

Vitamin A and vitamin E in human blood

1. Levels of vitamin A and carotenoids in British men and women, 1948-57*

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(Received 1 May 1959—Revised 28 November 1959)

The work to be described in these communications followed earlier studies (Leitner & Moore, 1946; Leitner, Moore & Sharman, 1947), which were mainly concerned with the lowered blood vitamin A in certain diseases. For purposes of comparison it was desired to know the levels of vitamin A prevalent in normal subjects, and the advisability of obtaining more adequate information became apparent. It was known that the blood vitamin A varied widely in different normal individuals, and that men tended to have higher levels than women (Kimble, 1938-9), but knowledge was scanty on the influence of age or season of the year. Moreover, at the time of our earlier work, dietary restrictions, imposed during the Second World War, were still in force in this country. It was of interest, therefore, to study the effect on the blood vitamin A of the changes in the national food supplies which followed the gradual relaxation of controls.

Specimens of blood were taken for a long period from numerous subjects, with the aim of collecting a mass of information large enough to counteract the disturbing effect on averages of the wide individual variations. Estimations of total carotenoids were made parallel with those of vitamin A. Vitamin E is known to be capable of intervening in the metabolism of vitamin A (Moore, 1939; Bacharach, 1940; Hickman, Harris & Woodside, 1942), so our programme was extended to include estimations of vitamin E. The presentation of our results on vitamin E has, however, been assigned to a later communication (paper no. 2 of this series), and paper no. 3 will deal with observations on chronic hospital patients.

EXPERIMENTAL

Collection of specimens. Blood was collected by venepuncture from volunteers who came to one of us (Z. A. L.) for medical examination. Some were young men in good health, who were examined for purposes of life insurance or for their fitness to do arduous work abroad. Most of the subjects, however, had some complaint, and were examined with a view to diagnosis and treatment. To this extent, therefore, their health was not completely normal. On the other hand, it was possible, as the result of

* Read in part before The Nutrition Society on 4 December 1959 (Leitner, Moore & Sharman, 1960).

the examination, to exclude any subjects in whom systemic disease of the heart, lungs, intestinal tract, liver or kidneys was present. Each examination included a thorough physical overhaul, chemical analysis and microscopic examination of the urine, blood counts, estimation of the blood sedimentation rate, and all biochemical and radiographical investigations relevant to the case. The subjects could mostly be described as middle class, but a few were manual workers.

The blood specimens were collected without the use of an anticoagulant. Specimens of whole blood or of separated serum were posted to Cambridge and examined within a few days of their arrival. Any specimen showing more than slight haemolysis was discarded.

Estimation of vitamin A and carotenoids. Our procedure differed only slightly from Yudkin's (1941) modification of Kimble's (1938-9) method. Serum, 6 ml, was mixed with the same volume of ethanol and 12 ml of light petroleum (b.p. 40-60°) and was shaken for 10 min in a closed tube. After centrifugation for 30 sec, 10 ml of the light petroleum layer were withdrawn and evaporated to dryness on a water-bath under diminished pressure. The residue was dissolved in 5 ml of a mixture of 7 volumes ethanol with 20 volumes light petroleum, the ethanol being used to prevent turbidity. A portion of this solution was transferred to the cuvette of a photo-electric absorptiometer, and carotenoids were measured by their yellow colour. The solution was then returned quantitatively from the cuvette to the evaporation flask, the contents of which were again evaporated. For estimation of vitamin A the residue was dissolved in 1.0 ml chloroform, and 0.3 ml portions were added to 2.0 ml portions of antimony-trichloride reagent, which had already been placed in the cuvette in position in the absorptiometer. In order to correct for the contribution of carotenoids to the blue colour in the antimony-trichloride reaction, the value in μg found for carotenoids, multiplied by 0.42, was deducted from the gross value found for vitamin A in i.u.

Photo-electric absorptiometer. A simple, single-cell absorptiometer, of the type originally used for vitamin A estimations by Dann & Evelyn (1938), was constructed. Wratten filters red, no. 26, and blue, no. 48, were used for estimating vitamin A and carotenoids, respectively. The galvanometer readings of the absorptiometer were calibrated for vitamin A against halibut-liver oil or vitamin A acetate, and for carotenoids against β -carotene. Carotenoids were calculated as μg of carotene, the slight error introduced by the different molecular weights of other carotenoids being neglected. In making the correction for the contribution by carotenoids to the antimony-trichloride reaction the factor 0.42, mentioned above, was based on the intensity of the blue colour produced by β -carotene. Possible variations between the chromogenic powers of different carotenoids were neglected. In order to check that the calibration of the instrument was remaining constant throughout the long period of our investigation, readings were frequently made in which the cuvette was replaced by standard Lovibond glasses. No significant variations in the behaviour of the instrument were detected.

Change in international standard for vitamin A. In maintaining the constancy of the calibration of our absorptiometer for vitamin A, a special problem arose from the official adoption in 1950, as a new international unit and standard, of 0.3 μg vitamin A,

in the form of 0.344 μg of vitamin A acetate (World Health Organization, 1950). This change implied the acceptance of a factor of 1900 for converting $E_{1\text{cm}}^{1\%}$ (328 $\text{m}\mu$) into i.u./g. Before 1950 a conversion factor of 1600 was generally accepted, and was used by us for calculating the number of i.u./g, from the value from $E_{1\text{cm}}^{1\%}$ (328 $\text{m}\mu$) in the specimen of halibut-liver oil first chosen for our calibration. It eventually became clear, however, that the difference in conversion factor was not reflected by any corresponding difference in the intensity of the antimony-trichloride reaction produced by halibut-liver oil and vitamin A acetate. After the completion of our work, therefore, all our results up to 1950 were recalculated on a basis of a common conversion factor of 1900 for both oil and acetate. Presumably, the same correction should be applied to results obtained by most other workers before 1950, whether by measurement of ultraviolet absorption or by the antimony-trichloride reaction.

Statistical treatment of results. The large number of our results made it possible to examine the influence of several factors, including sex, age, period and season, on levels of vitamin A and carotenoids. Our general procedure was to plot the means for one variable, vitamin A, for instance, against another variable such as age. We also compared the separate graphs for men and women.

Since collections of blood had to be made whenever the subjects came for examination, and had sometimes to be discontinued during our absences on holiday, we could not ensure that equal numbers of specimens were collected in each year, or in each season of the year. Slight variations in the distribution between the sexes, and in the average age, were also unavoidable. We feel confident, however, that these imperfections were not sufficiently serious to invalidate our general conclusions.

Over the decade of the investigation blood was collected from 742 men and 526 women. Since specimens were occasionally taken more than once from the same subject the total numbers of estimations were slightly larger, being 796 for men and 536 for women. There seems no reason to believe that the repetition of the analysis for a few of the subjects, in different years, had any significant disturbing influence on the findings. In the statistical treatment of our results, therefore, all estimations have been given equal weight, irrespective of whether they were the first or later readings for the same subject. In view of the known differences between the sexes it seemed advisable first to calculate the means for vitamin A and carotenoids separately for men and women. When it was desired to combine the results for both sexes means were taken of the means for each sex.

RESULTS

Vitamin A and carotenoid levels in men and women. For men (mean age 46) throughout the whole investigation vitamin A averaged 174 i.u./100 ml serum, and carotenoids 121 $\mu\text{g}/100$ ml. For women (mean age 45) the corresponding values were 142 i.u. and 131 $\mu\text{g}/100$ ml. The means for men and women combined, giving equal weight to the mean for each sex in spite of the differences in the numbers of readings, were therefore 158 i.u. and 126 $\mu\text{g}/100$ ml.

Histograms for the distribution of various arbitrary ranges of vitamin A values in men and women are given in Fig. 1. It will be seen that for men the modal interval

for vitamin A was 150–169 i.u./100 ml. The central 95% of the observations lay between 70 and 305 i.u. For women the modal interval was 130–149 i.u. The central 95% of observations lay between 54 and 259 i.u. Similar histograms for carotenoids are given in Fig. 2. For men 90–109 μg was the modal interval range, and 95% of observations lay between 44 and 254 μg . For women the corresponding ranges were 110–129 and 54–245 μg .

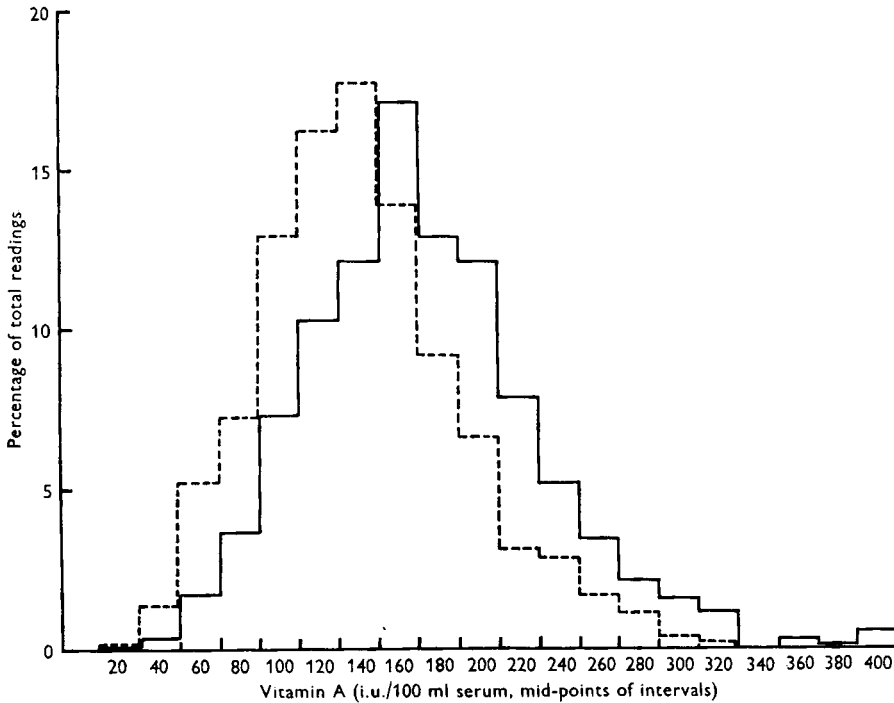


Fig. 1. Distribution of vitamin A values in the blood of British men and women. —, males; ----, females.

Vitamin A and carotenoids in special groups. As already mentioned, some of our subjects had no complaints, but were healthy young men who were examined as applicants for employment or life insurance. The mean results for those groups were:

Applicant for	No. of men	Mean age (years)	Carotenoids ($\mu\text{g}/100\text{ ml serum}$)	Vitamin A (i.u./100 ml serum)
Employment	55	30	109	159
Insurance	36	34	112	168

When allowance is made for the low mean ages in these special groups (see p. 162) the means for both vitamin A and carotenoids are almost identical with those found for men throughout the whole investigation.

Vitamin A in relation to carotenoids. In Fig. 3 mean values for vitamin A have been plotted against selected ranges of carotenoid values. It will be seen that in men vitamin A rose slightly but smoothly with increasing carotenoid values. For women the

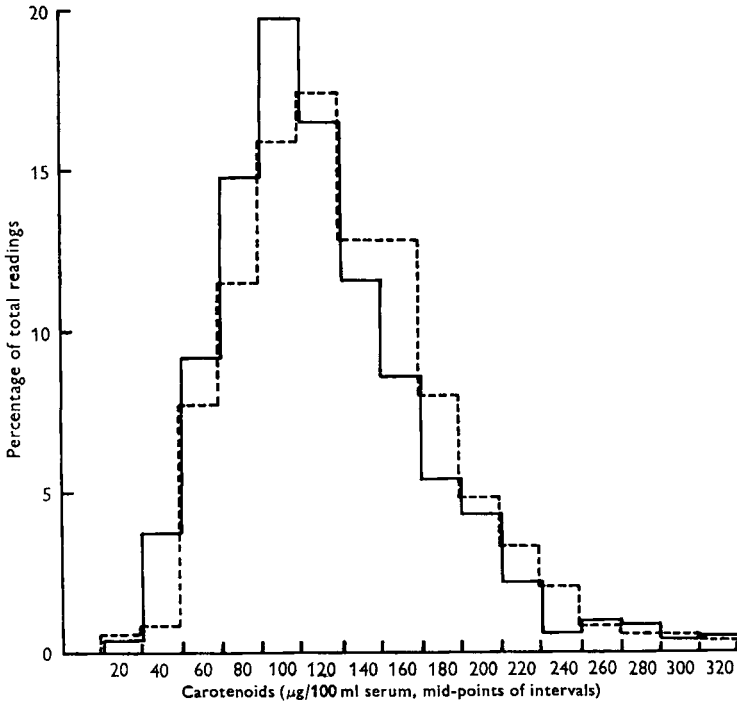


Fig. 2. Distribution of carotenoid values in the blood of British men and women. —, males; ----, females.

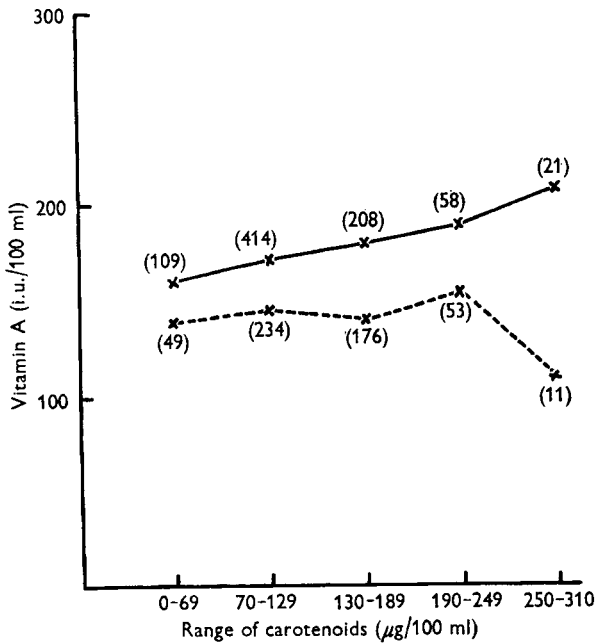


Fig. 3. Vitamin A levels compared with carotenoid levels in the blood of British men and women. (Numbers of readings are shown in parentheses.) —, males; ----, females.

graph for vitamin A was less regular, with a slight rise for the carotenoid range 190–249 μg followed by a pronounced fall in the range 250 μg and over. Although there were only eleven readings in the last group the mean was significantly different ($0.01 < P < 0.02$) from the mean for the carotenoid range of 190–249 μg in women. For men and women in the carotenoid range 250 μg and over the difference between the means for vitamin A also was significant ($0.001 < P < 0.01$).

Influence of age. The results for each sex, divided up according to selected age groups, are shown in Fig. 4 for vitamin A. In men the mean rose steadily from 149 i.u. in the age group 10–19 years, up to a maximum of 191 i.u. in the age group 50–59 years. There was then a decline in the 60–69-year group to 178 i.u. In

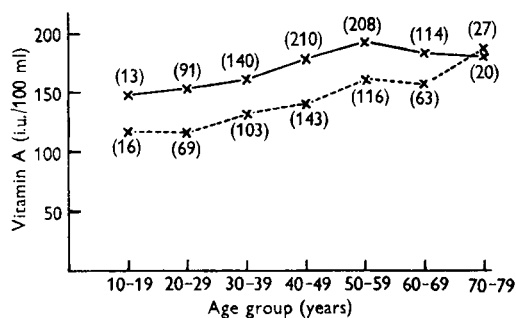


Fig. 4

Fig. 4. Vitamin A in the blood of British men and women compared with age. (Numbers of readings are shown in parentheses.) —, males; ----, females.

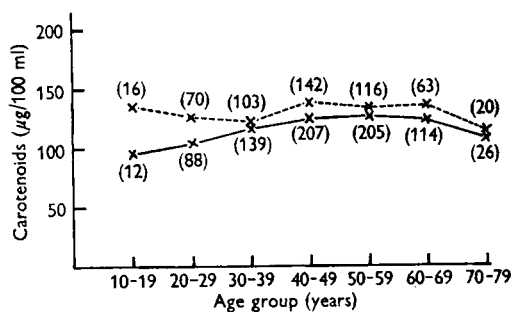


Fig. 5

Fig. 5. Carotenoid levels in the blood of British men and women compared with age. (Numbers of readings are shown in parentheses.) —, males; ----, females.

women the graph ran at a lower level, starting at 116 i.u. in the 10–19-year group and reaching 161 i.u. in the 50–59-year group. A slight fall, not statistically significant, followed at 60–69 years, and then a sharp rise at 70–79 years. This final high mean value for women was derived from only twenty readings, but was significantly different ($0.01 < P < 0.02$) from the mean for women aged 60–69 years. The difference between the means for men and women aged 70–79 years was not significant.

Fig. 5 shows mean values for carotenoids in the same age groups as for vitamin A. As expected, the graph for carotenoids ran at a consistently higher level for women than for men. The mean values for men rose smoothly from 96 μg in the 10–19-year group to a plateau between 40 and 69 years, with a value of 126 μg at 50–59 years. A decline to 107 μg at 70–79 years followed. For women the graph ran parallel to that for men between the ages 30 and 79 years. In the age groups 10–19 years and 20–29 years, however, the means for women were higher than would have been expected from the means for men.

Seasonal changes in vitamin A and carotenoids. Means were calculated for each sex for the periods January–March (winter), April–June (spring), July–September (summer) and October–December (autumn). From Fig. 6 it will be seen that in women vitamin A remained almost constant throughout the four seasons. In men, however,

vitamin A rose slightly in summer, and considerably in autumn. The difference between the means for men in April–June and October–December was statistically significant ($0.001 < P < 0.01$). From Fig. 7 it will be seen that carotenoids rose in both sexes during spring and summer. The increases in those seasons were, however, greater in women than in men. The superiority of women over men in the carotenoid content of their serum also was much more pronounced in spring and summer than in autumn and winter. It may be relevant in this connexion that Kon & Mawson (1950) found no seasonal trends in the vitamin A content of human milk, but a definite one in that of carotenoids.

Vitamin A and carotenoids in successive biennial periods. When the results were averaged for periods of 1 month, or even of 1 year, fluctuations occurred for which no reasonable explanation could be found. Presumably these irregularities arose through the wide variations between individuals and through the difficulty of keeping up a

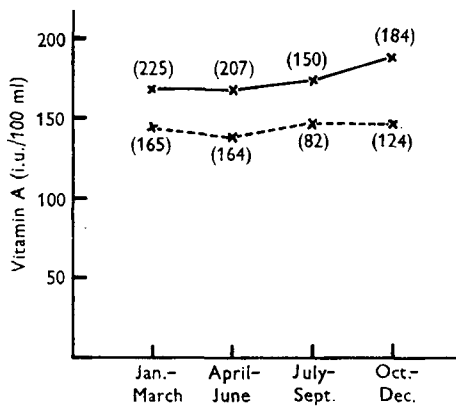


Fig. 6

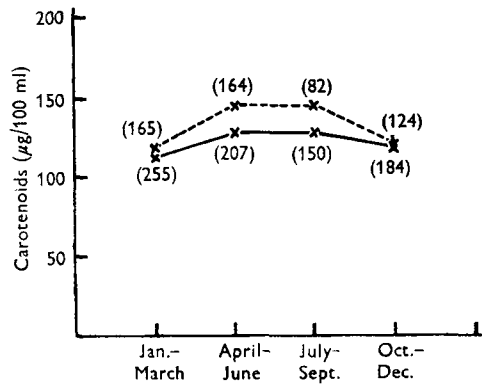


Fig. 7

Fig. 6. Vitamin A in the blood of British men and women in different seasons. (Numbers of readings are shown in parentheses.) —, males; ---, females.

Fig. 7. Carotenoids in the blood of British men and women in different seasons. (Numbers of readings are shown in parentheses.) —, males; ---, females.

uniformly high standard of accuracy in the estimations over a period of many years. Means were therefore calculated for periods of 2 years.

Fig. 8 shows such mean values for vitamin A in men and women, and Fig. 9 shows the means for carotenoids. It will be seen that the mean values for vitamin A were always higher for men than for women, and that the difference remained more or less constant in successive 2-year periods. For carotenoids the relationship was reversed, with the mean value for women invariably exceeding that for men. The difference between the sexes was, however, smaller for carotenoids than for vitamin A, and varied in magnitude. In Fig. 10 the results for men and women have been combined, by taking the mean of the 2-year means for each sex, and are compared with data, kindly supplied by the Ministry of Agriculture, Fisheries and Food, for the intake of sources of vitamin A, including provitamins, over the same 2-year periods. This information on intakes has been derived both from the Consumption Level Enquiry and from the

National Food Survey. Investigations under these headings have been described in reports by the Ministry of Food: National Food Survey Committee (1951, 1952, 1953, 1954) and Ministry of Agriculture, Fisheries and Food: National Food Survey Committee (1955, 1956, 1957, 1958, 1959). Two separate graphs which have run parallel during recent years are, therefore, shown for intake.

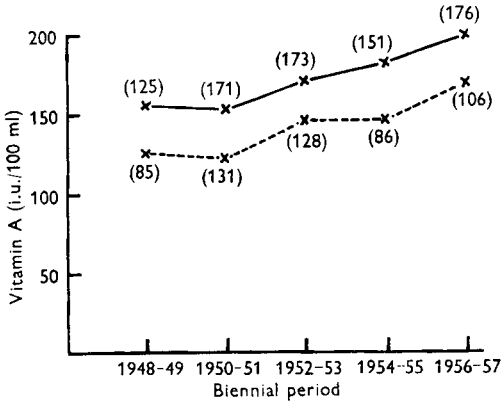


Fig. 8

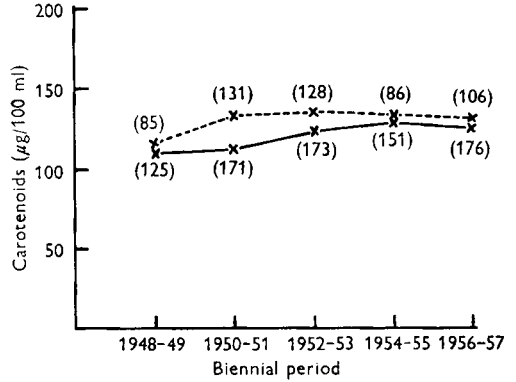


Fig. 9

Fig. 8. Vitamin A in the blood of British men and women in successive biennial periods. (Numbers of readings are shown in parentheses.) —, males; ----, females.

Fig. 9. Carotenoids in the blood of British men and women in successive biennial periods. (Numbers of readings are shown in parentheses.) —, males; ----, females.

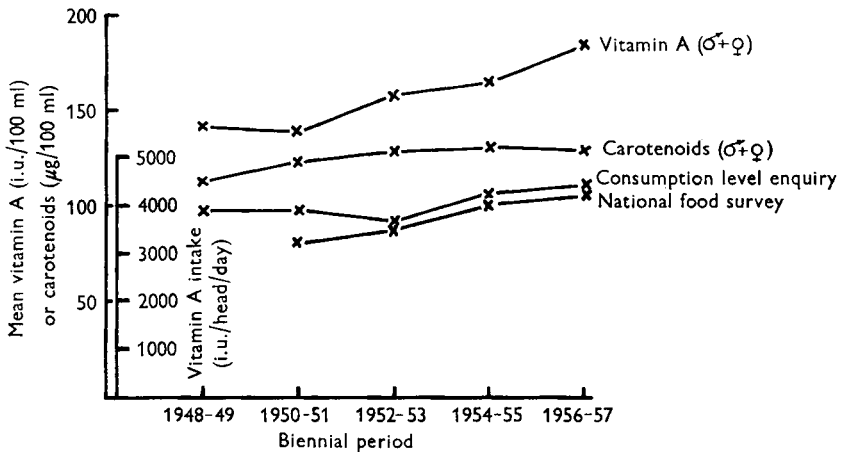


Fig. 10. Combined averages for British men and women for vitamin A and carotenoids in blood in successive biennial periods compared with daily intakes of vitamin A over the same periods according to the National Food Survey and Consumption Level Enquiry (see pp. 163, 167).

DISCUSSION

Collection of specimens. It seems inevitable that plans for collecting specimens so that the sample may be representative of a large population must always be a compromise between statistical perfection and practical convenience. This may be particularly true when the specimen has to be collected under conditions which demand the willing co-operation of the volunteer and arrangements for his comfort, as with a venepuncture. In many similar investigations the volunteers have belonged to well-defined groups, such as students or laboratory workers, or have been members of the same institution, such as a hospital or school. In such circumstances the subjects may all belong to a limited age group or have all subsisted on the same diet. Our method of collecting specimens, mostly from members of the general population who had been indisposed but in whom serious illness could safely be excluded, has therefore definite advantages to compensate for the possible criticism that most of the subjects had sought medical advice. In young men, as we have seen, mean values for both vitamin A and carotenoids were almost the same for those who had attended the doctor as patients or had merely been examined in regard to their fitness for employment or insurance.

Incidence of low vitamin A levels. Experiments in which volunteers have been kept on a diet deficient in vitamin A (Hume & Krebs, 1949) showed that dark adaptation became defective only when the level of vitamin A in the blood fell to about 40 i.u./100 ml. If we take our limit as 50 i.u., to allow for the effect on calibration of the new vitamin A international unit, it appears that only three of our male subjects and eight of our females would have been expected to be functionally deficient on this basis. For both sexes combined, therefore, the incidence of values under 50 i.u. was less than 1%.

Influence of sex and age. Our results confirm that sex has an important effect on the level of vitamin A in the blood, with a consistent superiority of the male mean over the female of about 23%. For carotenoids the difference is smaller, less regular, and in the opposite direction. Earlier reports of these findings and of other differences in vitamin A metabolism between the sexes have been discussed in detail by Moore (1957). We hope to discuss in a later communication the possibility that the conversion of carotene may be more efficient in men than in women, and so account at least partly for the sex differences in blood levels.

The influence of age also on vitamin A levels is consistent, at least until extreme old age. Thus the mean for both sexes increased steadily up to a maximum in the groups aged from 50 to 59 years (Fig. 4). In old age the means tended to decrease in both sexes, except for an unexpectedly high finding in the group of women aged from 70–79 years. Carotenoid values tended to follow those for vitamin A but with flatter curves, except for high values for women between 10 and 29 years (Fig. 5). Adlersberg, Schaefer & Steinberg (1956) have found higher levels for cholesterol and phospholipids in females than in males up to the age group 23–27 years, after which the relationship is reversed until middle age.

If it was necessary to compare results obtained from dissimilar groups of subjects,

therefore, allowances for both sex and age would be necessary. In spite of the general finding that the level of vitamin A is higher in men than in women, we might, for example, expect a slightly higher mean for a group of elderly women than of young men.

Kimble (1938-9) could find no correlation between the levels of vitamin A and carotenoids in healthy men or women. Our own findings, based on a much more extensive set of readings, suggest that in men mean levels for vitamin A rise slightly as the mean carotenoid levels rise (Fig. 3). In women the level is irregular, with the suggestion of a fall in vitamin A when carotenoids are very high. Admittedly the correction factor for carotenoids in the antimony-trichloride reaction is hard to assess with accuracy. Obviously if our correction factor were too low the rise in the curve for men could be explained on this basis, but the same consideration would necessarily imply a definite downward tendency in the curve for women. Irrespective of the correction factor, therefore, it seems clear that the ratio between the levels of vitamin A in men and in women increases as the levels of carotenoids rise. Again the possibility of a more efficient conversion of carotene in men than in women must be considered.

Influence of season. Our finding for both sexes of slightly higher mean values for carotenoids during spring and summer than during autumn and winter (Fig. 7) seems consistent with the increased supply of fresh vegetables and fruits during the warmer season. For vitamin A the seasonal variation in women was slight, but for men the means were slightly higher in summer and autumn than in winter and spring (Fig. 6). This finding suggests that vitamin A derived from the summer abundance of carotene may be first stored and later mobilized into the blood stream. Again a higher efficiency in the conversion of carotene in men than in women may be involved.

Biennial variations in vitamin A and carotenoids. The graphs in Figs. 8-10 suggest strongly that the level of vitamin A in the blood of inhabitants of this country has shown a general upward tendency since about 1950. Such an increase might well have been expected, since during and after the Second World War blood levels of both vitamin A and carotenoids appeared to be lower in Britain, where food was rationed, than in the U.S.A., where food was more freely obtainable. We have seen already that comparisons between groups of subjects may be complicated by differences in sex and age. The results of certain investigations are, however, comparable at least in concerning large groups of adults of both sexes:

Reference	Vitamin A (i.u./100 ml serum)	Carotenoids (μ g/100 ml serum)
U.S.A.:		
Abels, Gorham, Pack & Rhoads (1941)	160	195
Harris, Hickman, Jensen & Spies (1946)	204	210
U.K.:		
Sinclair (1947)	86	94
Moore & Leitner (1949)	121	92
Campbell & Tonks (1949)	108	80

The dates are those of publication, and the actual dates of some of the observations may have been much earlier. The observations of Moore & Leitner, for example, were made during the years 1944-5. If we neglect, for the moment, questions of calibration

it appears that the American means for vitamin A tended to be nearly twice as high as those found in Britain, and means for carotenoids fully twice as high.

During recent years both Britain and the U.S.A. have been free from dietary restrictions, and presumably the difference between the dietary patterns in the two countries is smaller than it was during the war. It might have been expected, therefore, that the difference between the blood levels of vitamin A and carotenoids would also diminish. When comparing our most recent results for vitamin A with earlier findings, however, we must allow for the effect of the change in the factor for converting the values for $E_{1\text{cm}}^{1\%}$ (328 m μ) to i.u./g, which occurred when the new international unit was adopted in 1950. The increase of this factor from 1600 to 1900 presumably implies that many early results must now be increased by nearly 20% to make them comparable with modern findings. Such an increase must not, however, be made to the value reported by Harris *et al.* (1946), who used a factor of 2000 even before the change. When recalculated for a conversion factor of 1900 instead of 2000 the American average is reduced to 191 i.u., which may be compared with 158 i.u. found in the whole of the present investigation, or 185 i.u. for our final biennial period. Thus the gap between current British and early American values for vitamin A seems to have closed. For carotenoids the differences remain large. Harris *et al.* (1946) found mean values of 210 μg , compared with 130 μg in the final biennial period of our investigation.

The increase in blood vitamin A which appears to have occurred in Britain since the decontrol of food supplies runs roughly parallel with the increases in vitamin A intake found in the National Food Survey. This Survey measures the quantities of food obtained by purchase or from gardens or allotments or other similar sources for consumption in the home or in packed meals carried and eaten away from home; other food eaten outside the home is not included, nor are sweets, soft and alcoholic drinks, fish-liver oil or vitamin tablets. Results are calculated each year for observations made on samples of the population which are, over the year, nationally representative. There is fair agreement, for the last three biennial means, with results obtained in the Consumption Level Enquiry (see Fig. 10), which are based on the total supplies of foods estimated to be available at the retail stage of distribution. These include meals, snacks and ice-cream obtained outside the home, sweets and soft drinks and all food consumed in institutions. They do not include alcoholic drinks or fish-liver oil or vitamin tablets.

The problem of whether the change in the international standard and unit from β -carotene to vitamin A, made in 1950, implied a 15% reduction in the actual amounts of preformed vitamin A necessary to satisfy official assessments of human requirements is both interesting and intricate, but beyond the scope of this communication.

Significance of the blood levels of vitamin A and carotenoids. The degree of reliance which can be placed on values for blood vitamin A and carotenoids as an index of nutritional status is difficult to assess. There is ample evidence from experiments in which volunteers have subsisted on deficient diets to show that first the dietary carotenoids, and later vitamin A, fall to very low levels (Hume & Krebs, 1949). It is clear also that hospital dietaries, though not grossly deficient in vitamin A, may neverthe-

less give rise to levels of vitamin A and carotenoids in the blood which are lower than in the general population (Leitner, Moore & Sharman, 1952). From the present work it appears that the blood levels over a period of years have reflected the amount of vitamin A available in the food.

We must not forget, however, that high levels of vitamin A in groups of subjects who presumably are receiving much the same diet may be associated with characteristics such as middle age or the male sex. It is perhaps incautious, as once suggested by an American committee (New York State Joint Legislative Committee on Nutrition, 1947) to classify as 'excellent' all findings for blood vitamin A and carotenoids above arbitrarily chosen levels. We have seen that blood vitamin A is higher in men than in women, it reaches a peak in the age group from 50-59 years, and it has apparently increased in this country in recent years. The pattern of variation is thus reminiscent of the incidence of atherosclerosis and coronary heart disease. It would be just as unwise, however, to conclude that the similarity implies a causal relationship between vitamin A and these diseases as to accept high levels of vitamin A, without question, as a sign of a particularly commendable nutritional status. For the present, values for both vitamin A and carotenoids in the blood must be interpreted with caution, and with due regard to the characteristics of the subjects to whom they relate.

SUMMARY

1. Vitamin A and total carotenoids were estimated during the decade 1948-57 in the blood serum of more than 700 British men and 500 women in whom no serious disease could be detected.
2. Wide individual variations were found in both sexes. The mean values for equal numbers of each sex were 158 i.u. vitamin A and 126 μg carotenoids per 100 ml serum.
3. In groups of men, whether arranged according to age, season or biennial period, mean values for vitamin A were always about 20% higher than for women. For carotenoids the relationship was reversed, with mean values about 8% higher for women than for men. The difference between men and women in the values for vitamin A tended to widen with increasing carotenoid levels.
4. In men mean values for vitamin A increased with age until a maximum was reached in the age group 50-59 years. In women also vitamin A increased with age until at 70-79 years the usual sex difference had disappeared. Mean carotenoid values in men ran almost parallel with vitamin A, but in women unexpectedly high values were found under the age of 30 years.
5. In both sexes higher mean values for carotenoids were found in spring and summer than in autumn and winter. In women, vitamin A varied little at the different seasons, but in men the mean values in summer and autumn were slightly higher than in winter and spring.
6. In both sexes blood vitamin A appears to have increased since the removal of wartime food restrictions. The increases appear to have run roughly parallel with increases in the intake of vitamin A as estimated in the National Food Survey. Increases in blood carotenoids over the same period were less pronounced.

7. It seems probable that the sex differences in the levels of vitamin A and carotenoids may be due, at least in part, to greater efficiency in the conversion of carotene into vitamin A by men than by women.

Our thanks are due to Dr L. J. Harris for his interest and criticism, to Miss D. F. Hollingsworth for valuable advice, to Mrs Aileen Bright and Mrs Pamela Richards for technical assistance, and to Mrs Richards and Miss Margaret Smith for help in the laborious calculations.

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