THE VITAMINS IN MEDICAL PRACTICE

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PREFACE

AS THE title indicates this work is essentially concerned with the study of vitamins in their application to medical practice. The difficulties of the practising physician in this field are not lessened by the fact that a small proportion only of the massive literature on the subject appears in journals devoted purely to clinical medicine. In the selection of material, the influencing factor has been that it should definitely relate to the physiological and pathological processes of the body. A primary consideration has been that the subject should be covered as concisely as possible without sacrificing essential material. It is hoped that, in its sphere, the book will satisfy the needs of the practising physician and prove helpful to those reading for higher medical examinations.

In design the book falls into three parts. Following an introductory chapter, the first part comprises a description of the individual vitamins. The second is concerned with the accepted major clinical syndromes referable to body depletion of one or more of the vitamins. Finally, the individual systems are considered in relation to the vitamin status of the body, and the value of vitamins in affections which are not attributable to their deficiency is carefully assessed. The problems peculiar to pregnancy, infancy and childhood are dealt with in this section.

The material has been culled from an extensive survey of the literature; the author acknowledges his indebtedness to the existing published works on vitamins. A debt of gratitude for most valuable assistance is due to Professor Arnold Sorsby, Mr. W. Price, Dr. A. Markson, Miss C. M. Wood and Dr. W. S. Cormack; and particular thanks are tendered to Mr. Julian J. Shafar. The help and co-operation of the publishers are deeply appreciated.

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CHAPTER ONE

GENERAL AND INTRODUCTORY

THE TERM 'vitamine' was introduced by Funk in 1911, primarily in connexion with beriberi. The vitamins are naturally occurring organic substances, although the body is capable of synthesizing some of them, and they are essential factors for the conservation of the normal functioning of cells. Even today it is not yet possible to enumerate all the vitamins.

In man, apart from experimental conditions, nutritional deficiency involves an inadequacy of several essential factors, although the features of deficiency of one or two may predominate over those of the others. The growth of knowledge of vitamins accruing from controlled experiments with animals has not been unmixed with confusion. The analysis of a diet at any one period will be in terms of the then known constituents of foods so that the results of any studies may be misinterpreted at the particular time at which they were instigated.

The species factor will also influence the picture and lack of a specific nutrient may yield different syndromes in respective species. Some animals have the capacity, not present in others, to synthesize certain vitamins; for example, the dog is able to synthesize vitamin C while the guinea-pig cannot. Formerly, experimental diets were composed of natural foodstuffs, and the findings were accordingly confused because of unrecognized components.

Insufficient intake of an accessory food factor may result in derangement of the status of other vitamins by virtue of disturbance of normal vitamin inter-relationships. Furthermore, changes may accrue from the secondary or non-specific effects of the specific vitamin deficiency. Among the latter are loss of weight, retardation or failure of growth, impairment of appetite and gastro-intestinal dysfunction. Anorexia will be attended with accentuation of any tendency to a state of inanition.

It is thus important to differentiate between the primary and secondary effects of a vitamin deficiency. Starvation is distinguished from deficiency disease by the fact that in the latter minute rather than gross components are lacking. Recognition of the difference in response of the body to an acutely severe vitamin deficiency of short duration and to a chronic moderate deficiency is important, the pathological consequences of the chronic type being of greater severity and the response to treatment much slower.

Man may exhibit the effects of nutritional deficiency in several ways. A frank deficiency state may exist and offer no difficulty in

diagnosis. Minor degrees present a clinical problem; their manifestations are not characteristic of any specific syndrome and usually take the form of general lassitude, fatigability, diminished appetite and, in children, impairment of growth. Some subjects, although presenting a semblance of health, live in the 'twilight zone of nutrition' with no factor of safety, and when pregnancy or illness supervenes an overt deficiency syndrome is made apparent [2].

In general, nutritional deficiency may originate either in the primary form, occasioned by an inadequate dietary, or, in the secondary or conditioned form, in which there is some other abnormal condition responsible for or precipitating the malnutrition. Inadequate intake may arise from economic factors; ignorance of the elements of nutrition, food fads, racial customs, anorexia and mental derangement are among the other causes of primary malnutrition. Consumption of nutritionally inferior foods may have a similar effect and these include highly milled grain products, alcohol and sweetmeats.

Conditioned malnutrition is reviewed by Jolliffe [3]. It is produced by interference with ingestion, absorption or utilization of the vitamins or by factors which increase their requirements, destruction or excretion. The interpretation and correction of these conditioning agencies is as essential as the treatment of the vitamin-deficiency state. Gastro-intestinal disorders, including gall-bladder disease, may diminish the ingestion of food as may the loss of appetite associated with febrile illness, congestive cardiac failure, pregnancy and post-operative states. Therapeutic restrictions of diet should be such as to ensure an adequate supply of the vitamins, for deficiency disorders have followed ill-balanced diets prescribed for peptic ulcer, renal disease, allergy, colitis, diabetes mellitus and obesity. The voluntary reduction of food intake in an attempt to reduce weight is not commonly associated with vitamin deficiency since the low caloric content of the diet affords some measure of protection; if persisted with, however, serious effects may ensue. Under certain circumstances an increased vitamin requirement arises. Fever, hyperthyroidism, pregnancy and lactation, abnormal degrees of activity and therapeutic measures such as thyroid and dinitrophenol administration, artificially induced fever and high carbohydrate diets may be mentioned as examples. Defects of absorption may be associated with achlorhydria, obstructive jaundice and disease of the alimentary tract. Jolliffe also draws attention to the adverse effects of severe catharsis, and also of certain medicaments, such as liquid paraffin and colloidal adsorbents. Factors interfering with utilization are present in hepatic disease, hypothyroidism, malignancy and the use of sulphonamide drugs. Polyuria and lactation may account for increased excretion of vitamins and there also

remains the possibility of increased destruction of vitamins in the body necessitating an increased intake.

The rate of development of the signs and symptoms of vitamin deficiencies will depend on the amount of prenatal stores present in the infant (reflected in the maternal dietary) and, in the later stages of life, on the body reserves of vitamins prior to the commencement of the faulty dietary regime. Vitamins A, E and K are readily stored while vitamins B_1, C, D and riboflavin can be retained in the tissues in only moderate amounts. It is almost axiomatic that if human dietaries are deficient in one factor they are likely to be deficient in many.

Growth is a condition meriting special attention and nutritional defects in children tend to appear or to be accentuated at three periods – infancy, second dentition and puberty – when the nutritional needs are at their greatest. The metabolic level greatly influences the development of signs of a deficiency state, for even in the presence of a markedly deficient intake no effects may be evident while the patient is confined to bed.

The detection of nutritional deficiency is obtained from a study of the dietary habits, the medical history, the physical examination and from special methods of investigation. Vitamins are primarily created in vegetable sources and thence appear in animal tissues. Reduction of vitamin content from the original level arises from the several processes to which the foodstuff is subjected prior to its ingestion by man. Harvesting, transport, storage and cooking will all tend to lower the quantity of vitamins contained. The amount of vitamin present in the consumed article does not represent that made available to the body for loss from excretion and non-absorption must also be taken into consideration. Hence assessment of the value of a diet in respect of its vitamin adequacy must take account of all possible losses. The distinction between a satisfactory and a poor diet is largely referable to the quantities of milk, lean meat, fresh vegetables and fruit included.

As in all clinical examinations a careful and detailed medical history is of paramount importance. The possibility of a bodily disorder as the conditioning cause of a nutritional defect must be investigated. The clinical signs may accordingly represent a combination of those attributable to the primary disease and those occasioned by the lack of vitamins. Spies [4] lists the following symptoms as suggestive of a possible vitamin deficiency state: loss of weight and strength, headaches, dizziness, burning sensations in the skin, roughness and dryness of the skin, burning of the eyes, blurring of vision, lachrymation, photophobia, night blindness, burning and cramping of the stomach, burning of the tongue and lips, swelling and ulceration of the oral and lingual mucous membranes, saliva-

tion, diarrhoea, burning and cramping of the feet, insomnia, nervousness, loss of memory and emotionalism. In children an appraisal of the general nutrition is made and attention is directed to some special points in the physical examination. The head should be palpated for evidence of delay in closure of the anterior fontanelle, craniotabes and parietal bossing; cracks, sores or scars at the angles of the mouth, and gingival changes and bleeding should be sought as should signs of glossitis. Examination of the teeth with regard to date of eruption and the existence of any abnormalities is indicated and the presence of dermal changes around the nares, forehead and eyes is determined. The eyes may offer important information and if necessary slit-lamp microscopy should be adopted. Other bony changes of rickets may exist in the form of enlarged epiphyses, beading of the ribs, thoracic deformities and genu valgum or varum. The skin is examined for abnormalities of the follicles ('toad skin') especially at the medial sides of the thighs and for any evidence of haemorrhage. Changes in the condition of the hair are also important. In adults the examination of the tongue and mouth, the nasolabial folds and the eyes is conducted as in children. Follicular hyperkeratosis and other skin lesions are looked for, including a bilateral symmetrical dermatitis, pigmentation, thickening and darkening of the skin, purpura, 'Casal's necklace' and dermatitis of the scrotal and vulval areas. Vaginitis may be a manifestation of a deficiency disease. Neurological examination is essential as is the determination of the patient's mental state.

Laboratory methods for assessment of the vitamin status of the body are numerous. Among them are the vitamin concentration of the blood, the excretion of the vitamin or its excretory products in the urine, vitamin 'tolerance tests', biopsy studies and various functional tests such as measurement of dark adaptation, blood phosphatase, blood pyruvic acid and capillary fragility. Specialized tests have their limitations and their interpretation is often difficult. As an example, the value of the blood level of a vitamin has been criticized by Kruse [5] who points out that it shows ready fluctuations and does not necessarily reflect the tissue stores of the vitamin; the blood concentration may fluctuate intermittently while the concentration in the tissues alters very slowly.

The prevention of vitamin deficiencies is a matter of supply of adequate quantities of the correct types of food and of the education of the public. Qualitative aspects are as important as quantitative. Vitamin concentrates should not be utilized when natural foodstuffs are available in sufficient amounts. Certain measures adopted by governments can do much in the prophylactic sphere and the compulsory addition of vitamins A and D to margarine and the

legislation regarding bread in Great Britain have gone far in improving the protective value of the diet. In this respect the investigation of Sydenstricker [6] of the nutrition of Britain under wartime conditions produced significant results. After three and a half years of rationing, an examination of 5,000 unselected civilians showed occasional mild folliculitis but no other evidence of vitamin-A deficiency; only one case of mild pellagra was encountered, 8 women had signs of riboflavin deficiency and 38 others had corneal vascularization characteristic of riboflavin deficiency. Education in fundamental dietary principles should be instituted in schools and in the adult population, and individual idiosyncrasies of diet and faulty racial dietary customs should be overcome. The medical profession can play a most important part in the dissemination of such knowledge. On the other hand the indiscriminate consumption of synthetic vitamin preparations because of their supposed 'tonic' effects is greatly to be deprecated. As McLester [2] so aptly phrases it: 'For the maintenance of health a person should look not to the druggist but to the grocer and the dairyman.' Advances in nutrition of the industrial worker have been made by the institution of proper canteens, but it remains for the nations of the world to act together in the proper distribution of food to all countries [7]. The other aspect which has been stressed already is that of recognizing the possibility of deficiency states developing in the face of increased requirements or conditions detrimental to adequate nutrition. Careful consideration should be paid to the convalescent stage of illness or injury and the nutritional defects accruing from them made good during this period.

Vitamins are administered either as supplementary preparations or for therapeutic purposes [8]. The former provide an amount sufficient to ensure an adequate intake and this quantity is supplementary to that supplied by the diet. Therapeutic dosages are larger. Both measures include one or more essential factors and precautions should be taken against the precipitation of a vitamin imbalance from the use of heavy doses of a single vitamin. The question of what constitutes the normal requirements of each vitamin has revealed differences of opinion, some authorities holding that the prevention of ill-health is the basic consideration while others would desire a state of saturation of the tissues with the essential nutrients. Sir John Boyd Orr expressed the physiological ideal as a state of well-being which cannot be improved upon by a change in the diet. Dann and Darby [9] recognize five zones of nutrition – saturation, unsaturated but functionally unimpaired, potential deficiency disease, latent deficiency disease and manifest deficiency disease. Supplementary vitamin administration is exhibited when the diet is unsatisfactory or when an

increased demand for the vitamin exists. Alterations of diet for medical reasons, infant feeding and food fads are included in this category [9A]. The dosage will be based on the requirements recommended by the National Research Council of the United States, allowances being made for the vitamin content of the food consumed. With the exception of vitamin D, there is no occasion for supplementing a well-balanced diet with vitamins in infancy or childhood in the absence of increased requirements or of any disorder interfering with normal absorption and metabolism of the accessory food factors. Vitamins prescribed in therapeutic doses may be either for the rectification of a deficiency disease or for their pharmacological effect on a disorder of non-nutritional origin. Deficiency disease in man implies a lack of many nutrients and for its treatment a satisfactory intake of all the vitamins is essential, particularly large quantities of the vitamin, the clinical signs of whose deficiency are most prominent, being supplied. Brewers' yeast, brewers' yeast extracts, crude extracts of whole liver, liver concentrates, desiccated liver, wheat germ and rice-bran extracts offer excellent sources of the entire vitamin-B complex. The other vitamins may be given twice daily for the first seven to ten days and thereafter once daily in accordance with the following formula:

Vitamin A	25,000 units
Vitamin D	1,000 units
Thiamine	5 mg.
Riboflavin	5 mg.
Nicotinamide	150 mg.
Vitamin C	150 mg.

The figures are those recommended by Jolliffe [8] who advises for the specific lesions as they exist, 50,000 to 150,000 i.u. of vitamin A, 10 to 100 mg. of vitamin B_1, 5 to 15 mg. riboflavin, 100 to 1,000 mg. of nicotinamide and 100 to 1,000 mg. of vitamin C; in acute deficiency states a few days or weeks of treatment may suffice but for chronic deficiency disease treatment may be necessary for much longer periods.

The oral route is the best in vitamin therapy but certain conditions may necessitate the parenteral administration. Patients may be unable or unwilling to take food by mouth, or a defect of intestinal absorption may render oral intake unsatisfactory, and the disease may be first seen in so critical a stage as to demand a circumvention of the delay of intestinal absorption [10].

So many vitamin preparations have been introduced into the market that the physician is confused as to their respective value and the dosage. The dose should refer to quantities of the particular preparation only if the amount of vitamin contained therein

is clearly understood. Vitamins are measured in units or milligrammes and the excellent presentation of Asher [11] should be consulted for the concentration of the vitamins in the various proprietary articles and for their relative costs.

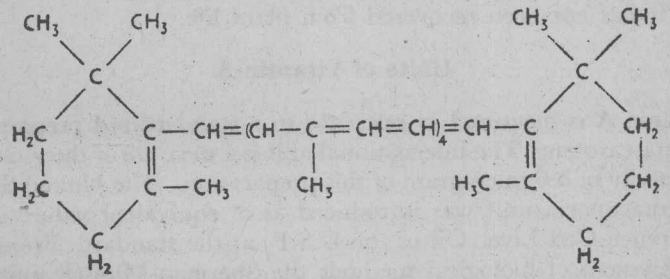
VITAMIN A

VITAMIN A is also known as the anti-xerophthalmic vitamin, axerophthol and the anti-infective vitamin. Xerophthalmia, a manifestation of severe vitamin-A deficiency, presents but one aspect of the deficiency syndrome, and is too limited to serve as a satisfactory designation. Axerophthol is an infrequently used term. The descriptive name 'anti-infective vitamin' originates from a misconception of the properties of the vitamin in relation to infective processes; it should no longer be employed as a synonym for vitamin A. Vitamin A includes vitamin A_1 and vitamin A_2 and the naturally occurring precursors are referred to as provitamins A.

Vitamin A_2. – The features which distinguish vitamin A_2 from vitamin A_1 will be given briefly and in the subsequent discussion vitamin A will be considered to refer to vitamin A_1. There is a difference in distribution, vitamin A_2 predominating in fresh-water fish and vitamin A_1 in salt-water fish. The vitamin A pattern of the species is largely determined by genetic factors. Vitamin A_2 is absent from the livers of mammals unless the vitamin has been present in large supply in the diet. Both vitamins appear to have common precursors since when carotene is fed to fish such as perch both vitamins can be formed [12]. There is still dubiety regarding the exact chemical structure of vitamin A_2. Little significance can be attached to the rôle of vitamin A_2 in the human body although biologically its functions would seem to be the same as those of vitamin A_1.

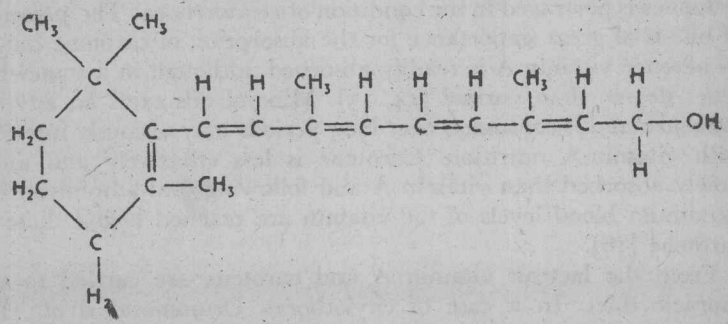
Properties of Vitamin A and its Provitamins. – The carotenoids include vitamin A and a group of plant pigments. The latter possess similar chemical structures and properties and their natural distribution is in association with fats to which they give the distinctive coloration. Certain of the carotenoids, known as the carotenoid pigments, occur widely in the plant kingdom, and carotene is a term employed to include these carotenoid pigments. Carotene is synthesized in plants but vertebrates do not possess this capacity. The function of carotene in plants is not clear but with certain exceptions its concentration in green leaves parallels that of the chlorophyll. Some carotenoid pigments can be converted into vitamin A – the vitamin-A-active group – while this property is not present in the members of the vitamin-A-inactive group. Of the former, four are of particular importance, beta-carotene, alpha-carotene, gamma-carotene and cryptoxanthin. Beta-carotene is the most abundant and its activity is about twice as great as that of the alpha- and gamma-derivatives.

Chemically the carotenes are unsaturated hydrocarbons made up of a long aliphatic chain which contains 18 carbons in those compounds capable of conversion to vitamin A. The various pro vitamins are distinguished from one another by the composition of the groups at the end of the chain. Since the beta-ionine ring is an essential component of vitamin A this offers an explanation of the manner whereby beta-carotene gives rise to two molecules of the vitamin. Both the end groups of beta-carotene are composed of a beta-ionine ring whereas the other provitamins show the latter structure in only one end group and can thus yield but one molecule of the vitamin. The graphic structure of beta-carotene is shown below:



Vitamin A is probably formed by hydrolytic rupture of the middle of the aliphatic chain although recently it has been suggested that oxidation is concerned in the process of conversion. Carotenes are insoluble in water but soluble in fats, and they form esters with fatty acids. They are readily inactivated by oxidation and by light. The naturally occurring provitamins A are found in only small proportions in the free form and exist chiefly in combination with proteins or as esters. Characteristic absorption bands in the visible spectrum are exhibited by the carotenes.

Vitamin A, an unsaturated alcohol, is present in the unsaponifiable portion of certain fish oils and can be obtained in synthetic form. The formula is $C_{20}H_{30}O$ and its structural composition is



Vitamin A is soluble in fats and certain fat solvents and forms esters with fatty acids. The fatty acid esters are more stable than the vitamin which is sensitive to light (hence cod-liver oil is stored in dark-coloured bottles) and to oxidation. Vitamin-A concentrates are composed principally of the esters which are obtained by molecular distillation of the fish oil. The vitamin is heat resistant in the absence of air but is destroyed in the presence of oxygen. In contrast to the reddish-yellow colour of carotene, vitamin A is almost colourless, and with antimony trichloride a green-blue colour is given by the former substance and a deep blue by the vitamin. Within the tissues vitamin A exists both in the free state and as esters. Its occurrence is restricted to the animal kingdom and it has not been recovered from plant life.

Units of Vitamin A

Vitamin A is measured in reference to a standardized preparation of beta-carotene. The international unit is a measure of the vitamin-A activity of 0·6 microgram of this preparation. The United States Pharmacopoeia unit was introduced as of equivalent value, using Reference Cod Liver Oil of the U.S.P. as the standard. From the employment of biological methods the Sherman-Munsell unit has been suggested but has proved of little value. Blue units are referable to the intensity of the blue colour produced with antimony trichloride.

Metabolism and Physiology of Provitamin and Vitamin A

Absorption of carotene and vitamin A proceeds from the alimentary tract through the wall of the duodenum and upper jejunum [13]. Carotene is absorbed as such, while the esters of the vitamin are first hydrolysed and then reappear in the lacteals in the esterified form. High fat diets facilitate their absorption but beyond a certain dietary fat content no increase in the absorptive mechanism occurs. In general those factors which affect the absorption of fats also affect the absorption of vitamin A and its provitamins. This influence is portrayed in the condition of steatorrhoea. The presence of bile is of great importance for the absorption of carotene but in its absence vitamin A is readily absorbed, although in a somewhat lesser degree than normal [14, 15]. Mineral oils exert an adverse influence and if consumed over long periods may seriously interfere with vitamin-A nutrition. Carotene is less effectively and more slowly absorbed than vitamin A and following oral administration maximum blood levels of the vitamin are reached before those of carotene [16].

From the lacteals vitamin A and carotene are carried to the thoracic duct. In a case of chylothorax Drummond *et al.* [17]

found that reasonably large quantities of vitamin A were returned almost quantitatively in the chyle although the recovery of carotene was far short of quantitative. Within the intestinal lumen oxidative destruction may take place and the stability of both substances rests on the nature and amount of anti-oxidants available. Of particular importance as protective agents are the tocopherols whereas rancid fats exert profoundly deleterious effects.

Carotene is converted into vitamin A in the body. The chief site for the transformation is the liver, and an enzyme, carotinase, is concerned in the reaction. Incubation of carotene with fresh liver tissue, or with an aqueous extract of liver, promotes the change; the enzyme is inactivated by heat [18]. The work of Sexton *et al.* [19] indicates that the intestinal wall may also be a possible site for the conversion of the provitamin. Participation of the thyroid in carotene conversion has been suggested by the change in colour of the milk of thyroidectomized goats from the normal white to yellow, due to the inability of the animals to change carotene to the colourless vitamin A [20]. There is no evidence that the opposite reaction, the reversal of vitamin A to carotene, can take place in the body.

A species difference in the storage depots of vitamin A exists. The liver of rats and rabbits yields about 95 per cent of the total amount present, while in certain varieties of fish the content in the intestinal wall exceeds that of the hepatic stores. In man it has been estimated that the liver holds some 95 per cent of the vitamin A. The fat depots and fat cells scattered throughout the body normally are not rich in the vitamin but in view of their large mass they rank second to the liver in tissue storage of vitamin A [21]. Other sites of storage include the skin, muscles and bones. Popper [21] stated that the normal kidneys contain no vitamin A but that in renal disease its presence was demonstrable. An opposite conclusion was reached by Lawrie *et al.* [22] who considered that it is the healthy kidney that stores the vitamin whereas it disappears from the diseased organ. Little is known of the factors influencing the discharge of vitamin A from the liver into the blood stream. The nervous system would appear to play a considerable rôle in the mechanism, and sympathomimetic drugs, such as adrenaline, effect an elevation of the plasma vitamin-A level [23]. Peculiarly enough alcohol exerts a similar action [24].

Vitamin A and carotene are present in the serum but not in the erythrocytes; the vitamin is transported both in the free and esterified forms of which the much smaller and variable proportion exists as the free alcohol. With normal average nutrition the plasma vitamin-A concentration remains at steady levels during the course of the day and from day to day. The normal value of the plasma

vitamin A is usually given as between 100 and 300 international units per c.c. The normal total carotenoid content of blood serum ranges from 50 to 300 micrograms per c.c. but may be much higher [25]. Gross changes in the dietary content of the vitamin or its provitamins do not permanently affect the vitamin-A level. Administration of vitamin A results in an elevation of the plasma concentration but after twenty-four hours the original value is usually restored; doses as high as 100,000 units did not delay this return [26]. Continued intake of large supplements of the vitamin were ineffective in establishing a persistent elevation of the blood vitamin-A level [27]. In addition to nutritional deficiency other processes are capable of reducing the serum values.

Carotene plasma levels show little fluctuation following an average meal. High consumption of carotene, as such or contained in food, produces an increase in the plasma content, the degree and duration depending on the amount ingested and on the stores of carotene in the body. As the dose rises there is a proportionate reduction in its effects on the plasma carotene level owing to increased loss in the faeces [28]. Large doses of carotene display their influence on the plasma levels over a considerable period and Ralli *et al.* [29] found that the peak was not reached until seventy-two hours after administration following a dose of 600 mg. of carotene in oil and that a slow return to normal figures proceeded thereafter for over a week; continued ingestion of carotene is reflected in a steady rise in the serum content and there appeared to be no limit to the possible elevation which might be reached. Associated with the increased carotene serum values there is a response of the vitamin-A concentration but this is much less pronounced and much more fleeting. Diets from which all sources of the vitamin are absent effect a fall in the plasma carotene, the vitamin-A concentration being undisturbed until the former is reduced to very low values [30]. Wide variations of the carotene serum content are obtained under ordinary conditions and reported figures range between 50 and 420 micrograms per cent [28]. There is a richer content of carotenoid pigments in the fat deposits of elderly subjects as compared with those of younger individuals, a fact which has been offered in explanation of the lower carotene and higher vitamin-A plasma concentrations found in the latter [31].

Intraperitoneal or subcutaneous injection of carotene produced no increase in the hepatic stores of vitamin A in the rat and, although capable of remedying the manifestations of the deficiency state, the amount required is 10 to 100 times as great and the effect less prolonged than when the carotene is given orally; only a portion of the carotene in these sites is available to the animal