published the details of an extensive experimental study of vitamin A deprivation in man in which workers from a number of different laboratories had participated. It is upon the results of this study that the recommended amounts for the requirements of vitamin A are based today. In the following years many advances were made in vitamin A research and in 1957 these were brought together by Moore in his monograph on the vitamin. Apart from one other publication in Russian this is believed to be the only book devoted entirely to vitamin A.

Further highlights in the progress of vitamin A chemistry include the introduction by the American Chemical Society in 1960 of the name 'retinol' for the preformed vitamin. The name was based on Morton's 'retinal'. In 1968 Goodman and co-workers isolated and named retinol binding protein (RBP), the carrier protein responsible for the conveyance of retinol in blood (Kanai *et al.* 1968). In 1975 Bjelke published a paper suggesting an association between vitamin A and cancer. It is interesting, even provocative, that of all the many substances examined as cancer preventive agents during recent years the most promising should be the nutrient vitamin A. However, this subject is a very complex one involving as it does the retinoids—artificial derivatives of retinol.

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