The acute clinical effects of solar ultraviolet radiation (UVR) on human skin have been well described, especially the minimal erythemal dose; SSR, solar-simulated radiation. The mechanisms of UVR-induced inflammation are incompletely understood (Clydesdale et al, 2001) but there is increasing evidence that cutaneous nerve cells may play a part by the UVR-induced release of neuropeptides and neurotransmitters such as calcitonin gene-related peptide (CGRP) and \( \alpha \)-melanocyte-stimulating hormone (Seiffert and Granstein, 2002).

In addition to inflammation it is commonly appreciated that UVR frequently gives rise to altered skin pain sensitivity. Notably, sunburnt skin exhibits tenderness in which the threshold for applied stimuli to produce pain is reduced (allodynia) and the degree of pain elicited by suprathreshold stimuli is enhanced (hyperalgesia) and this is seen with both mechanical and thermal stimuli. For simplicity we refer to these changes here as hyperalgesia. This type of hyperalgesia is observed in a variety of inflammatory conditions (reviewed in Raja et al, 1999) and it can be of considerable clinical importance. The mechanism of such hyperalgesia is not fully understood. It may arise because of a sensitization of the nociceptive sensory neurons innervating inflamed tissue and it may have a contribution from altered spinal cord processing of sensory information (Julius and Basbaum, 2001). The peripheral mediators of hyperalgesia are also not well characterized. A large number of inflammatory mediators, such as prostaglandins, leukotrienes, bradykinin, and nerve growth factor can produce some forms of sensory neuron sensitization, but it is not known which are specifically responsible (see Levine and Reichling, 1999). The nonsteroidal anti-inflammatory drugs target prostaglandin synthesis, but the limited effectiveness of these drugs in many clinical conditions argues for the involvement of other mediators. The hyperalgesia associated with sunburn was first reported by Harrison et al (1996) and has been little studied since. Apart from providing a better understanding of fundamental pain mechanisms, the definition of such changes is important for the development and assessment of effective treatments for sunburn, and perhaps other inflammatory conditions of the skin. One recent study

Abbreviations: CGRP, calcitonin gene-related peptide; MED, minimal erythemal dose; SSR, solar-simulated radiation

Ultraviolet Radiation-Induced Inflammation as a Model for Cutaneous Hyperalgesia

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The effects of UVA-I and solar simulated radiation on skin sensitivity to thermal and mechanical stimuli were compared in normal volunteers. Individual minimal erythema doses (MED) for each source were determined and previously unexposed buttock skin was exposed to 1, 2 and 3 MED of each spectrum. Erythema, and mechanical and thermal pain thresholds were quantified from 3 to 72 hours post-irradiation. Irradiated skin did not exhibit pain but hyperalgesia and allodynia were provoked by the applied stimuli after exposure to 2 or 3 MED. There were highly significant decreases in thresholds for both stimuli in exposed skin compared with non-exposed skin. These changes began within a few hours of irradiation, peaked about 24 hours later and persisted throughout the test period. The sensitivity changes broadly followed the erythema response and did not extend beyond the irradiated area. There were only minor differences between the two spectra at comparable erythemal doses. These data demonstrate the usefulness of UVR-induced inflammation as a model of cutaneous hypersensitivity. This model has clinical relevance for the study of hyperalgesia in general and the abnormal sensitivity of sunburnt skin in particular. It is likely to be useful in the assessment of peripherally acting analgesic drugs.

Key words: erythema/pain threshold/sunburn/ultraviolet radiation.

The acute effects of solar ultraviolet radiation (UVR) on human skin have been well described, especially inflammation manifest as erythema/sunburn that is maximal at about 18 to 24 h after exposure to solar-simulated radiation (SSR) (Young et al, 1996; Harrison and Young, 2002). Several laboratories have shown that UVR exposure increases skin blood flow (Young et al, 1985; Diffey et al, 1987; Frodin et al, 1988; Andersen et al, 1991; Benrath et al, 2001). The wavelength dependency (action spectrum) for human erythema has been characterized (McKinlay and Diffey, 1987), most recently by Anders et al (1995) and Young et al (1998), and it has been established that UVB (280–320 nm) is 2 to 4 orders of magnitude more effective per unit UVR dose than UVA (320–400 nm). Analysis of action spectra for erythema suggests different chromophores for erythema induced by UVB and UVA (Anders et al, 1995). One study showed that UVA-induced erythema is oxygen dependent (as are many UVA responses) and that UBV-induced erythema is oxygen independent (Auletta et al, 1986).

The mechanisms of UVR-induced inflammation are incompletely understood (Clydesdale et al, 2001) but there is increasing evidence that cutaneous nerve cells may play a part by the UVR-induced release of neuropeptides and neurotransmitters such as calcitonin gene-related peptide (CGRP) and \( \alpha \)-melanocyte-stimulating hormone (Seiffert and Granstein, 2002).
reported the hyperalgesia associated after exposure to broad-spectrum UVR (Benrath et al, 2001). Two other recent studies reported a decrease of heat and mechanical pain thresholds in human skin after exposure to 3 minimal erythema doses (MED) of UVB radiation (Bickel et al, 1998; Hoffmann and Schmelz, 1999) but stated that limited doses of UVA had no effect. Here, we report on the time-course and dose dependence of sensory changes in the skin of sun-sensitive volunteers (skin types I/II) after exposure to clinically relevant doses of SSR and with comparable levels of erythema induced by UVA-I (340–400 nm). We were interested in determining if erythema per se is a reliable indicator of skin sensitivity, especially as it has been suggested that a UVA-induced erythema is not a sunburn (Willis and Cylus, 1977) because sunburn cells (apoptosis), typical of UVB, were not observed in the epidermis.

Some forms of inflammatory stimuli induce widespread sensory changes, extending well outside the treated area (Raja et al, 1999). We wished to determine whether the sensory changes occurring in UVR-induced inflammation colocalized with inflammatory responses or were more widespread, as this has both theoretical and practical implications for the interpretation of our data (see Discussion).

Results

Study I: Time-course and dose–response of thermal and mechanical hyperalgesia As expected, the irradiated sites showed a progressive reddening for about 24 h. At 24 h, skin exposed to a 1 MED SSR or UVA-I showed clear erythema with a boundary matching the area irradiated. Skin exposed to 2 and 3 MED also sometimes showed edema. No irradiated skin developed blisters, and volunteers did not report ongoing (unprovoked) pain at any of the sites. The erythema gradually faded over the next few days. The only apparent longer-term sequela of irradiation was tanning of the skin at irradiated sites.

The time-courses of changes in erythema and skin sensitivity after SSR and UVA-I Figure 2 shows the mean changes in erythema (Fig 2a), thermal pain threshold (Fig 2b), and mechanical pain threshold (Fig 2c) on sites exposed to 3 MED SSR and UVA-I. Erythema developed with both spectra, but with slightly different time courses. The SSR induced a more rapidly rising erythema, first significantly different (p < 0.001) from unirradiated sites at 3 h, and peaking at 24 h. UVA-I induced erythema developed more slowly, and did not peak until 48 h with this dose. The magnitude of erythema (measured as skin reflectance) was significantly higher (p < 0.001) for SSR than for UVA-I with a 3 MED dose at all time points except 3 and 48 h. Comparable results were obtained with 2 MED except that significant differences (p < 0.001) between the two sources were only seen at 6 and 9 h (data not shown).

As erythema developed there were very marked changes in thermal and mechanical pain thresholds. The thermal thresholds (Fig 2b) dropped progressively over the observation period. The mean peak decrease at 3 MED (± SEM, n = 12) were 7.3 ± 0.8°C for UVA-I and 6.2 ± 0.8°C for SSR at 24 and 48 h, respectively. These were significantly different (p < 0.001) from control skin (mean threshold = 45.8 ± 0.7°C). This thermal hyperalgesia reduced the thermal threshold to only a few degrees above normal skin temperature. The onset of thermal hyperalgesia developed quicker for UVA-I than for SSR (in contrast to the onset of erythema). As shown in Fig 2(b), there were significant differences between the spectra at 3, 6, and 24 h. After 24 h, the maximal thermal hyperalgesia was approximately maintained for both UVA-I and SSR for the remainder of the testing period. Sites treated with 2 MED showed similar time courses for the onset of hyperalgesia but with some reversal at 72 h (data not shown).

As shown in Fig 2(c), skin treated with 3 MED became hyperalgesic to mechanical stimuli with a time course that closely paralleled the development of erythema and there were no significant differences (p > 0.5) between the two spectra. Thus, mechanical threshold appeared to drop slightly faster for the SSR irradiated skin and became significantly different from control (p = 0.02) at 6 h. Mechanical hyperalgesia progressively increased in magnitude, reaching a maximum after 48 h. The average mechanical threshold (± SEM, n = 6) at control sites was 95.2 ± 5.0 g. At 24 h this had decreased to 26.7 ± 10.9 g and 31.7 ± 12.9 g for SSR and UVA-I, respectively. The mechanical hyperalgesia reached an approximate plateau for the remainder of the observation period. The drop in threshold was sufficiently pronounced that brushing the irradiated skin was sufficient to elicit pain in most volunteers (i.e., allodynia). The degree of mechanical hypersensitivity was uniform across the 3 MED site. Skin exposed to lower UVR doses showed a lesser effect but a similar time course of onset of hyperalgesia (data not shown). With 1 MED, mechanical hyperalgesia was less consistently observed, although when present it too appeared to be maximum 24 h after irradiation.

The statistical analyses, based on delta data, showed that for erythema there was a significant effect of time, source, and interaction between time and source. For heat pain, there was a significant effect of time, source but no interaction between time and source. In the case
of mechanical pain, there was a significant effect of time (9–72 h) but no interactions.

**The dose–response for erythema and hyperalgesia with SSR and UVA-I**

Figure 3 shows the mean changes in erythema (ΔEI) (Fig 3a), thermal pain threshold (Fig 3b), and mechanical pain threshold (Fig 3c) 24 h after irradiation (i.e., approximately peak changes) for different doses of SSR and UVA-I. All three parameters show a strong dose-dependency and this is statistically significant (p < 0.05). Figure 3(a) shows very comparable levels of 24 h erythema with 1 and 2 MED SSR and UVA-I; however, a clear plateau is seen with 3 MED UVA-I (at which edema was noted in a majority of volunteers), whereas increased erythema is seen with 3 MED SSR. Figures 3(b) and 3(c) show comparable 24 h mean dose–response curves for SSR and UVA-I-induced increases in skin sensitivity to heat and mechanical pain, respectively.

Statistical analyses showed a significant effect of SSR and UVA-I dose and source, and interaction between dose and source for erythema. The heat pain data show a significant effect of dose (p < 0.01) and an interaction between dose and source, but no effect of source. In the case of mechanical pain, there was a significant effect of dose (p < 0.05) but not effect of source or interaction between dose and source.

**Study II: Spatial distribution of mechanical hyperalgesia**

Figure 4 shows that, as expected, the mechanical pain threshold fell by about 50% within the irradiated area. Sites B and C are significantly different from sites A, D, E, and F (p < 0.001), even though site D is 3 mm from site C. In summary, the data show that mechanical hyperalgesia is highly localized to the area of inflammation.
Discussion

Our results show that SSR and UVA-I result in marked increases in skin sensitivity to thermal and mechanical stimuli. This sensitization can be so severe that moderate heating of the skin or gentle touch can produce pain. Our findings with SSR are in agreement with previously published work (Hoffmann and Schmelz, 1999; Benrath et al, 2001). That is, doses in excess of 1 MED lead to hyperalgesia that develops over several hours, peaks at about 24 h and then slowly declines over several days, at a rate that depends on the initial dose. We found the changes in skin sensitivity paralleled the erythema associated with SSR. The study by Benrath et al (2001) suggested that the erythema has two phases, one peaking at 12 h and the second at 36 h. This study and other studies (Young et al, 1985; Frodin et al, 1988; Andersen et al, 1991; Hoffmann and Schmelz, 1999; Harrison and Young, 2002) have observed a monophasic response, and it is not clear if this discrepancy relates simply to the sampling intervals used in the different studies. In any case, the sensory changes observed by Benrath et al (2001) were also monophasic. The SSR doses we examined are clinically relevant and could be obtained from summer sun within an hour or so at temperate latitudes.

Previous studies have concluded that UVA produces very limited hyperalgesia (Bickel et al, 1998; Hoffmann and Schmelz, 1999); however, both of those studies used very low doses. Bickel et al (1998) compared UVB and UVA. The UVB dose was defined as 3 MED. The UVA protocols were not clearly defined but appear to have been suberythemal. To compare the effects of UVA and the UVB content of SSR we chose to use comparable erythema doses. Whereas the mechanisms of UVA and UVB inflammation may differ (Auletta et al, 1986), we found that skin sensitization was broadly similar for UVA-I and SSR. The time-courses for SSR and UVA-I-induced changes in skin sensitivity were very similar as shown in Fig 2(b,c). Furthermore, the 24 h SSR and UVA dose–response curves for induced sensitivity to both heat and mechanical pain were very similar. Such UVA doses are higher than would normally be obtained from sunlight. Interestingly, as shown in Fig 3(a), the level of UVA erythema did not appear to increase between 2 and 3 MED (unlike SSR). This may have been a consequence of edema induced at this dose.

UVB accounts for under 10% of the UVR in the SSR source; however, when the SSR emission spectrum is biologically weighed with the CIE action spectrum for erythema (McKinlay and Diffey, 1987) the UVB accounts for about 90% of the erythemal efficacy of the SSR spectrum. The relationship between erythema (by SSR and UVA) and change in skin sensitivity suggests that it is primarily the UVB content of SSR that is responsible for its observed effects and obviously, conclusions about differences in the effects of UVB and UVA can only be drawn when erythemally equivalent doses are given.

There is evidence from experimental and action spectrum studies to suggest that the mechanisms of UVB- and UVA-induced erythema are different (Auletta et al, 1986; Anders et al, 1995) even though the slopes of the dose–response curves for UVB- and UVA-induced erythema are similar (Diffey and Farr, 1991). Our data suggest, however, that irrespective of differences in mechanism, the consequences as assessed by skin sensitivity are similar. We feel that this means that a UVA-induced erythema can be defined as a sunburn, contrary to the suggestion made by Willis and Cylus, (1977) whose definition was based on the lack of characteristic UVB-induced epidermal apoptosis after UVA exposure. Our data show that comparable degrees of erythema, whether caused by SSR (i.e., primarily by UBV) or UVA-I, result in comparable “tenderness” to mechanical and thermal stimuli. This “tenderness” is surely more important to the person with the sunburn than the histologic changes in the epidermis.

The mechanism of hyperalgesia is not revealed by these studies. It is known, however, that several algogenic chemicals are released with UVR-induced inflammation (Hruza and Pentland, 1993; Clydesdale et al, 2001). Several prostaglandins, including D2, E2, and F2 (Rhodes et al, 2001), appear in UVR inflammation within a few hours and some persists for several days. Prostaglandin E2 is capable of sensitizing the peripheral terminals of nociceptors to thermal stimuli (Levine and Reichling, 1999) and so could contribute to UVR-induced hyperalgesia. There is some evidence that cyclooxygenase inhibitors applied topically to UVR-inflamed skin can reduce some of the hyperalgesia (Bayerl et al, 1998). Several other inflammatory mediators are released in UVR-exposed skin, including histamine, bradykinin, cytokines, such as interleukins 1 and 10, tumor necrosis factor α, and nerve growth factor (Barr et al, 1999; Seiffert and Granstein, 2002). Again there is abundant

![Figure 4](https://example.com/figure4.png)

**Figure 4**

SSR-induced changes in sensitivity to mechanical pain are localized. A ring of skin was exposed to 3 MED SSR (a). Sensitivity to mechanical pain was assessed inside (A), within (B,C) and varying distances outside (D–F), the ring at 24 h. The sensitivity to pressure data (b) shown are mean ± SEM.
evidence that these mediators can induce sensitization in some nociceptors. There is also abundant evidence that nerve growth factor contributes to the hyperalgesia associated with many types of inflammation (McMahon and Bennett, 1999). Benrath et al (2001) have suggested that the sensory neuropeptides substance P and CGRP are released from nociceptors and contribute to the later phase of UVR-induced hyperalgesia. These agents are also thought to be involved in immunosuppression by UVR (Seiffert and Granstein, 2002). Whatever the mediators, a likely molecular mechanism for thermal hyperalgesia is the sensitization of transient receptor potential (TRP) channels expressed in primary afferent nociceptors. Most notably, the sensitization of TRPV1 (formerly vanilloid receptor 1, VR1) leads to a marked increased in heat sensitivity (see Di Marzo et al, 2002).

A particularly interesting issue is the cause of mechanical hyperalgesia, which was frequently marked to the extent that a light touch or brush-elicited pain (i.e., allodynia). Whereas a great many factors have been shown to induce a peripheral sensitization of cutaneous nociceptors to thermal stimuli, there are only occasional reports of mechanical sensitization in these fibers. There is a very considerable body of work showing that activity in nociceptors can trigger changes in the central (particularly spinal cord) processing of sensory information, and that this so-called central sensitization can account for some forms of mechanical hyperalgesia (Woolf and Salter, 2000). Because the central representation of the body surface has a finite resolution, however, centrally mediated mechanical hyperalgesia (also referred to as secondary hyperalgesia) is seen to extend beyond the boundaries of tissue injury (Raja et al, 1999). It is striking that the mechanical hyperalgesia seen with sunburn is restricted to the exact area of UVR exposure, as we explicitly examined and reported in this study. This very strongly suggests that the mechanism of this hyperalgesia is peripheral sensitization of nociceptors and that there must therefore be one or more peripheral mediators responsible for triggering it. As mechanical hyperalgesia is a common clinical problem associated with many disorders, identification of such mediators is likely to be of considerable clinical use and UVR inflammation offers the potential to do so.

Together, the current data demonstrate the usefulness of UVR-induced inflammation as a model of primary hyperalgesia. It is possible to use this stimulus quantitatively. Volunteers experience little or no discomfort during the irradiation and subsequently, whereas the skin becomes tender, there is no evidence of spontaneous tissue injury or pain. Multiple sites can be exposed, closely sited, and with different degrees of inflammation. Sensory changes are extremely robust and subjects are easily blinded with respect to treatments. Sunburn-associated hyperalgesia has self-evident clinical relevance in itself, and it can be used to study inflammatory hyperalgesia in general. UVR inflammation can be used for the assessment of peripherally acting analgesic drugs.

Materials and Methods

Volunteers and studies Eighteen adult volunteers of skin types I/II were identified by phenotype and questionnaire. They gave informed consent to take part in the study that was approved by the Ethics Committee of St Thomas’ Hospital, London, UK. The studies conformed to Declaration of Helsinki guidelines. All volunteers were healthy and not on any medication. The test sites were on previously unexposed buttock skin.

There were two studies and the population demographics are given in Tables I and II, respectively.

In study I, we assessed the dose- and time-dependent effects of SSR and UVA-I on the same 12 volunteers. The endpoints were changes in skin sensitivity to thermal and mechanical stimuli. In study II, we determined if any changes in skin sensitivity, to a mechanical stimulus, were localized to the site of irradiation. In six volunteers (and in different experiments from those described in study I) we irradiated an annulus of skin (Fig 4) with 3 MED of SSR. The annulus was 60 mm in diameter and had a 20 mm central unirradiated zone. Twenty-four hours after irradiation, we tested the mechanical sensitivity at sites illustrated in Fig 4 across the irradiated zone.

UVR sources and dosimetry SSR was obtained from a Solar Simulator (Oriel, Stratford, Connecticut) using a 1 kW xenon arc lamp (ORC Lighting Products, Azusa, California) in conjunction with a quartz collimator, quartz lens and a Schott WG320 filter (1 mm thick). Irradiance was routinely measured with a wide-band thermopile radiometer (Medical Physics, Dryburn Hospital, Durham, UK) calibrated with a double-monochromator spectroradiometer (DM150, Bentham, Reading, UK), which had been calibrated against a National Physics Laboratory (NPL) standard lamp. Irradiance was about 15 mW cm⁻² scanned between 280 and 400 nm (UVB 280–320 nm accounting for 8.5% of total output) at the skin surface (a distance of 11 cm). Broad-spectrum UVA-I (340–400 nm) was obtained from a UVASUN2000 (Mutzas, Munich, Germany). Routine irradiance was measured with an IL 442 radiometer (International Light, Newburyport, MA) and calibrated in the same way as the thermopile used for SSR. Irradiance was 78 mW cm⁻² (over the spectral range 340–400 nm) on skin surface (a distance of 10 cm); 98.88% of total output was UVA-I (340–400 nm), 1.11% was UVA-II (320–340 nm), and 0.01% was UVB (280–320 nm). The SSR and UVA spectra are shown in Fig 1.

Irradiation protocol Individual sensitivity to UVR was assessed by the determination of the MED defined as the dose required to produce a definite border erythema 24 h after exposure. This was done by exposing six 1 cm² areas of previously unexposed buttock skin to a UVR dose series with ×2 increments. The pain sensitivity studies were also performed on previously unexposed buttock skin. In study I, sites (2.5 cm × 2.5 cm) were irradiated with 1, 2, and 3 MED SSR on one buttock and with UVA-I on the other. Levels of erythema and pain thresholds to thermal and mechanical stimuli were assessed at each site 3, 6, 9, 24, 48, and 72 h after exposure. The irradiation room was air conditioned at 20 °C and a fan was positioned to blow over the UVA-I irradiated site to minimize any increases in skin temperature. In study II, the effects of 3 MED SSR were assessed at 24 h. The experimental detail is given in Fig 4.

Monitoring the biologic effects of UVR

Erythema Erythema expressed as the erythema index (EI) was measured with a reflectance device (Dia-stron, Andover, UK). The EI is log₁₀(reflected red light (reference spectrum)/reflected green light (which is absorbed by hemoglobin)) (Diffey et al, 1984). Triplicate readings were taken at each site. A control reading from an adjacent nonexposed site was always taken and subtracted on an individual basis from the values taken at irradiated sites. This value is referred to as ΔEI.

Skin sensitivity to thermal and mechanical stimuli Sensitivity of irradiated and control skin was determined by monitoring the pain threshold to graded thermal and mechanical stimuli. Prior to any
experimentation, the volunteers had a training session to familiarize themselves with the sensations caused by the test systems and define their levels of heat and mechanical pain thresholds. At this point the challenge was stopped. Volunteers could not see and were unaware of the specific UVR treatments to the test sites, including a nonirradiated control site on each buttock.

Sensitivity to thermal challenge was assessed with a TSA-2001 Thermal Sensory Analyzer (Medoc, Israel). A $2\times2$ cm probe was held against the subject’s skin at a site of irradiation. The initial application temperature of the probe was $30\pm1$ C. Skin temperature was then increased at a rate of $0.5\pm1$ C per s until the volunteer judged the heat stimulus painful, which was signaled by the subject with an electronic push button. A computer logged the temperature as the thermal pain threshold. Immediately after signaling the pain threshold, the thermal probe is actively cooled back to a temperature of $30\pm1$ C. For each subject and at each time point, eight skin sites were tested in pseudo-random order.

Sensitivity to mechanical challenge was assessed with an electronic von Frey System (Somedic, Hörby, Sweden). This device has a plastic monofilament (1 mm in diameter) attached to a transducer, which records applied pressure. The probe is held by the experimenter and pushed against the skin to increase pressure at a rate of 4 g per s. The pressure increase was monitored on a computer screen, and the experimenter matches the actual applied force against a template of required force. Pressure was increased until subjects judged the stimulus to be painful, which they indicated with an electronic push button. The force exerted at this time was recorded as the mechanical pain threshold.

Data analysis The data were analyzed in by ANOVA for mixed models using SAS Version 8.2. In study I, delta values were used in the time-course studies (i.e., 3 MED–0 MED). Raw data were used with the dose–response studies except for heat pain because the control values for each source (0 MED) were significantly different. The mixed models comprise (1) a random effect for subject, and (2) fixed effects for UVR source and time or dose, and interaction between UVR source and either time or dose. In study II, in which site was a fixed factor and subject a random factor, the Tukey procedure was used for multiple comparisons. Statistical significance was set at $p < 0.05$ ($^*$), $p < 0.01$ ($^{**}$), and $p < 0.001$ ($^{***}$) as indicated on the relevant figures.

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### Table I. Study I: Demographics and UVR sensitivity of volunteers (± SD) in dose–response and time-course studies

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### Table II. Study II: Demographics and SSR sensitivity of volunteers in spatial distribution study

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Barr RM, Walker SL, Tsang W, Harrison GI, Ettehadi P, Greaves MW, Young AR: Suppressed alloantigen presentation, increased TNF-alpha, IL-1, IL-1Ra,


