Our assays, although less sensitive than the above direct chemical tests, are the first to examine teichoic acid. They also present a more in vivo-related picture, since plasma fibronectin may serve as a receptor for microbial colonization and, in the instance of macrophages, for host defense [3,9]. As we observed, fibronectin-coated *S. aureus* was still able to adhere to nasal cells, although in fewer number on the environmentally important, most external, fully keratinized cells. This information, with the knowledge that the teichoic acid blockage of nasal cells produces the same effect, suggests that fibronectin is a secondary nasal cell receptor for the *S. aureus* adhesin teichoic acid. However, our preliminary immunofluorescent and proteolytic enzyme studies (unpublished data) could not detect the glycoprotein. Perhaps its nonantigenic receptive portion [1,10,11] or a different surface molecule that acts like fibronectin may be found.

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Increased Concentrations of Arachidonic Acid, Prostaglandins E_2, D_2, and 6-oxo-$F_{1\alpha}$, and Histamine in Human Skin Following UVA Irradiation

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The buttock skin of clinically normal human subjects was subjected to approximately 2.5 minimal erythema doses of ultraviolet A irradiation. Deep red erythema developed during irradiation, faded slightly within the next few hours, increased to maximum intensity between 9–15 h, and decreased gradually thereafter although still persisting strongly at 48 h. Suction blister exudates were obtained at 0, 5, 9, 15, 24, and 48 h after irradiation as well as suction blister exudates from a contralateral control site and assayed for arachidonic acid, prostaglandins D_2 and E_2, and the prostacyclin breakdown product 6-oxo-prostaglandin $F_{1\alpha}$ by gas chromatography-mass spectrometry, and for histamine by radioenzyme assay. Increased concentrations of arachidonic acid and prostaglandins D_2, E_2, and 6-oxo-prostaglandin $F_{1\alpha}$ were found maximally between 5–9 h after irradiation, preceding the phase of maximal erythema. Elevations of histamine concentration occurred 9–15 h after irradiation, preceding and coinciding with the phase of maximal erythema. At 24 h, still at the height of the erythemal response, all values had returned to near control levels. Hence increased concentrations of arachidonic acid and its products from the cyclooxygenase pathway, and of histamine, accompany the early stages up to 24 h. A causal role in production of the erythema seems likely for these substances although other mediators are almost certainly involved.

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Abbreviations:
AA: arachidonic acid
BSTFA: *bis*-trimethylsilyltrifluoroacetamide
GC-MS: gas chromatography-mass spectrometry
HPLC: high-pressure liquid chromatography
MED: minimal erythema dose
PG: prostaglandin
UVA: 315–400 nm
UVB: 280–315 nm
UVC: 100–280 nm

Increased concentrations of arachidonic acid (AA) and prostaglandins D_2 (PGD_2), E_2 (PGE_2), $F_{2\alpha}$ ($PGF_{2\alpha}$), and the prostacyclin breakdown product 6-oxo-prostaglandin $F_{1\alpha}$ (6-oxo-$PGF_{1\alpha}$) have previously been demonstrated by quantitative

combined gas chromatography-mass spectrometry (GC-MS) in suction blister exudate from human skin subjected to 3 minimal erythema doses (MEDs) of UVB (280–315 nm) irradiation [1, 2]. These increases developed in parallel with the increase in inflammatory erythema, reaching a peak at 24 h, and thus seemed to have some role in production of the inflammation, even though it persisted past 48 h, at which stage the AA and PG elevations had virtually returned to normal. Similar changes have also been noted following 6 MEDs of UVC (100–280 nm) irradiation for AA, PGE_2, and $PGF_{2\alpha}$, the increased concentrations also returning essentially to normal by about 48 h, but in this case the inflammatory erythema was also fading, such that the causal role for the AA and PG seemed much more likely [3].

The effects of UVA (315–400 nm) irradiation on human skin have only recently been easily studied in detail following the development of equipment with high UVA output and minimal UVB contamination [4,5]. UVA has also been found to produce an inflammatory erythema, but with different characteristics, in that it usually develops during irradiation, fades slightly within a few hours before increasing to maximum intensity and persisting for hours to days thereafter, depending on dosage [4,5]. Its erythema is also a much deeper red in color than that of either UVB or UVC inflammation. Finally, UV radiation doses about 1000 times greater than for UVB or UVC are needed to produce visible inflammation. Associated mediator production in the UVA type of inflammation has not previously been investigated.

The previous studies of UVB- and UVC-associated mediator production [1,3] have included measurement of $PGF_{2\alpha}$, which seems not to be a marked proinflammatory agent [6,7] and it has not therefore been investigated on this occasion. However, prostacyclin (assayed as its breakdown product, 6-oxo-$PGF_{1\alpha}$) has been shown to have a marked inflammatory effect* and has been studied instead.

Increased histamine-like activity has also been noted at different stages following UVB irradiation [8,9]; the more recent work suggests that after 3 MEDs of UVB, marked increase in histamine activity occurs immediately following the onset of erythema at about 3–4 h after irradiation, with a gradual return to normal by 24 h. Hence histamine is also a possible mediator of the first 24 h of UVB inflammation.

MATERIALS AND METHODS

Subjects

Five female and 3 male fair-skinned normal volunteers aged 18–37 years (mean ± SEM 28.6 ± 2.4 years) on no medication were irradiated over a 9-cm field site on untanned clinically normal buttock skin. For the histamine study 5 additional subjects of similar type were also included.

Irradiation

A 2.5-kW xenon-arc source with an f/1.5 quartz condensing lens system was used as the UVA source. The radiation was filtered through 6 cm of an aqueous solution of 7% copper sulfate and 7% cobalt sulfate in a quartz-based chamber and through a Schott WG 335 filter of 1 mm thickness. It was then projected from a distance of 15 cm onto the skin in a uniform (± 10% variability) 9-cm circular field on one buttock using an f/4 quartz lens and a UVA dichroic mirror set at 45° to the incident beam (maximum reflectance between about 320–400 nm). The irradiance was measured at 200 W/m^2 with an Oriel 7102 thermopile. The spectral irradiance was measured using an International Light IL 783 spectroradiometer, showing the UVB irradiance to be at least 5 orders of magnitude less than that of the UVA (Fig 1).

Erythema

This was assessed visually. The MED to UVA was first determined by irradiating 8 1 cm-diameter sites with increasing doses of radiation, the lowest dose being 2×10^5 J/m^2 and the dose increment on each occasion being 20%. The smallest dose to produce erythema filling the irradiation site at 24 h was assessed as the MED. Irradiation as described above with approximately 2.5 MEDs (range 1–1.2 $\times$ 10^6 J/m^2) was then carried out for the mediator studies; the irradiation time was approximately 1½ h.

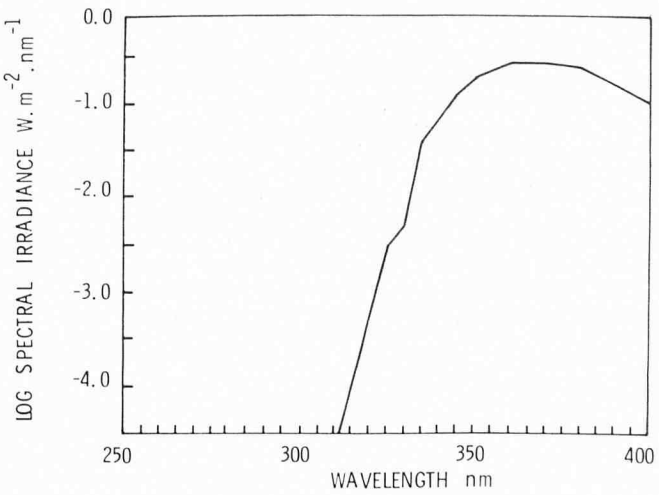

FIG 1. Spectral output of UVA irradiation apparatus.

Skin Temperature

This was measured on 3 subjects by means of a Digitec HT series 5810 thermometer. Measurements on irradiated sites during and after irradiation and on control sites, both normal and erythematous, were made.

Inflammatory Exudate

Exudate varying between 40–400 µl was obtained from suction blisters raised on erythematous skin. These were obtained by continuous application of suction through a special cup at 300–350 mm below atmospheric pressure [10]. The fluid took about 2–3 h to accumulate on each occasion and was aspirated at 5, 9, 15, 24, and 48 h after irradiation. In addition, zero time samples were taken by irradiating previously raised suction blisters on the normal buttock skin. The blister fluid was removed immediately after completion of the irradiation. Finally, control fluid was obtained from contralateral nonirradiated buttock skin.

Assay of Suction Blister Exudate

Skin exudates were equilibrated with 25 ng [3,3′,4,4′-^{2}H]-PGE_2, 25 ng [3,3′,4,4′-^{2}H]-6-oxo-$PGF_{1\alpha}$, 50 ng [5,6,8,9,11,12,14,15-^{2}H]-AA, and 0.006 µCi [5,6,8,9,12,14,15-^{3}H]-PGD_2, sp act 100 Ci/mmol. Each exudate was diluted to 2 ml, acidified to pH 3.5 with acetic acid, and extracted 3 times with 2 ml ethyl acetate. The bulked extracts were taken to dryness by evaporation under nitrogen.

AA and PGs were separated by high-pressure liquid chromatography (HPLC). The ethyl acetate extracts were dissolved in 60 µl solvent and applied to a Hibar LiChrosorb-Si60 silica column 250 × 4 mm, eluted by acetonitrile:methanol:acetic acid 100:3:1 (v/v) at 1.5 ml/min. Fractions containing AA, PGD_2, PGE_2, and 6-oxo-$PGF_{1\alpha}$ were collected and taken to dryness under nitrogen. The chromatography was calibrated using authentic radioactive standards which were located in the column eluate by collection and counting of 0.1-ml fractions. [1-^{14}C]-AA, [^{3}H]-PGD_2, [1-^{14}C]-PGE_2, [5,8,9,11,12,15-^{3}H]-6-oxo-$PGF_{1\alpha}$ were eluted by 2.9, 3.8, 5.2, and 6.1 ml of solvent, respectively.

Fractions containing AA and PGE_2 were converted to their corresponding methyl esters using diazomethane.

Methyl arachidonate fractions were rechromatographed on a Hibar LiChrosorb-RP18 reversed phase column, 250 × 4 mm. The solvent was methanol:water 95:5 (v/v) at 1 ml/min and a single fraction corresponding to authentic methyl arachidonate was collected.

Methyl PGE_2 samples were dissolved in 10 µl *bis*-trimethylsilyltrifluoroacetamide (BSTFA):piperidine 1:1 (v/v) and heated at 50°C for 60 min to give the PGE_2-methyl ester-trimethylsilyl ether-enol derivative [11].

The 6-oxo-$PGF_{1\alpha}$ *o*-methyloxime-trimethylsilyl ether-methyl ester was prepared as previously described [2]. Radioactivity in a 0.1 aliquot of each PGD_2 fraction from the HPLC was measured by scintillation

* Higgs EA, O'Grady J, Thrower PA, Moncada S: Prostacyclin: inflammatory effects in human skin. Presented at the Fourth International Prostaglandin Conference, Washington DC, 1979.

counting. A comparison of the [^{3}H]-PGD_2 found with that added gave the recovery of PGD_2 after extraction and HPLC. The remaining PGD_2 in each sample was reduced with sodium borohydride and the products purified by thin-layer chromatography as previously described [1]. The resulting $PGF_{2\alpha}$ was converted to the trimethylsilyl ether-trimethylsilyl ester using BSTFA.

The derivatives were analyzed by GC-MS using selective ion recording. Methyl arachidonate and the PGE_2 derivative were chromatographed on a 1 m × 2 mm 3% OV-101 on Chromosorb W HP column at a temperature of 220°C for PGE_2. The carrier gas was helium. The effluent was passed through a jet separator to a VG305 mass spectrometer and 2025 data system. The mass spectrometer was operated in the electron impact mode, source temperature was 200°C and electron energy 40 eV. The ions monitored were m/z 318 and 326 for methyl arachidonate and m/z 492 and 496 for the PGE_2 derivative.

The 6-oxo-$PGF_{1\alpha}$ and $PGF_{2\alpha}$ (formed from PGD_2) derivatives were chromatographed on a 12.5-m SE-30 fused silica column. Helium flow was 2 ml/min and temperature 250°C. A Ross solids injector was used. The effluent passed directly to a Riber 1010C mass spectrometer with a Sirdar data system. Source temperature was 130°C and electron energy 70 eV. The ions measured were m/z 481 and 485 for $PGF_{2\alpha}$ and m/z 570 and 574 for 6-oxo-$PGF_{1\alpha}$. Suitable deuterium/protium calibration curves were prepared for each compound.

Histamine was measured using a radioenzyme assay that is specific and sensitive to 0.1-ng amounts. The sample to be assayed was incubated with [^{14}C]S-adenosylmethionine (Sigma) in the presence of histamine methyltransferase, and the reaction product [methyl-^{14}C]-histamine was extracted in chloroform and the radioactivity counted on a scintillation counter [12,13].

Statistical analyses were performed using Student's *t*-test.

RESULTS

Erythema

Erythema became visible during irradiation and was deep red in color by completion. It faded slowly over the next few hours before intensifying to reach a maximum between 9–15 h after which it gradually decreased in intensity. However, it was still markedly evident at 48 h.

Skin Temperature

In 1 subject, the temperature of normal unirradiated skin was 31.4°C, while that of erythematous skin irradiated with 2½ MEDs of UVA 24 h earlier was 34°C. In the same subject, irradiated skin was 36.6°C during irradiation and 34.8°C 5 min after irradiation. Two other subjects respectively had normal unirradiated skin temperatures of 31.0 and 30.3°C, rising to 35.1 and 34.8°C during irradiation and falling to 31.0 and 31.3°C after irradiation.

Arachidonic Acid and Prostaglandins

The concentrations of AA, PGD_2, PGE_2, and 6-oxo-$PGF_{1\alpha}$ measured by GC-MS at 0, 5, 9, 15, 24, and 48 h after UVA irradiation and in control skin are shown in Table I. Increased amounts of all these substances were found 5–15 h after UVA irradiation. The rise in AA from 2122 ± 342 to 3597 ± 795 ng.ml^{-1} (mean ± SEM) was small ($0.05 < p < 0.1$). The increases in PG concentrations were more marked, each being significantly elevated by 9 h, declining somewhat by 15 h, and returning virtually to control levels by 24 h. PGE_2 rose from a control value of 36.9 ± 12.0 ng.ml^{-1} to 102.3 ± 32.3 ng.ml^{-1} at 5 h and 94.2 ± 22.5 ng.ml^{-1} at 9 h ($p < 0.05$). PGD_2 increased from 46 ± 10 ng.ml^{-1} to 180 ± 40 ng.ml^{-1} at 9 h ($p < 0.005$). Prostacyclin (assayed as 6-oxo-$PGF_{1\alpha}$) went up from 5.7 ± 1.7 ng.ml^{-1} to 26.5 ± 10.4 ng.ml^{-1} at 5 h and 17.3 ± 2.8 ng.ml^{-1} at 9 h ($p < 0.005$).

Histamine

Histamine concentrations rose from a mean base line level of 3.3 ng.ml^{-1} to 7.4 ± 2.8 ng.ml^{-1} at 9 h and 13.6 ± 8.6 ng.ml^{-1} at 15 h, with a return to baseline values by 24 h.

DISCUSSION

Our findings show elevations of AA, PGs, and histamine in association with the erythema due to long-wavelength ultraviolet (UVA) irradiation. That these elevations were the direct result of photochemical processes and not simply heat effects is suggested by the very small rise in skin temperature accompanying the irradiation. There were both similarities and differences by comparison with the erythema due to irradiation with short- and medium-wavelength ultraviolet (UVC and UVB, respectively). AA and PGE_2 reached maximum concentrations at 18–24 h in both UVC and UVB erythema. In contrast, the present results indicate that the peak rises occur much earlier in UVA erythema, at around 5–9 h. UVA also caused an early rise in PGD_2 and 6-oxo-$PGF_{1\alpha}$ (about 5 h for UVA compared with about 6 h for UVB and UVC).

These pharmacologic differences correspond closely with differences in the clinical time course of the UV inflammatory reactions since the erythemal response to UVA appears and develops earlier than that due to UVC or UVB. They thus lend further support to the view that the earlier stages of UV erythema are mediated by the PG products of AA metabolism. At 48 h, PG activity is at or near baseline levels whatever the wavelength of UV radiation and despite persistence of the erythema at this time. Increased histamine activity has been shown previously in UVB erythema [8,9]. In the present study, increases in histamine activity occurred to a variable extent after UVA irradiation and, when present, were associated with the early phase of the erythemal reaction. Its relationship both to the erythema and to the associated increase in PG activity is unknown.

We conclude that increased PG activity is a consistent accom-

TABLE I. *Concentration of AA, PGE_2, PGD_2, and 6-oxo-$PGF_{1\alpha}$ in human skin exudates following 2.5 MEDs of UVA irradiation*

	Concentration of metabolite (ng.ml^{-1}) (mean ± SEM)						
	Control	0 h	5 h	9 h	15 h	24 h	48 h
AA	2122 ± 342 n = 7	2455 ± 324 n = 4 .6 > *p* > .5	3597 ± 795 n = 6 .1 > *p* > .05	3561 ± 1041 n = 5 .2 > *p* > .1	2577 ± 369 n = 7 .4 > *p* > .3	2389 ± 439 n = 7 .7 > *p* > .6	1917 ± 547 n = 4 .8 > *p* > .7
PGE_2	36.9 ± 12.0 n = 8	36.4 ± 11.3 n = 7 1.0 > *p* > .975	102.3 ± 32.3 n = 7 .1 > *p* > .05	94.2 ± 22.5 n = 7 .05 > *p* > .025	59.8 ± 20.4 n = 7 .4 > *p* > .3	61.8 ± 16.4 n = 7 .3 > *p* > .2	24.5 ± 10.4 n = 4 .6 > *p* > .5
PGD_2	46 ± 10 n = 8	38 ± 8 n = 7 .6 > *p* > .5	161 ± 42 n = 7 .02 > *p* > .01	180 ± 40 n = 7 .005 > *p* > .001	127 ± 61 n = 7 .2 > *p* > .1	56 ± 10 n = 6 .6 > *p* > .5	31 ± 15 n = 4 .4 > *p* > .3
6-oxo-$PGF_{1\alpha}$	5.7 ± 1.7 n = 8	4.5 ± 0.9 n = 7 .6 > *p* > .5	26.5 ± 10.4 n = 7 .1 > *p* > .05	17.3 ± 2.8 n = 7 .005 > *p* > .001	11.1 ± 1.9 n = 7 .1 > *p* > .05	9.2 ± 1.8 n = 7 .2 > *p* > .1	2.8 ± 0.6 n = 4 .3 > *p* > .2

TABLE II. *Concentration of histamine in human skin exudates following 2.5 MEDs of UVA irradiation*

Concentration of histamine ($ng.ml^{-1}$) (mean ± SEM)					
1 h	5 h	9 h	15 h	24 h	48 h
5.0 ± 2.1	4.6 ± 1.7	7.4 ± 2.8	13.6 ± 8.6	2.0 ± 0.4	0.7 ± 0.7
n = 4	n = 7	n = 8	n = 8	n = 15	n = 3

Average baseline value = 3.3 $ng.ml^{-1}$ (range 0–6 $ng.ml^{-1}$).

paniment of irradiation of skin over the whole UV wavelength spectrum and we suggest that this activity plays an important role in the onset and development of the earlier stages of the inflammatory response. This response should therefore be reduced by administration of cyclooxygenase inhibitors, e.g., indomethacin, and although one previous study [14] has not confirmed this, further such work needs to be undertaken. The mediators of the later stages of the inflammatory response remain unknown and further work is required to elucidate their nature.

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Noninvasive Assessment of Local Nicotinate Pharmacodynamics by Photoplethysmography

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The local pharmacodynamics of a topical vasodilator (methyl nicotinate) has been followed noninvasively using photopulse plethysmography. This technique is sensitive to changes in blood flow through the cutaneous microcirculation and responds to the pharmacologic stimulus of the vasoactive agent employed. Five different application sites for the drug were studied and the time course of the local effect (i.e., onset, duration, and decay) was recorded. The applied amount of drug elicited, within a short period, a response which was saturable such that the observed increase in blood flow reached a plateau level. The decay of the elevated perfusion required approximately 1 h, suggesting a half-life for elimination of the drug from the skin of about 10 min. This result agrees closely with other reported values and suggests that the pharmacodynamic measurements of this study may prove useful in elucidating aspects of dermal pharmacokinetics.

Information about the time course of drug behavior at and within the region of topical application is of considerable importance to the rational design of dermatologic therapy for use in the clinical situation. A convenient way to investigate in vivo the cutaneous action of vasodilatory or vasoconstrictive drugs is through their effects on the cutaneous microcirculation. Among the currently available techniques [1], which include direct visualization, plethysmography in its various forms, thermal measurements, dye techniques, radioisotope clearance methods, and laser Doppler spectroscopy [2], photoplethysmography (PPG) [3] offers certain distinct advantages over many of the alternative methods. In PPG, a small probe that

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Abbreviations:
PPG: photoplethysmography
PWA: pulse wave amplitude