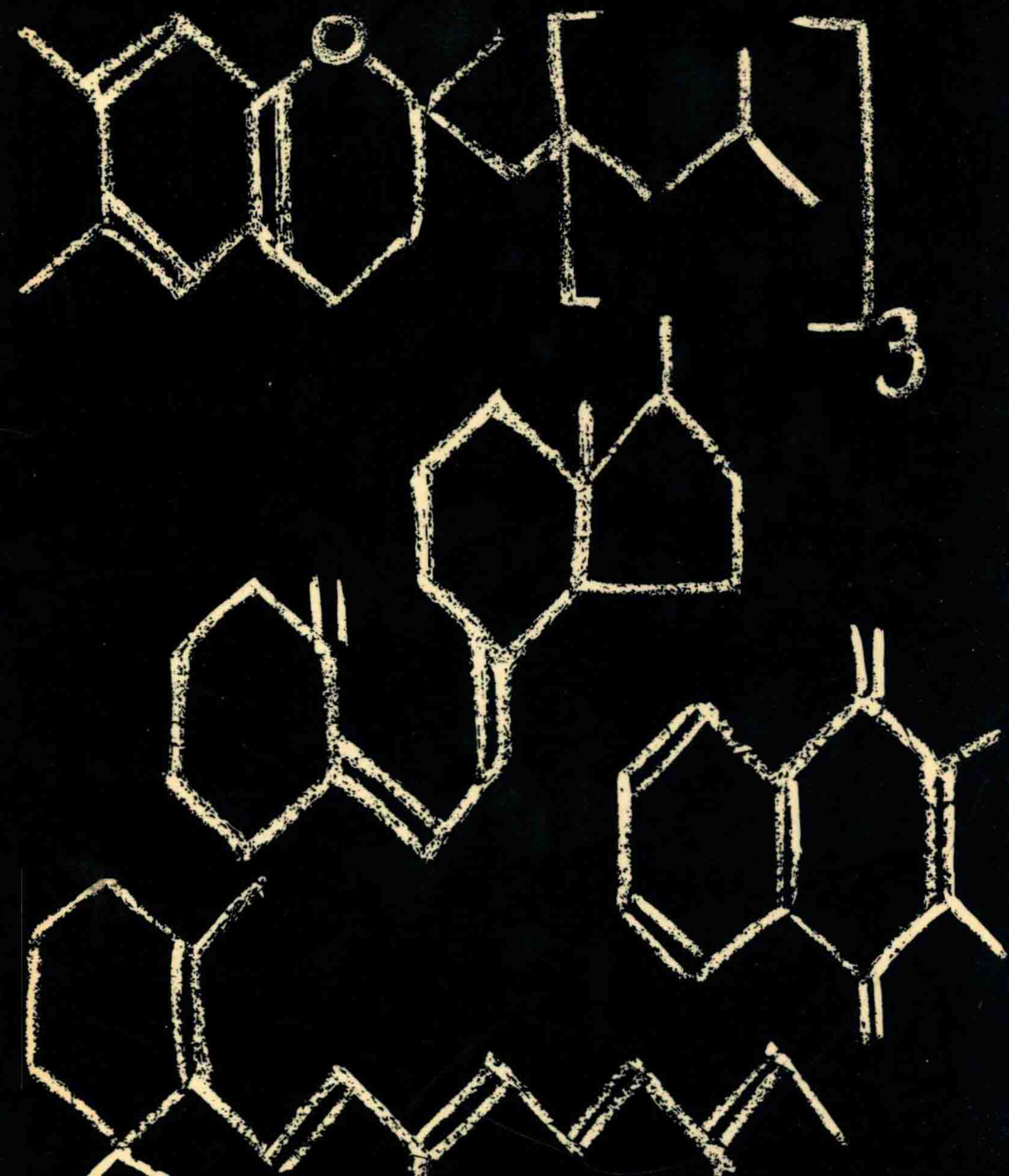
FAT-SOLUBLE VITAMINS

Their biochemistry and applications

Edited by Anthony T Diplock PhD DSc



FAT-SOLUBLE VITAMINS

Their Biochemistry and Applications

Edited by
ANTHONY T. DIPLOCK

With contributions by Anthony T. Diplock, David E.M. Lawson, George A.J. Pitt, and John W. Suttie

Foreword by Thomas Moore

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This book is dedicated to the memory of
Alan Morton, Egon Kodicek, Karl Mason and Henrik Dam,
four great pioneers in research on the fat-soluble vitamins

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Foreword

In inviting me to write a Foreword for this important book, Professor Diplock referred to my association with the field over a long period of time, which might enable me 'to set the scene from an historical viewpoint'.

If a long memory is the thing mostly required for the acceptance of this pleasant and honourable literary task, then I am certainly well qualified for it. Indeed I can remember the days, soon after the First World War, when I first heard of the mysterious substance called 'Fat-Soluble A'. In my ignorance I thought that it must be some strange form of fat that was soluble in water! Later, I was privileged to meet the great E.V. McCollum, co-discoverer of fat-soluble A with M. Davis, on many occasions, notably when I attended a conference organized in his honour in Baltimore in 1951. At an earlier conference on vitamin E, held in New York in 1949, I had the pleasure of meeting his fellow countryman, the charming Karl Mason, one of the four great pioneers to whom this book is dedicated.

For many years I shared with another honoured pioneer, Henrik Dam, the duty of representing the Nomenclature Committee of the International Union of Nutrition Sciences at joint meetings with other international bodies. I always had profound admiration for the genius of this modest, almost apologetic little man, with his tremulous Danish accent. We last met in 1968 at Bellagio, on the shore of Lake Como, where we had gone for a joint meeting between IUNS and IUPAC. At a final hotel lunch with Henrik and his wife, I suddenly realized that the frontier clocks were set an hour earlier than in Bellagio, so that I could not linger over my coffee. Nevertheless, with typical kindness, both the Dams came to the bus stop to wave me off, and sadly we never met again (Henrik Dam died in April, 1976).

Egon Kodicek came from Prague to the Dunn Nutritional Laboratory, Cambridge, shortly before the outbreak of World War II, and about twelve years after Leslie Harris started operations there, joined shortly afterwards by myself. Apart from breaks for holidays and conferences, I met Egon,

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who was Deputy Director, almost daily for the next twenty-five years, for the last two of which he succeeded Harris as Director. Eventually, Egon followed me into semi-retirement at the Strangeways Research Laboratory, Cambridge, where we both finished up, through the kindness of Dame Honor Fell and Dr John Dingle, sharing the same minute office in one of the Strangeways' numerous back corridors.

Alan Morton came into my life much earlier than any of the other three pioneers. We first met as contemporary chemistry students in 1919 at Liverpool University, when many of the undergraduates attended lectures, often rowdy, still dressed in khaki, or in naval or air-force blue. From then on our careers, although at different levels of academic status, influence and wordly honour, ran remarkably parallel. I think I was marginally the earlier in entering the vitamin A field, although Alan was the pioneer, apart from early Japanese workers, in introducing spectroscopy, his first speciality, into research on vitamins.

Our long friendship approached its end in 1976, when we both attended a conference in Bangalore on Polyprenoids, which was organized in Alan's honour by his old research student Homi Cama, and which was sadly followed by his unexpected death within a few weeks of his return to Liverpool. Like me, Tony Diplock, George Pitt and John Suttie must feel gratified that they also went to Bangalore, and so did not miss the chance of hearing Alan giving his expert views on vitamin A and vision for the last time.

The main purpose of this book, however, is not to gossip about past pioneers, but to survey the harvest that is now being reaped by the stalwart workers who have inherited the fertile land that the pioneers have opened up for them. If the land has been fertile, so much the greater has been the responsibility of each of our four contributors in giving an adequate and balanced account of the particular vitamin, A, D, E and K, that has been assigned to him. In his preface, our Editor comments that these four vitamins have only tenuous structural similarities, and nothing in common in their function, so that they are linked together only by all being soluble in fat and even with this common solubility, one might add, their bodily distributions show remarkable differences. With retinol and α-tocopherol both miscible with fat, and both capable of forming esters, for example, why should dietary excess of the former be concentrated in the liver, while excess of the latter is mainly held by the adipose tissues throughout the body? Why, in the later stages of pregnancy, should the level of blood tocopherol tend to rise, but retinol to fall. From a practical point of view, however, biochemists who are accustomed to working on one fat-soluble vitamin should have little difficulty in transferring their skill to work on another. For equally practical reasons, incidentally, the fat-soluble vitamins are much less suitable than the water-soluble group for further studies in an improvised laboratory after one's official retirement. Ether is much more expensive than water, and highly inflammable!

For his contribution on vitamin A Dr George Pitt has drawn up an impressive table of contents. He reiterates the key question 'Why cannot animals synthesize carotenoids, and why cannot plants effect the apparently simple conversion of β-carotene to retinol?' Perhaps 'bacteriorhodopsin', a purple retinoid derivative present in a halophilic bacterium, will open up fresh research on this point. Among much else, Pitt deals comprehensively with 'retinol-binding protein' (RBP), with retinol in the visual cycle, and with his own important work which groups together vision and the protection of the testes as functions for which retinol cannot be replaced by retinoic acid. For those 'systemic functions' of the vitamin which are equally supportable by retinol as retinoic acid, he points out, the exact mechanisms involved are much less clearly understood than for vision.

Pitt also devotes much space to the hundreds of artificial retinoids that have been laboriously synthesized in recent years for trials as pharmacological agents against cancer or skin disease. Nevertheless, the primary importance of vitamin A, he stoutly maintains, lies in the prevention or cure of non-carcinogenic disease processes. The urgent need to get adequate supplies of the vitamin to parts of the world where children are being blinded, or are even dying, from its lack must never be overshadowed.

Dr Eric Lawson deals with vitamin D mainly, but not exclusively, from biochemical aspects. His account has been written with commendable concentration and attention to detail, which will demand corresponding concentration on the part of readers. Briefly, the story is that vitamin D, ingested in the diet or formed in the skin mainly as cholecalciferol, must undergo metabolic changes, mainly the introduction of further hydroxyl groups into its molecular structure, before it can exert its essential action as a putative hormone in calcium metabolism. It has been a complicated story, difficult to unravel. 'Then why not be content' readers may ask 'to ensure that the diet contains a sufficiency of vitamin D, and then let it metabolize itself along whatever paths Nature decrees?' Unfortunately, things are not so simple. In certain obscure diseases, such as vitamin D-resistant rickets in childhood, failure in vitamin D metabolism may be involved, and knowledge of the normal path becomes necessary if things are to be put right. Incidentally, it is a sobering thought that fifty-six years have now elapsed since Harris and I reported, from the Dunn Nutritional Laboratory, the first experiments in England on hypervitaminosis D, the last item to be discussed in Lawson's chapter.

Professor Tony Diplock, in his chapter on vitamin E, deals adequately with his own fascinating speciality, the molecular placement of α-tocopherol into biological membranes. He does not allow this speciality, however, to deflect him from paying equal attention to other matters, and thereby writing a well-balanced review of the whole field. Indeed, his interests range from the effects of domestic cooking on the vitamin E contents of human food, to the value of vitamin E in treating some human diseases. A whole long book could be devoted, of course, to the complex interactions between the tocopherols, aided by their partial substitutes such as DPPD, methylene blue, and selenium, and their targets or antagonists, notably the polyunsaturated fatty acids. With the present furore about excessive dietary fat as a cause of heart disease, Professor Diplock will probably agree that vitamin E, so vitally concerned in fat metabolism, should no longer be left out of the picture.

Professor John Suttie, from the American Mid-West, contributes his chapter on vitamin K, for the discovery of which, now fifty-five years ago, Henrik Dam received his Nobel Award. His masterly review emphasizes that the phenomenon of blood clotting, with the involvement of a chain of about 10 blood proteins, is a very complicated process. Almost equally complicated are the many different forms of vitamin K. All of them, Suttie tells us, are based on a framework of 2-methyl-l-4 naphthoquinone, but with side-chains of greatly varying lengths attached in the 3 position, and made up either of isoprene units or of geranyl and farnesyl units. Yet another complication arises from the fact that some forms of vitamin K are plant products and others are synthesized by bacteria. In animals that depend on their own intestinal bacteria for a part or all of their supply of vitamin K, therefore, deficiency may sometimes arise from the use of antibiotics.

Suttie's chapter goes on to tell us that human adults are ordinarily in no risk of vitamin K deficiency, even when they are intentionally restricted to a vitamin K-free diet. Neonates, however, may be at risk from the low transfer of the vitamin through the placental barrier, and may require supplementation. Even adults may be at risk, moreover, if they consume, either by accident or design, substantial amounts of either a natural or artificial antagonist to vitamin K. Thus, coumarin derivatives derived from rotted clover may act as powerful natural antagonists to vitamin K and, in purified form, may find therapeutic usage as anti-bloodclot agents. The drug, or rat poison, 'warfarin' is an artificial vitamin K antagonist.

Finally, before leaving readers to peruse for themselves this book's well-filled pages, I may perhaps be allowed to raise two rather interesting points, both concerning vitamin E. First we may wonder, now that Henrik Dam is no longer here to be questioned, how he came to test methylene blue as a tocopherol substitute. Was he inspired by its power as a hydrogen acceptor, as evidenced by its loss of colour in vacuum tubes used for biochemical experiments on succinate dehydrogenase? Or had he in mind that in bygone days the dyestuff was used as a medicine.

Thus, an entry to be found in an old, non-professional *Illustrated Family Doctor* (Amalgamated Press London, ca 1933 p. 468), but nowhere else that I can find, tells us that the dyestuff was used 'both internally and externally as a remedy'. In lotions it was said to be feebly antiseptic, and useful for washing out the bladder, or infected surfaces. Taken internally it was analgesic and anti-pyretic, with a power to colour the urine green.

Secondly, can it be more than a coincidence that the hydroxylation and activation of cholecalciferol, as so fully explained by Dr Lawson, occurs in the same place in the kidneys that also shows evidence of *post-mortem* autolysis in rats deficient in vitamin E? In work at the Dunn Nutritional Laboratory, carried out long before Lawson arrived there from Liverpool, this somewhat recondite phenomenon, which we might well call Renal Autolytic Diathesis (RAD), found application in an officially commanded programme of work on the effects of flour improvers on the nutritive value of bread.

The kidneys of rats given bread made from flour treated with chlorine dioxide showed destruction of the epithelium of the convoluted tubules, the same site responsible for the hydroxylation of cholecalciferol. Perhaps it may be difficult to see any parallelism between a system in which cholecalciferol takes up oxygen under controlled conditions, and another in which the tissues that perform this oxidation are themselves protected by tocopherol from destruction associated with the toxic effects of oxygen. But workers on vitamin E, and indeed on the other fat-soluble vitamins, must be stimulated, rather than depressed, by the challenge of complications. This book should prove invaluable in enabling keen workers in the garden of their own chosen vitamin to look over the wall, and see what is going on in their neighbours' gardens.

Thomas Moore
Cambridge

Preface

The accessory growth factors in food were categorized by McCollum and Davis in 1915 into two groups: a fat-soluble group, called group A, and a water-soluble group, called group B. The term vitamin A was first used by Sir Jack Drummond in 1920 for the principal fat-soluble anti-xerophthalmic component of group A. The term vitamin D was applied by McCollum and his associates in 1925 to a group of substances that had anti-rachitic activity, distinguishable from the anti-xerophthalmic activity of vitamin A. The observation in 1920 that a semi-purified diet containing all the then known vitamins failed to support reproduction in rats led to the discovery by Evans and Bishop in 1922 of a further fat-soluble vitamin that they called vitamin E. Somewhat later than this, Henrik Dam in 1929 reported that chicks given diets that had been extracted with non-polar solvents developed sub-dural or muscular haemhorrages and had a long blood clotting time. Dam then went on to show that an anti-haemhorragic factor was present as a lipid-soluble component of many vegetables and animal products, and in 1935 he proposed that this was a further fat-soluble vitamin which he called vitamin K. The fat-soluble vitamins were thus all discovered within a fifteen-year period and their chemical structures established at the same time or shortly afterwards.

With the hindsight of more than fifty years it may seem strange to discuss these four chemical substances together at all. They have nothing in common in their function, they have some rather tenuous structural similarities, but they are nevertheless linked together because they are fat-soluble vitamins as originally defined. We have therefore chosen to consider the fat-soluble vitamins together in the present volume in an attempt to provide both an up-to-date account of their properties, and of our knowledge of their functions, with as exhaustive a bibliography as possible to enable researchers and others interested in these substances to have access to their literature. The usage of the terms vitamin A, vitamin D, vitamin E and vitamin K, rather than their chemical names retinol, cholecalciferol, α-tocopherol and phylloquinone, persists in the literature, in contrast to most of the water-soluble vitamins. Elucidation of the functional role of the water-soluble vitamins as enzyme co-factors is now largely complete, except that vitamin C still presents some problems. Unravelling the function of the fat-soluble vitamins at the molecular level has proved to be a more daunting undertaking, and it is only quite recently that their function has begun to be understood, although the nature of the systemic functions of vitamin A is still something of an enigma despite intensive research during many years.

Anthony T. Diplock

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Contents

CHAPTER 1

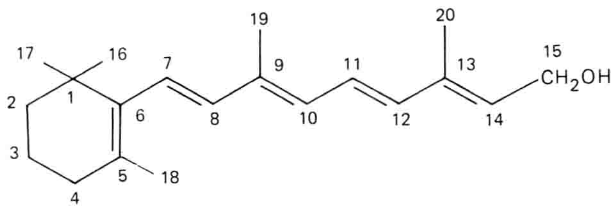
Vitamin A

George A.J. Pitt

1.1 Chemistry and nomenclature

1.11 Nomenclature and structure

The early history of vitamin A has been well described by Moore (1957). McCollum and Davis (1915) found growth factors in food fell into two classes according to their solubility, called by McCollum and Kennedy (1916) fat-soluble A and water-soluble B. Fat-soluble A was renamed vitamin A by Drummond (1920). Its structure, **1**, was deduced by Karrer *et al.* (1931). For many years it continued to be called vitamin A or vitamin A alcohol and this usage has not completely died out. But in accordance with the principle that once the structure of a vitamin is known, a specific chemical name should be given to the molecule, it is now designated retinol (International Union of Pure and Applied Chemistry, 1960; International Union of Pure and Applied Chemistry–International Union of Biochemistry Joint Committee on Biochemical Nomenclature, 1982).



1 Retinol (formerly vitamin A or vitamin A alcohol), showing numbering system

The term vitamin A is now used as a generic descriptor for all derivatives having the same (β-ionone) ring and showing qualitatively the biological activity of retinol, excluding the provitamin A carotenoids discussed later

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