HYPOVITAMINEMIA A.

*Effect of Vitamin A Administration on Plasma Vitamin A Concentration, Conjunctival Changes, Dark Adaptation and Toad Skin**

By JOHN ESBEN KIRK, M.D.** AND MARGARET CHIEFFI, M.D.†

IN A PREVIOUS study by the present authors[1] a correlation was demonstrated between the plasma vitamin A concentration and the frequency of occurrence of localized conjunctival thickening and toad skin (follicular hyperkeratosis). The ocular lesion observed in the patients with hypovitaminemia A consisted of a raised subconjunctival thickening of triangular shape, having its base at the corneal border and showing some resemblance to pinguecula. No significant correlation was found between the plasma vitamin A concentration and the dark adaptation time.

The present study was undertaken with the purpose of observing the effect of prolonged administration of a dispersion of vitamin A alcohol on various clinical findings, which in the previous investigation by us were shown to have a correlation with hypovitaminemia A. For this reason, a group of individuals who had very low vitamin A plasma concentrations were given a daily supplement of vitamin A for a period of one year, during which time the plasma vitamin A values were followed and the effect on existing conjunctival lesions, blepharo-conjunctivitis, adaptation time and follicular hyperkeratosis recorded. After discontinuation of the vitamin A treatment, the chemical and clinical studies were continued for a seven-month period.

EXPERIMENTAL

The investigation included 23 individuals, 10 men and 13 women, who were inmates or patients of the St. Louis City Infirmary and City Infirmary Hospital. The mean age of the men at the outset of the study was 74 years, and of the women 69 years. None of the individuals suffered from obvious gastrointestinal or hepatic diseases.

The plasma vitamin A concentration of the group was determined in September, 1947, and was found to range between 1 and 13 micrograms per 100 cc. with a mean value of 7.2 micrograms per 100 cc. (s.d. = 4.3). In order to verify the validity of the low plasma vitamin A values of the patients, the determinations were repeated in June 1948, immediately before the commencement of the vitamin A therapy. The analyses showed that the plasma vitamin A concentration had remained low, the values now ranging between 0 and 15 micrograms per 100 cc. with a mean value of 5.1 micrograms per 100 cc. (s.d. = 4.9). During this interval of 9 months the patients received only the ordinary diet of the institution, which

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* Vitamin studies in middle-aged and old individuals X

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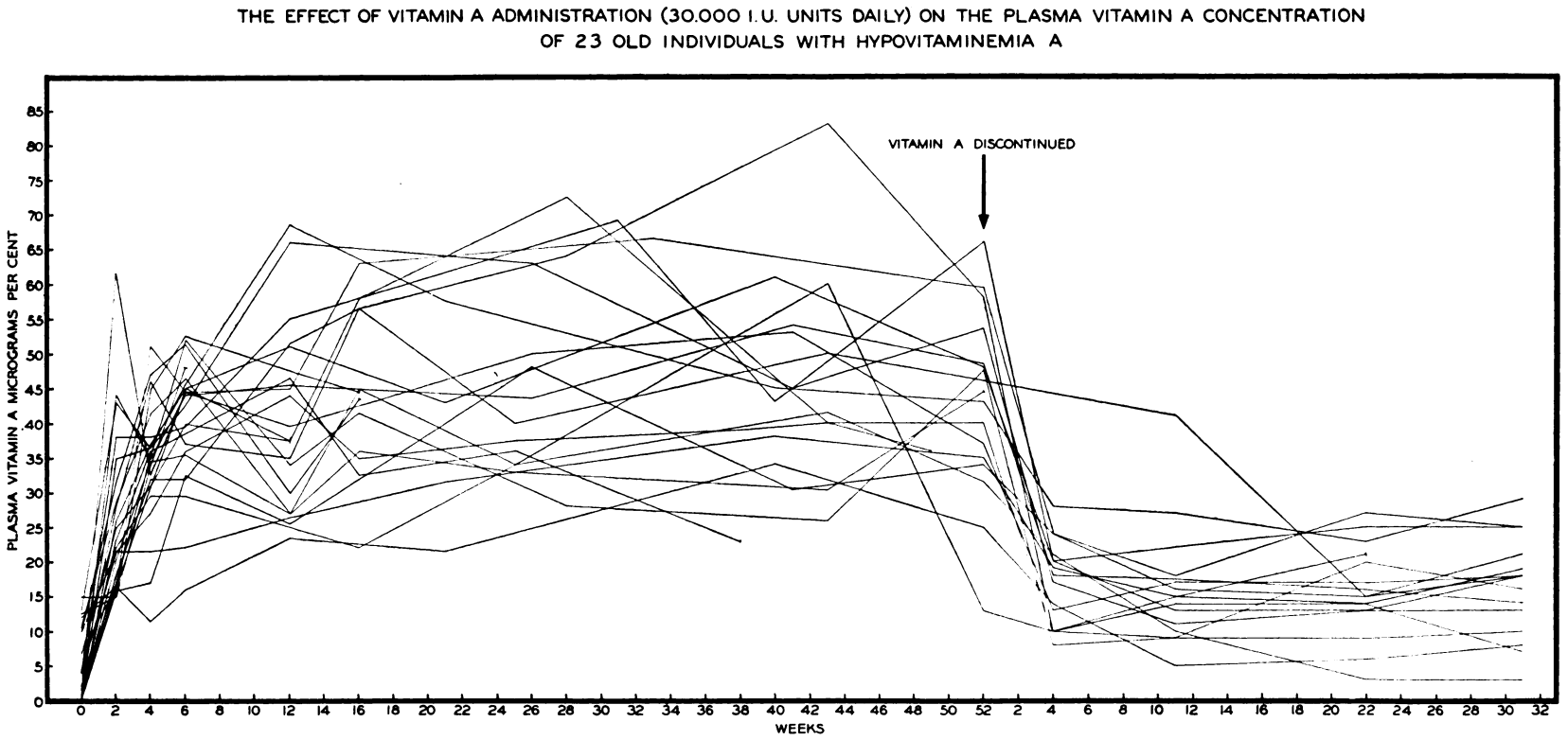

Fig. 1. The effect of vitamin A administration (30,000 I.U. daily) and subsequent discontinuation on the plasma vitamin A concentration in 23 old individuals with hypovitaminemia A.

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on direct analysis of the prepared food was found to contain about 10,000 units of vitamin A daily.

Treatment with 30,000 units of vitamin A daily was started on July 1, 1948 and continued until June 30, 1949. The vitamin preparation used was a dispersion of the natural vitamin A acetate which was supplied by Hoffmann-La Roche, Inc. The vitamin was given to the patients in a mixture of grapefruit juice and orange juice each morning, the vitamin preparation being measured off by means of a pipette or measuring cylinder and thoroughly mixed with the fruit juice. The vitamin was administered under supervision by a nurse and was taken willingly by the patients.

The plasma vitamin A determinations were performed as described in detail in a previous publication.[4] The method employed was a modification of the Carr Price procedure recommended by the Association of Vitamin Chemists.[6] The analyses were carried out at intervals of from two to several weeks. All determinations were made in duplicate on fasting blood samples.

Measurement of the dark adaptation time was made by means of a Feldman adaptometer. Since 6 of the 23 patients had to be excluded from the test because of the existence of lenticular opacities or other severe eye lesions, the determination of the adaptation time was performed in only 17 of the 23 subjects. The measurement of the adaptation time and the evaluation of the clinical condition were generally undertaken on the same days the plasma vitamin A level was determined.

Results

Plasma Vitamin A Concentration. The effect of the oral administration of vitamin A on the plasma vitamin A level of the individual patients is presented in Fig. 1, whereas the average vitamin A concentrations for the group are reproduced in Fig. 2. It will be seen from Fig. 1 that the vitamin A plasma value in most of the subjects showed a marked and rapid rise following the commencement of vitamin A administration, and that none of the patients failed to show a definite increase. When the values for the group as a whole are considered (Fig. 2) it will be noted that after 2 weeks of treatment the mean plasma vitamin A value had increased from 5.1 to 26.0 micrograms per 100 cc. During the following month the plasma vitamin A level rose further, to 40.0 micrograms per 100 cc., and 4 months after the beginning of therapy reached a value of 44.5 micrograms per 100 cc., at which level the plasma concentration was maintained during the remaining 8 months of treatment. Following discontinuation of the vitamin A supplementation after 1 year of therapy, the vitamin A plasma concentration dropped sharply, and after 4 weeks had reached a level of 18.7 mi-

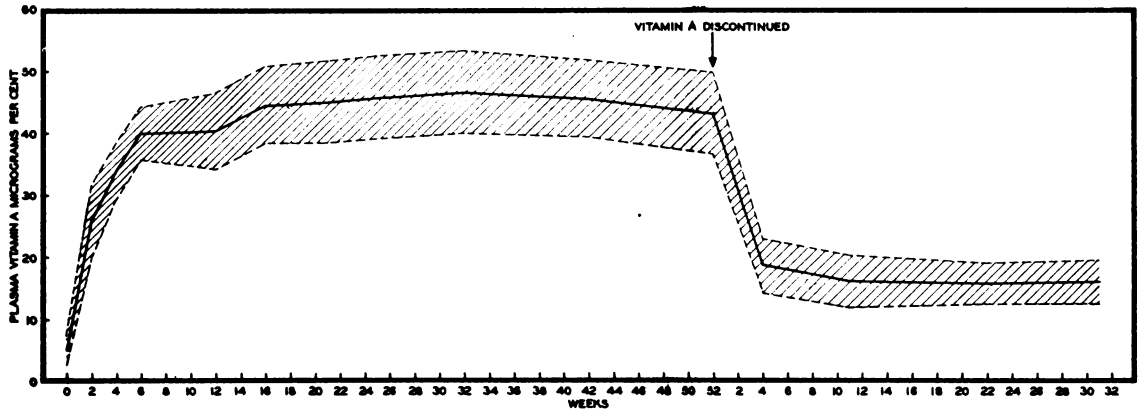

Fig. 2. The effect of vitamin A administration (30,000 I.U. daily) and subsequent discontinuation on the mean plasma vitamin A concentration of 23 old individuals with hypovitaminemia A. (The shaded area represents ±0.5 s.d.)

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crograms per 100 cc. A further decrease to about 16 micrograms per 100 cc. occurred during the following weeks, and this level was maintained during the remaining period of observation.

It should be noted that during the 12 months of vitamin administration the number of individuals in the group decreased from 23 to 17 as a result of deaths; in the 7-month period following discontinuation of the therapy the number was reduced further, so that at the end of the 19-month study only 15 individuals remained.

Conjunctival Thickening. The existence of conjunctival thickening was found in 7 of the 23 patients with hypovitaminemia A. As seen from Fig. 3, the treatment with vitamin A was not followed by any immediate noticeable effect on the lesion. Thus, after 4 months of treatment the conjunctival thickening was still present in all the patients. After that time, however, a demonstrable improvement set in, and after 10 months of therapy the lesion had disappeared in the 7 subjects. At the end of the one-year period of treatment 6 of the original 7 patients were still alive.

When the patients were reëxamined 7 months after discontinuation of the vitamin A therapy the conjunctival thickening had recurred in 3 of the 5 individuals and had further appeared in 3 of the other patients in the hypovitaminemia A group.

Blepharo-conjunctivitis. Blepharo-conjunctivitis of varying severity was observed in 16 of the 23 patients included in the study (Fig. 3); among these were the 7 individuals with localized conjunctival thickening. The response of the blepharo-conjunctivitis to the treatment with vitamin A was not rapid, but after 4 months of therapy the lesion had disappeared in 4 of the subjects and at the end of one year's treatment remained in only 2 patients. No local treatment of the conjunctiva or the eyelids was given. Of the 16 patients 14 were alive at the end of the one-year period.

On reëxamination of the patients in January 1950, 7 months after discontinuation of the vitamin A therapy, the blepharo-conjunctivitis was found to persist in the same 2 patients, had recurred in 4 individuals, and had developed in one of the other subjects in the hypovitaminemia A group.

Dark adaptation time. In the previous investigation by the present authors[1] the average dark adaptation time as determined by the Feldman method was found to be 396 seconds for individuals in the age group 60 to 90 years. The mean value of the adaptation time for the 17 patients with hypovitaminemia A included in the present study before the commencement of vitamin A therapy was found to be 434 seconds, a figure which is not significantly different from the average value for individuals of this age ($t = 1.7$).

As will be seen from Fig. 4, the treatment with vitamin A did not result in any notable decrease in the adaptation time for the group as a whole. An analysis of the measurements

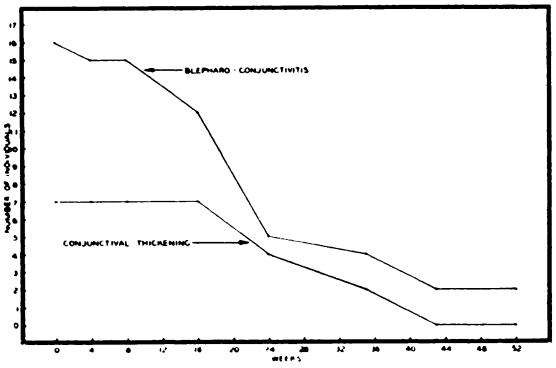

Fig. 3. The effect of vitamin A administration on the incidence of conjunctival thickening and blepharo-conjunctivitis in a group of old individuals with hypovitaminemia A.

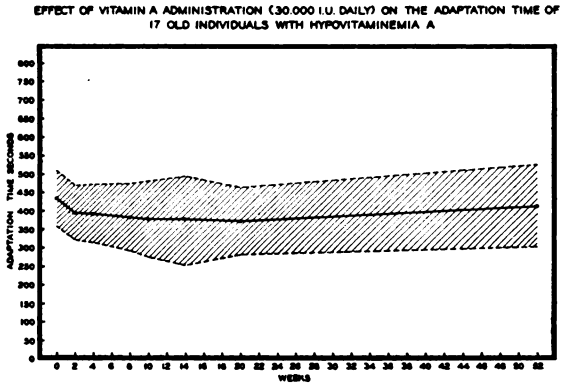

Fig. 4. The effect of vitamin A administration on the mean adaptation time of a group of old individuals with hypovitaminemia A. (The shaded area represents ±0.5 s.d.)

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for the individual patients revealed, however, that in 4 of the 17 subjects the vitamin therapy was followed by a significant reduction of the adaptation time values. The data for these 4 patients are given briefly below.

No. 5. Female, 84 years. Original adaptation time 585 seconds; after 42 days' treatment 300 seconds; during the remaining part of the one-year period of vitamin A therapy, 195 seconds.

No. 12. Female, 80 years. Original adaptation time 810 seconds; after 92 days' treatment, 300 seconds; after one year's therapy, 225 seconds.

No. 17. Female, 58 years. Original adaptation time 300 seconds; after 30 days' therapy, 180 seconds; after 75 days' treatment, 90 seconds. The value remained at the latter level during the remaining part of the one-year period of treatment.

No. 22. Female, 59 years. Original adaptation time 390 seconds; after 30 days' treatment, 180 seconds, at which level the adaptation time remained until, after 153 days, the value decreased further to 75 seconds.

The observed effect of the vitamin A therapy in these 4 patients suggests that the prolonged adaptation time was due, at least in part, to vitamin A deficiency.

Five of the 17 patients in the group died during the course of the year.

Toad skin. The effect of the vitamin A administration on the follicular hyperkeratosis in the regions of the forearms, upper arms, thighs and buttocks is presented in Fig. 5, which shows that the skin lesion responded slowly to the vitamin therapy. This was particularly the case with regard to the toad skin on the forearms; thus, after one year's treatment with vitamin A the follicular hyperkeratosis in this area, although frequently somewhat ameliorated, still persisted in 5 of the 8 patients, in whom this sign was present at the onset of the study. In contrast to the toad skin on the forearms, the hyperkeratosis on the upper arms at the end of one year of therapy had disappeared in all the 6 patients having the skin lesion in this region. Of a total number of 13 individuals with toad skin in one or more regions, 10 were alive at the end of the 12-month treatment period.

On reëxamination 7 months after discontinuation of the vitamin A therapy, follicular hyperkeratosis had reappeared on the forearms in 2 patients, and on the upper arm in one patient. Toad skin on the forearms had further appeared in one of the other patients in the hypovitaminemia A group. None of the patients at the time of reëxamination had toad skin on the thighs, but follicular hyperkeratosis in the region of the buttocks was found in the 2 subjects in whom the lesion had not disappeared during the period of vitamin A treatment.

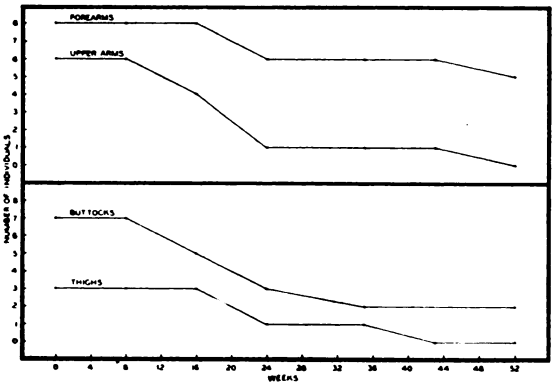

Fig. 5. The effect of vitamin A administration on the incidence of follicular hyperkeratosis in various skin regions in a group of old individuals with hypovitaminemia A.

Discussion

Investigations on the effect of prolonged vitamin A administration on the plasma vitamin A concentration in a large group of adults have not previously been reported. The data presented in the present publication indicate that elderly individuals with hypovitaminemia A are capable of absorbing appreciable amounts of vitamin A when the vitamin is given as a supplement in the form of pure vitamin A dispersion. This finding is in agreement with the results reported by Yiengst and Shock[8] on the basis of vitamin A tolerance curves observed in old subjects.

Robertson and Morgan[7] treated a group of student nurses, several of whom had pinguecula-like elevations of their conjunctivae, with 50,000 units of vitamin A daily for periods up to two years. No effect on the conjunctival lesion was noted. Since plasma vitamin A analyses were not performed at the commencement of the study, it

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remains uncertain whether hypovitaminemia A was present. The demonstrated effect in the present investigation of the vitamin A therapy on the localized conjunctival thickening supports the contention of a causal relationship between the vitamin A nutrition and this sign.

The finding in 4 out of 17 individuals of a definite improvement of the dark adaptation following the treatment with vitamin A suggests that impairment of adaptation in some instances is related to A hypovitaminosis. This observation is not necessarily in conflict with the lack of demonstration in a large group of subjects of a significant correlation between the plasma vitamin A level and the dark adaptation time.

Information is lacking in the literature on the effect of vitamin A treatment on follicular hyperkeratosis in patients for whom concomitant plasma vitamin A analyses are available. Several reports, however, have been published on the effect of vitamin A treatment on toad skin in individuals in whom the skin lesion on the basis of the dietary history might be presumed to be caused by a vitamin A deficiency. All were young or middle-aged subjects.

Frazier and Hu[2] in 1931 treated 15 soldiers, between 19 and 33 years of age, who suffered from keratomalacia and showed marked follicular hyperkeratosis, with 15 ml. of cod liver oil daily for periods up to 2 months. The keratotic papules decreased slowly in size but still were present at the end of the observation period. In a later publication (1936) by the same authors[3] on a larger group of patients it is stated that from 2 to 3 months of vitamin A therapy is generally required for the skin to regain its normal appearance.

Youmans and Corlette[9] treated 3 adults, aged 29 to 48 years, with 15 ml. of cod liver oil or 12,000 to 25,000 units of vitamin A concentrate daily. Improvement of the toad skin was noted in from 4 to 8 weeks; disappearance of the lesion in these patients occurred after a total of 8, 18 and 22 weeks of treatment. Finally, in a study by Lehman and Rapaport[5] on a group of children, maximal improvement of the follicular hyperkeratosis was obtained in from 2 to 4 months with a daily dose of 100,000 to 300,000 units of vitamin A.

The observations in the present investigation indicate that in elderly individuals an even longer period of treatment with vitamin A than in children and younger adults is frequently necessary for effecting the disappearance of the toad skin. Since in the present group of patients the plasma vitamin A concentration was found to rise to a normal level within a few weeks after the commencement of peroral vitamin A supplementation it seems reasonable to conclude that the slower response of the skin lesion to vitamin A therapy, in spite of adequate plasma levels, may not have been conditioned by an inadequate supply of vitamin A, but rather by the more advanced age of the patients.

Summary

The effect of vitamin A therapy on the plasma vitamin A concentration, conjunctival lesions, dark adaptation time and toad skin was studied in 23 elderly individuals with hypovitaminemia A. A dose of 30,000 units of natural vitamin A acetate was given daily by mouth for a period of one year.

The treatment resulted in a rise of the mean plasma vitamin A concentration from 5.1 to 44.5 micrograms per 100 cc., at which latter level the plasma vitamin A content was maintained. Following discontinuation of therapy the plasma vitamin A concentration decreased to about 16 micrograms per 100 cc.

A definite beneficial effect on existing localized conjunctival thickening, blepharoconjunctivitis and toad skin was observed, but the response was generally slow.

The adaptation time in 4 out of 17 patients decreased markedly following vitamin A therapy, but in the remaining patients was not influenced significantly.

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Resumen

Hypovitaminemia A. Efecto de la administración de vitamina A sobre la concentración de vitamina A en el plasma, alteraciones conjuntivas, adaptación a la obscuridad e hiperqueratosis

En 23 sujetos de edad avanzada con hipovitaminosis A se ha estudiado el efecto de la vitaminoterapía A sobre: la concentración de vitamina A en el plasma, el tiempo de adaptación a la obscuridad, y la hiperqueratosis ("piel de sapo"). Una dosis de 30,000 unidades por día de vitamina A natural fué administrada oralmente durante un año.

El tratamiento ocasionó un aumento de la concentración media de vitamina A en el plasma de 5.1 a 44.5 microgramos por 100, nivel al que el contenido en vitamina A del plasma se mantenía. Al descontinuar la terapéutica, la concentración de vitamina A en el plasma disminuyó a unos 16 microgramos por 100.

Se observó un efecto beneficioso marcado en los casos de infiltración conjuntiva localizada, de bléfaro-conjuntivitis, y de hiperqueratosis, pero en general la respuesta se produjo con retardo.

En 4 de los 17 pacientes, el tiempo de adaptación a la obscuridad fué considerablemente reducido, pero en los demás no fué notablemente afectado.

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