TABLE V—EFFECT OF MILK TYPE ON SERUM IgE CONCENTRATIONS

Feeding category	Serum IgE		
	<2·5 MOMs	>2·5–4·0 MOMs	>4·0 MOMs
(A) Breast-fed for at least 3 months	86 (77%)	6 (5%)	20 (18%)
(B) Breast-fed 1–2 months	28	3	11
(C) Breast-fed <1 month or not at all	69 (81%)	2 (2%)	14 (17%)
Total	183	11	45

wholly breast-fed infants, only 15% of the bottle-fed infants were definitely affected.

18% of children breast-fed for at least 3 months had IgE levels greater than 4 MOMs compared with 17% of the mainly bottle-fed (table V).

Discussion

Unselected reference values for serum IgE levels in childhood are not yet well documented. There does, however, appear to be agreement that IgE levels in cord blood are very low[13–16] and that the IgE is of fetal not maternal origin. It also seems to be agreed that there is a gradual rise from birth to adult life but the rate of the rise varies in reported series. Yet the mean (or median) seems mainly to be below 5 IU/ml at 6 months of age, and at 1 year it is between 5 and 10 IU/ml. Because of the wide variations it becomes more difficult to define what is abnormal above the mean. In our own series we have defined it as over 4 MOMs (98th centile), but there is a strong suggestion that over 2·5 MOMs would be clinically more useful since only 1 child in category 3 and 7 children in category 2 had IgE levels between 2·5 and 4 MOMs.

Table III and figures 1–3 confirm the close association which exists between the eczema-asthma syndrome and raised serum IgE. Figures 1, 2, and 3 show the compact phalanx of normal results in category 1 and the wide distribution of results in category 3, with 50% of them being above 2·5 MOMs. Only 2 of those in category 3 had asthma alone which suggests that immunologically as well as clinically the eczema is the primary condition. However, 9% of apparently unaffected children had high levels of IgE and 50% of the definitely affected had normal serum IgE, so the relation is not absolute.

As a result of our findings in table IV we cannot agree that breast-feeding for 3 months or more protects the infant against the development of eczema up to the age of 2 years. 22% of the breast-fed infants and 15% of the bottle-fed were affected. This is in accord with other recent reports.[7, 8]

Similarly in table V our figures suggest no correlation between type of feeding and IgE levels. Others[2, 3] have demonstrated lower levels in breast-fed than in bottle-fed infants and in non-eczamatous than in eczematous infants but these lower and higher levels are within the limits of what we would call normal. In our series 17% of the bottle-fed and 18% of the breast-fed infants had what we would call high serum IgE concentrations . Not only does cow's milk in 3 months of life not cause eczema it does not even increase serum IgE in the first two years any more than does breast-milk.

Although we agree that breast-milk is best for small infants, we do not believe that it should be recommended as a means of preventing the asthma-eczema syndrome. Especially since a mother from an allergic family is likely to feel that she has failed her child if she cannot breast-feed for "long enough" to prevent the development of the syndrome.

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INCREASED SKIN PIGMENT REDUCES THE CAPACITY OF SKIN TO SYNTHESISE VITAMIN D_3

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Summary To determine the effect of increased skin pigment on the cutaneous production of vitamin D_3, circulating vitamin D concentrations were determined in two lightly pigmented Caucasian and three heavily pigmented Negro volunteers after exposure to a single standard dose of ultraviolet radiation (UVR). Exposure of Caucasian subjects to 1 minimal erythemal dose of UVR greatly increased serum vitamin-D concentrations by up to 60-fold 24–48 h after exposure, whereas this dose did not significantly change serum vitamin-D concentrations in Negro subjects. Re-exposure of one Negro subject to a dose of UVR six times larger than the standard dose increased circulating vitamin D to concentrations similar to those recorded in Caucasian subjects after exposure to the lower dose. These results indicate that increased skin pigment can greatly reduce the UVR-mediated synthesis of vitamin D_3.

Introduction

VITAMIN D_3 is made in the human skin by the photoconversion of 7-dehydrocholesterol (7-DHC) to

previtamin D_3, which, in turn, thermally isomerises to vitamin D_3.[1] It has been suggested that the presence of the chromophore, melanin, in high concentrations in skin could limit vitamin-D synthesis by competing with 7-DHC for ultraviolet photons.[2,3] As a consequence, dark-skinned individuals living in northern latitudes might be at greater risk of vitamin-D deficiency than their white-skinned neighbours. Early surveys[4] and more recent reports[5,6] revealed a higher incidence of rickets among Negro children than among Caucasian children in the U.S.A. There has also been speculation that dark skin could be a predisposing factor to vitamin-D deficiency, which is common in Asian immigrants in Britain.[7]

To study the effect of skin pigmentation on the production of vitamin D in man, we measured circulating vitamin D concentrations in lightly pigmented Caucasian and in heavily pigmented Negro volunteers after exposure to a single standard dose of ultraviolet radiation (UVR).

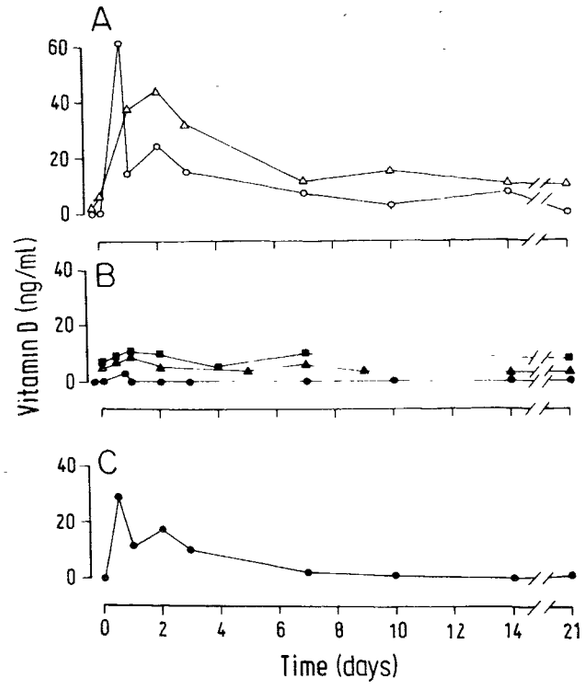
Subjects and Methods

UVR was delivered in a walk-in irradiation chamber (National Biological Corporation, Cleveland) equipped with 16 vertically arranged fluorescent sunlamps (Westinghouse FS40). Spectral irradiance, as measured by a spectroradiometer (International Light, model 700) at wavelengths in a 280–315 nm band 10 cm from the source, was 800 $\mu W/cm^2$. The spectral power distribution of the lamps ranged from 280 nm to 450 nm with a broad power peak at 313 nm. Two lightly pigmented (White) Caucasian volunteers (male; mean age 28 years: skin type III[8]) and three heavily pigmented (Black) Negro volunteers (two males and one female; mean age 33 years; skin type VI) were each exposed to 0·054 J/cm^2 over the entire body. This dose was 1·5 times the minimum erythemal dose (MED) for White subjects.[9] Serial blood-samples were obtained for 21 days after exposure to UVR and were stored at −20°C until assay.

Vitamin D (vitamin D_2 and D_3) was measured in serum (3 ml) after its extraction and sequential purification, first on 'Sep-Pak' cartridges[10] and then by successive high-pressure liquid chromatography (HPLC) steps. Initial reverse-phase HPLC was performed on a 'Radial-Pak' A column (Waters Associates) in 2% water in methanol at 2·0 ml/min. Final purification and measurement were achieved by straight-phase HPLC on a 'Zorbax-SIL' column (DuPont Instruments, Wilmington) in 2% isopropanol in n-hexane at 1·5 ml/min; vitamin D was measured by UV absorbance at 254 nm. Peak areas were integrated by a Waters model 730 data module, and the relative amounts were related to known concentrations of vitamin D_3 by reference to a standard curve. The normal range of serum vitamin-D concentrations in subjects living in Boston ranged from <0·5 ng/ml to 18 ng/ml (n=21). 25-Hydroxyvitamin D (25-OH-D) was measured in serum by the method of Preece et al.[11] after its extraction and sep-pak chromatography (normal range: 5–50 ng/ml). 1,25-Dihydroxyvitamin D (1,25-$(OH)_2$-D) was determined by a modification of the method of Eisman et al.[12] after serum extraction, sep-pak chromatography, and straight-phase HPLC (normal range: 27–61 pg/ml).

Results

Exposure to 0·054 J/cm^2 (1·5 MED) resulted in pronounced transient increases in serum vitamin-D concentrations in 2 Caucasian subjects. Serum concentrations of vitamin D rose from basal values of 0·5 and 6 ng/ml to peak values of 44 and 61 ng/ml, respectively, 1–2 days after irradiation (see accompanying figure, A). Vitamin-D concentrations then declined rapidly and reached basal concentrations by 7 days. Serum 25-OH-D concentrations increased (30–50% over basal concentrations) but remained



Changes in serum vitamin D.

In two lightly pigmented Caucasian (A) and three heavily pigmented Negro subjects (B) after total-body exposure to 0·054 J/cm^2 of UVR. (C) Serial change in circulating vitamin D after re-exposure of one Negro subject (● in panel B) to a 0·32 J/cm^2 dose of UVR.

entirely within the normal range, whereas 1,25-$(OH)_2$-D concentrations were unchanged over the three-week period. Exposure of three Negro subjects to 0·054 J/cm^2 UVR had little if any effect on circulating vitamin-D concentrations (fig., B). The greatest increase in vitamin-D concentration observed in any of the Negro subjects was 5 ng/ml, which occurred in one subject 2 days after irradiation. There were no significant changes in either 25-OH-D or 1,25-$(OH)_2$-D concentrations in any of the Negro subjects exposed at this dose level; however, when one of the Negro subjects was re-exposed to a 6-fold greater dose of UVR (0·32 J/cm^2), there was a clear-cut increase in serum vitamin-D concentration (fig., C). After this larger dose of UVR, the time course of appearance and disappearance of vitamin D was similar to that recorded in Caucasian subjects after exposure to UVR, but the peak concentration (29 ng/ml) was still below those seen in the Caucasian subjects exposed to 0·054 J/cm^2. The increase in serum vitamin D in the Negro subject after re-exposure to 0·32 J/cm^2 of UVR was accompanied by an increase in the 25-OH-D concentration from 10 ng/ml before exposure to 23 ng/ml on the seventh day post-irradiation. 1,25-$(OH)_2$-D concentrations did not change.

In some cases, re-chromatography of the vitamin-D fractions on reverse-phase HPLC was performed to separate the endogenously produced vitamin D_3 from the synthetic form, vitamin D_2, which can be obtained in the diet. The chromatograms showed that the increases in serum vitamin-D concentrations were entirely due to an increase in vitamin-D_3 concentrations.

Discussion

Exposure to sunlight is known to be important in maintaining adequate levels of vitamin D, but up to now it was not certain whether dark skin, per se, limited endogenous vitamin-D production. In 1922, Hess demonstrated that the same dose of UVR was more effective in curing rickets in

white rats than it was in black rats.[1] In addition, recent work from our laboratory,[3] which evaluated the formation of previtamin D_3 in human skin samples exposed in vitro to simulated solar radiation, showed that heavily pigmented skin required much longer exposure times to achieve maximum formation of previtamin D_3 than did lightly pigmented skin. These results suggested an inhibitory effect of melanin on vitamin-D synthesis, but Stamp et al. found that the increases in serum 25-OH-D concentrations in Negro and Asian subjects after repeated exposure to UVR were similar to those recorded in identically exposed White subjects, and he concluded that pigmentation had no significant effect on the cutaneous synthesis of vitamin D.[13] Our studies, which measured vitamin D itself, clearly demonstrate that the presence of melanin in high concentrations in skin markedly reduces the amount of vitamin D_3 that is made in vivo after a single exposure to a relatively small dose of UVR. However, our studies also show that increased pigmentation is not an absolute barrier to vitamin D_3 synthesis, inasmuch as re-exposure of one of the Negro subjects to a sixfold greater dose of UVR resulted in a pronounced increase in the vitamin-D_3 concentration followed by a small increase in the 25-OH-D concentration. It is likely, therefore, that the post-irradiation increase in serum 25-OH-D in pigmented subjects reported by Stamp et al. was the result of large, cumulative doses of UVR.

The re-emergence of rickets and osteomalacia among Negro infants in Northern cities in U.S.A.[5,6] and in Asian immigrants in Britain[7] suggests the possibility that dark skin could predispose to vitamin-D deficiency. Vitamin-D deficiency in both of these populations is probably due to a combination of factors including vegetarianism (low dietary vitamin-D intake) and reduced exposure to sunlight. From our studies, we speculate that increased skin pigment in these individuals would further increase their risk of developing vitamin-D deficiency.

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TOPICAL GLYCERYL TRINITRATE AS ADJUNCTIVE TREATMENT IN RAYNAUD'S DISEASE

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Summary The effects of topical glyceryl trinitrate in Raynaud's disease were compared with those of placebo in a double-blind, crossover trial in 17 patients with bilateral Raynaud's disease and an associated collagen disease, who were receiving oral sympatholytic agents at the maximum levels they could tolerate. 1% glyceryl trinitrate ointment or a placebo of lanolin was applied to one hand only for 6 weeks, then patients changed to the other preparation for 6 weeks. The results were evaluated every 2 weeks. The frequency of attacks, severity of attacks, and size of ulcers in the treated hand were significantly lower when the patients were using glyceryl trinitrate ointment than when they were using placebo. The treatment of Raynaud's disease may be improved by using topical glyceryl trinitrate ointment as an adjunct to a basic regimen of oral sympatholytic agents. Glyceryl trinitrate ointment may obviate the need for more aggressive treatment, such as intra-arterial reserpine, in selected patients.

Introduction

THE treatment of Raynaud's disease remains unsatisfactory, especially in patients with an associated collagen disease.[1] The effects of the various treatments are inconsistent, and their benefits are frequently not maintained.[2–4] Abnormalities of both the central sympathetic nervous system and local digital vessels are implicated in the vasospasm, but the exact contributions of the two types of abnormality in each patient are not well understood.[5] It seemed worth while to assess the clinical usefulness of commercially available glyceryl trinitrate ointment as a vasodilator in patients with Raynaud's disease.

Patients and Methods

In the trial there were 13 women and 4 men, aged 21–63 years, with bilateral Raynaud's disease diagnosed by the characteristic phasic colour changes, with or without pain, on exposure to cold. Patients had had symptoms for varying periods from 8 months to 10 years. All 17 patients had an associated collagen vascular disease: 13 patients had progressive systemic sclerosis (PSS); 3 patients had systemic lupus erythematosus (SLE); and 1 patient had rheumatoid arthritis (RA). All 13 patients with PSS were receiving either methyldopa (10 patients) or guanethidine (3 patients) at the maximum levels they could tolerate (methyldopa, 1–2 g/day; guanethidine, 10 mg/day) but still had persistent symptoms of Raynaud's disease. The drugs were maintained at the same levels for at least 1 month before and throughout the study. The 3 patients with SLE were receiving oral prednisone, and the patient with RA was receiving aspirin. The levels of these drugs were also maintained throughout the study period. 1 patient with PSS had undergone bilateral cervical sympathectomy 3 years before the study. All patients were having at least one episode of bilateral vasospasm per week on entry to the study.

Glyceryl trinitrate 2% ('Nitro-bid ointment', Marion Laboratories) was mixed with equal parts of lanolin to a final concentration of 1%. Initial trials with full strength (2%) preparations had been terminated owing to a high incidence of nitrite headache. The placebo preparation consisted of lanolin alone. Patients started with one preparation, and after 6 weeks each