Vitamin C in Health and Disease

T. K. BASU and C. J. SCHORAH

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T. K. Basu, BVSc., MSc., PhD, Associate Professor of Nutrition, University of Alberta, Edmonton, Canada

C. J. Schorah, BSc., PhD, Lecturer in Chemical Pathology, University of Leeds, Leeds, England

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FOREWORD

The past decade has witnessed an information explosion on the subject of vitamin C, with some thousand new research papers appearing annually. Countless studies describe the role of vitamin C in the metabolism of connective tissue, particularly collagen, in cholesterol turnover, in immunological processes, in the detoxification of xenobiotics, in the transmission of interneuron information and in numerous other areas. Consequently, there is an urgent need that these facts be sorted out not only to facilitate their retrieval but also to promote an understanding of their significance for human health and disease alike.

Although an exact knowledge of the mechanisms involved in the biological functions of vitamin C still evades us today, new facts have helped us to realise that the need for vitamin C is not necessary uniquely for the prevention and treatment of scurvy. Classical medicine has failed to appreciate that scurvy is but the ultimate symptom of an absolute vitamin C deficiency and that there exists the danger of a covert marginal deficiency which is likely to disrupt the finer biochemical mechanisms and thereby bring about a deterioration of the health of large population groups. We are not as yet in a position to estimate precisely the degree of this risk to human health, but it is possible that a chronic vitamin C deficiency is involved in the origin of atherosclerosis and cancer – two of the biggest killers of mankind.

The authors of this monograph, Dr T. K. Basu and Dr C. J. Schorah, have eschewed the use of the simple method of uncritical compilation. Instead, they have focused particularly on the controversial problems. In many instances, the present state of knowledge does not permit them to draw definitive conclusions and, therefore, one should not look for many certainties in this domain. However what one will find here are intelligently asked questions. Although one need not and probably will not see eye to eye with everything presented by the authors (personally I consider the recommended daily dose of 60 mg vitamin C to be rather low), the book, as a whole, impresses the reader as being persuasive in its evidence, critical in its judgments and interpretations of data, restrained in its conclusions, but above all, as providing inspiration. Simultaneously, it provides a large quantity of well arranged documentary data on the metabolism of vitamin C and its biochemical

roles, on the determination of body vitamin C reserves, on therapeutic aspects of ascorbic acid and on the risks possible in extreme vitamin C dosages.

As implied above, this book will not be the final word on the subject of biological roles of vitamin C, yet it will make readers think, whether they are vitaminologists, nutritionists, physicians, or one of the host of researchers concerned with problems relating to what we have come to call diseases of our civilisation.

Emil Ginter, PhD,
Institute of Nutrition,
Bratislava,
Czechoslovakia

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The authors would like to thank colleagues, patients and volunteers whose contributions to, and assistance with, their work on vitamin C have helped to make this book possible. We would also like to thank our wives and families who have not only helped and encouraged us during the preparation of this book but who have also tolerated the disruption it has inevitably produced in family life.

INTRODUCTION

Scurvy, the deficiency disease which develops in the absence of adequate dietary vitamin C, was once a common condition in Europe but the introduction of root crops into the diet towards the end of the Middle Ages, unintentionally reduced the prevalence of the disease. Later the discovery that fruit juice could be used to treat sailors with scurvy (Lind, 1753) led eventually to the prevention of the disease during long sea voyages. The isolation of the antiscorbutic factor, vitamin C, from fruit juice (Szent-Györgi, 1928) would seem to complete the picture, all these factors helping to make a disease, common among the ancients, relatively rare in the United Kingdom today.

However, despite knowledge about its prevention, scurvy has not been eliminated and the incidence of the disease has recently been found to be surprisingly high in the elderly. In addition, although there has been considerable scientific investigation over the last 50 years, vitamin C itself remains an enigma. There are large differences in vitamin C reserves between different population groups, and recent evidence has suggested that in those groups where low levels are most frequently found, many individuals have reserves which are inappropriate. This situation is complicated by the fact that there is a difference of opinion on the amount of vitamin C to be recommended for daily ingestion, both in health and disease. Some workers hold the view that the requirement for this vitamin to maintain optimal health is much greater than is necessary for the prevention of scurvy. Furthermore, there is an increasing number of reports suggesting that the regular intake of vitamin C in large amounts is beneficial in a number of pathological conditions which are apparently quite unrelated to scurvy. Upon the existing evidence, it appears that these views are neither inadmissible nor incompatible. However, following publication of a popular book by Pauling (1970), there has been a widespread interest in self-medication with megadoses of vitamin C. This in turn has led to several clinical studies which have revealed little convincing evidence to support claims of clinical efficacy for megadose therapy, at least in most cases. Furthermore, in recent years there have been some isolated reports suggesting that the prolonged and regular intake of vitamin C in large doses may be potentially hazardous, at least to certain individuals.

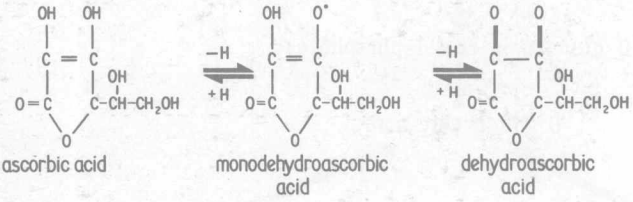
All these claims certainly need to be evaluated.

The biochemical function of vitamin C is also unclear. Recent work has indicated a role for the vitamin in hydroxylation reactions. However, there is evidence for many other functions of vitamin C for which the mechanisms are not clearly understood.

It is these unresolved and often controversial areas that we have examined in most detail in this book. We have primarily considered evidence from research undertaken in the human, but have reported animal work where this has been appropriate. We have, in many cases, been unable to draw any final conclusions, but having critically summarised current evidence, we have made provisional recommendations, indicated those theories which seem the most probable, and suggested areas where further research is most needed. We have also suggested intakes and body reserves of vitamin C which, in the light of recent findings, should be appropriate for maintaining health and combating disease.

1 METABOLISM OF VITAMIN C

Vitamin C is essentially two compounds, L-ascorbic acid and its oxidised derivative L-dehydroascorbic acid. Although upwards of 90 per cent of vitamin C in animal tissues is in the form of ascorbic acid, both compounds have biological activity and are readily interconvertible by oxidation and reduction reactions through a short-lived intermediate, monodehydroascorbic acid (Equation 1.1). Some of the enzymes responsible for these interconversions are considered later (Section 3.1) and illustrated in Figure 3.1.

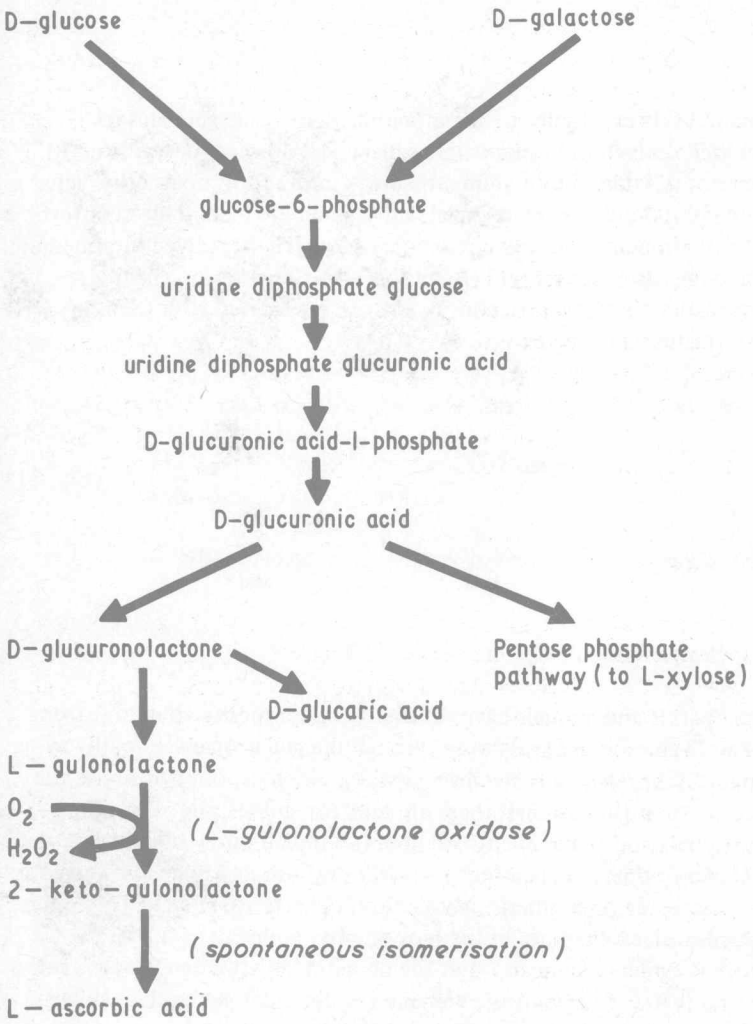


(Eq. 1.1)

1.1 Biosynthesis

Most plants and animals have the ability to synthesise vitamin C from either D-glucose or D-galactose through the glucuronic acid pathway (Figure 1.1). There are, however, species which cannot synthesise the vitamin; in higher animals these are humans, guinea pigs, apes, fruit-eating bats and the red-vented bulbul (an Indian bird). In addition, there is evidence that insects, other invertebrates, fish and microorganisms are also incapable of synthesising vitamin C (Chatterjee *et al.*, 1975). These organisms lack enzymes in the biosynthetic pathway of the vitamin. Current evidence indicates that the defect in all vitamin C dependent species is the absence of the enzyme L-gulonolactone oxidase (Figure 1.1), which catalyses the final step in the biosynthesis of vitamin C (Burns, 1957; Sato, Nishikimi and Udenfriend, 1976; Sato and Udenfriend, 1978). A recent study has provided evidence showing that scurvy, the condition which develops in the absence of adequate tissue concentrations of vitamin C, can be prevented by providing this enzyme, together with its substrate L-gulonolactone, to guinea pigs (Sato, 1980). In practice, however, scurvy is prevented by providing

Figure 1.1: The Biosynthesis of L-Ascorbic Acid



exogenous sources of vitamin C, and as a result this vitamin is considered to be an essential dietary requirement in the species lacking L-gulonolactone oxidase activity.

At the chromosomal level, the genes coding for the missing enzyme might be entirely absent as a consequence of deletion of genetic