Four groups of female Dutch-belted rabbits (Oryctolagus cuniculus) were given methoxsalen (12 mg/kg) or placebo by oral intubation and 1 hr later were exposed to UVA for either 2 or 8 hr. This procedure was repeated 5 days each week for 18 mo. A fifth group received no drug and no UVA exposure. The skin of the animals given methoxsalen and UVA showed signs of acute and chronic phototoxicity. Multiple peripheral blood parameters of hepatic, renal and hematologic function were normal and were not different between groups. Complete ophthamoscopic examinations were performed periodically. No cataracts were seen in any of the animals. This data provides the perspective that in one species the daily dose of methoxsalen and UVA required to induce chronic cutaneous photosensitization is lower than the daily dose required to induce cataracts. It is inadvisable to interpret this data as suggesting that no risk exists for patients being treated with oral methoxsalen phototherapy. The experimental evidence supporting photosensitization as a cause of cataracts and implicating a role of lens DNA in this cataractogenesis is reviewed. Because methoxsalen-UVA alterations of lens DNA or protein could lead to delayed onset of cataracts, and because of the serious nature and potential preventability of phototoxic lens opacification, appropriate protective eye wear is recommended for all patients receiving oral psoralen photochemotherapy.

Oral psoralen phototherapy [1] employs a photosensitizing dose of methoxsalen (8-methoxyspsoralen) and subsequent UVA (longwave ultraviolet radiation, 320-400 nm) exposure and is an effective method of controlling psoriasis [1-3]. The short-term hazards of this therapy, which has been termed PUVA, consist of inflammation of skin and alteration of the proliferation kinetics and viability of epidermal and dermal cells (cutaneous phototoxicity). These hazards are related to both the drug dose and UVA exposure dose and, with experience and careful dosimetry, can be kept at subclinical or tolerable levels. The potential long-term side effects of PUVA are the same as those effects known to occur from ultraviolet exposure and include "actinic" alteration of skin, skin cancer and cataracts. However, compared to the effects of ultraviolet alone, PUVA is of special concern because: (a) the effects of PUVA at the molecular level include cross-linking of DNA strands; (b) repair of the psoralen-DNA photoproducts may not be as rapid, effective, or error-free as the repair of ultraviolet-induced DNA lesions; (c) UVA penetrates more deeply into the skin and eye than does shorter wavelength ultraviolet radiation; and (d) solar radiation contains far more UVA than shorter wavelength ultraviolet radiation and the UVA radiation passes through ordinary window glass.

Cataracts are an especially serious risk. Unlike most cutaneous skin cancers, symptomatic cataracts may markedly diminish the quality of life and require the patient to consider surgical extraction of the lens, at present the only effective treatment for cataracts. UVA alone can lead to cataracts in rabbits [4-6] and monkeys [7-9] and alters the lens protein of mice [10]. Solar UVA may contribute to cataracts in humans [11,12]. Systemically administered methoxsalen reaches the lens of guinea pigs [13,14] and it is known that PUVA in repeated large doses (causing destruction of skin) causes cataracts in experimental animals [15-18].

It is important to estimate the magnitude of the ocular risks of PUVA therapy not only because of the potential widespread use of the therapy and the seriousness of cataracts, but because cataracts may be preventable by appropriate eye protection. To help place the risks in some perspective, rabbits were treated with phototoxic doses of PUVA 5 days each week for 18 mo. Because of the evidence that UVA radiation alone induces cataracts, the design for the experiment includes UVA radiation, with and without methoxsalen, at 2 exposure doses. Dutch-belted laboratory rabbits (Oryctolagus cuniculus) were chosen as the model system for this study for a number of reasons: (a) like most humans the animal is pigmented; (b) a chronic 18-mo study could be performed over a major portion of the animal's lifetime; (c) the lens of the Dutch-belted rabbit eye is large and is structurally and functionally similar to the human lens; (d) experimental cataracts have been induced in this species [19]; and (e) the animal is relatively easy to manage.

MATERIALS AND METHODS

Female pigmented Dutch-belted rabbits (Dutchland Laboratories, Inc., Denver, Pa.) were maintained in separate open-mesh wall mounted cages and fed Purina Rabbit Chow Checker (G)5301. Multiple preliminary experiments varying methoxsalen dose (0.2 to 48 mg/kg), UVA dose (0.1 to 100 J/cm²) and time between ingestion and irradiation (% to 8 hr) were performed to determine PUVA dose-responsiveness parameters in the skin of this species. One hundred and nineteen adult rabbits were then distributed into 5 experimental groups so that each group had approximately the same average weight and weight distribution. To evaluate chronic phototoxicity of skin unprotected by fur, a 2-inch-wide band representing approximately 10% of the body area, and extending from the shoulder of the foreleg to the haunch of the hind leg on each side was clipped at least weekly using Oster Model No. A2 clippers with a No. 40 blade.

Experimental Groups

The 5 experimental conditions were as follows:

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>UVA</th>
<th>No. of animals entered in study</th>
<th>No. of animals completed study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Methoxsalen</td>
<td>8 hr</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>B</td>
<td>Placebo</td>
<td>8 hr</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>C</td>
<td>Methoxsalen</td>
<td>2 hr</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>D</td>
<td>Placebo</td>
<td>2 hr</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>E</td>
<td>Placebo</td>
<td></td>
<td>24</td>
<td>18</td>
</tr>
</tbody>
</table>

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Reprint requests to: John A. Parrish, M.D., Department of Dermatology, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts 02114.
Drug

Milled methoxsalen crystals (Hoffmann-LaRoche, Inc.) dissolved in a water suspension containing 0.1% carboxymethyl-cellulose and 0.4% Tween 80 were administered daily, Monday through Friday, by oral intubation in a dose of 12 mg/kg rabbit body weight. Each rabbit was given a constant volume (2.0 ml) of either methoxsalen suspension or the placebo (carboxymethyl-cellulose and Tween 80). The rabbits were weighed weekly and a computer program was designed to calculate the appropriate methoxsalen concentrations for intubation and a recipe for mixing each methoxsalen suspension.

Irradiation

UVA exposure began 1 hr after methoxsalen administration, and was provided by a planar vertical array of 20 eight-foot Sylvania 96-T12BLB instant-start lamps located between each unit of 5 cages stacked on top of one another. The 39-inch-wide array of lamps extended 8.5 inches in front of and 8.5 inches behind the cage and was 5.5 inches from the side of the cage. UVA irradiance along selected planes inside the cages was monitored on a periodic basis for the duration of the experiment with an International Light Model IIA41 UVA meter and a Model SEC-010 detector, with W-UVA 40 filter and diffuser. Spectral power distribution of the source has been published [1,2]; a continuous spectrum is present between 320 and 390 nm with peak emission at 365 nm and less than 0.3% radiation of wavelengths shorter than 310 nm.

Because the UVA sources were located on the 2 sides of the cages, the irradiance within the cages was not uniform and was a function of both position of the probe within the cage and the orientation of the detector plane at each point. A planar view of typical UVA intensity measurements at 5 points 5 inches above the cage floor (the approximate height of a resting rabbit’s eye) is shown in the figure. The irradiance along the vertical planes at those points remained relatively constant (± 10%) above the level of the splash guards. The irradiance on various vertical planes within the cages varied approximately 7-fold. To study animal activity and behavior within the cages during experimental and ambient lighting and to estimate probable UVA dosage to the eyes, rabbit movement was monitored by video recording and direct observation. Ambient lighting was provided to all groups by incandescent fluorescent lights with essentially no UVA emission. Ambient lighting was delivered seven days per week and was on sixteen hours each day, encompassing the daily UVA exposure periods.

Plan view of rabbit cage. Irradiance in mW/cm² on vertical planes at +5” above cage floor. Cage is 15” high with 2½” splash guard around all bottom edges.

To acclimate the rabbits to the UVA exposure, the daily UVA exposure time was gradually increased during the first several weeks of the experiment. By the end of 4 weeks for the 8 hr groups and 2 weeks for the 2 hr groups, daily exposure times were at their specified final values.

Housing and Care

The UVA sources were mounted in separate air-conditioned closed systems to remove heat and to allow manual access to each cage. Lighting was delivered seven days per week and was on 16 hr and 8 hr groups. Each housing system had its own 8 hr or 16 hr cycle, and each was separated from the remainder of the animal facility by walls, with only 1 common air exhaust duct. Each housing system was maintained at 18.3 ± 2.8°C and 40 ± 8% relative humidity for the duration of the experiment. Minor medical problems were cared for on an individual basis and rabbits with serious problems were isolated and appropriate samples were collected for microbiological studies. Since no systemic medication other than methoxsalen was given to any animal during the study, rabbits which could not be returned to the experiment for health reasons were sent for euthanasia and necropsy.

Ophthalmoscopic Examinations

Documented examinations were performed on all rabbit eyes initially and after 2, 6, 12, 24, 36, 48, 60, 72, and 78 weeks of the experiment. At each examination, the rabbit was inspected for gross abnormalities of the anterior segment of the eye. After mydriasis was induced (10% Neosynephrine, USA and 1% Mydriacyl), the animal was enucleated in a specially-constructed box and biomicroscopic examination was performed with a Zeiss photolamp. At each examination a series of stereo photographs (lateral anterior, sagittal anterior, medial anterior, lateral posterior, sagittal posterior, medial posterior and a fundus reflex view) was obtained. After the final examination, the eyes were enucleated at the time of sacrifice. One eye from each animal was preserved intact in buffered formalin; the contralateral eye was opened with a scalpel and the lens placed in 0.9% saline solution and photographed under an Operating Microscope using techniques previously published [20,21]. After photography, the lens and the remaining parts of the eye were placed in buffered formalin for histological studies, which were subsequently evaluated without knowledge of experimental group.

To determine the frequency and type of nuclear and structural phototoxicity by dermatologists who did not know the animal number or experimental group. The presence and extent of erythema, edema, scaling, epidermal thickening, and keratoses was recorded. Immediately prior to the 12-mo and 18-mo inspection a new photograph was taken of 34 animals ranging in age from approximately 1 yr to over 3 yr.

Skin Evaluation

Rabbits were examined daily by technicians and any skin abnormality was brought to the attention of a dermatologist and veterinarian. If marked acute phototoxicity (marked erythema, edema, or blistering) occurred, the affected area was temporarily shielded with topical application of sunscreen (Piz Buin #6). If very severe phototoxicity occurred, the rabbit was temporarily withdrawn from the study and not exposed to UVA again until the signs of damage diminished.

On six occasions during the study (at 4, 7, 10, 12, 16, 18 months), each rabbit was carefully examined for signs of acute and chronic phototoxicity by 2 dermatologists who did not know the animal number or experimental group. The presence and extent of erythema, edema, pigmentation, scaling, epidermal thickening, and keratoses was recorded. Immediately prior to the 12-mo and 18-mo inspection a new area of skin adjacent to the continuously clipped site was clipped so that previously unexposed (hair covered) skin could be compared with the chronically exposed skin site. Because the color of the hair and skin of the normally pigmented region of the Dutch-belted rabbit varies considerably, pigmentation was evaluated in the belted (white-haired) region of the animal. Although the hairs remain white, the skin of this region is capable of tanning.

Termination Examinations

At the termination of the experiment, 20 ml of blood was obtained for hemoglobin, hematocrit, red blood cell count, white blood cell count, differential white cell count, reticulocyte count, prothrombin time, clotting time, calcium, phosphorus, blood urea nitrogen, creatinine (BUN/creatinine ratio), glucose, uric acid, cholesterol, total bilirubin, direct bilirubin, total protein, albumin, globulin (A/G ratio), alkaline phosphatase, serum glutamic oxaloacetatic transaminase, serum glutamic-pyruvic transaminase, lactic acid dehydrogenase, gamma-glutamyl transpeptidase, triglycerides, iron, total lipids, sodium, potassium, and chloride. Whole animal and organ weights were obtained. The gross and microscopic examination of 14 separate organs of each animal was performed by an experienced veterinary pathologist.
RESULTS

Although there was evidence of chronic cutaneous phototoxicity in both of the psoralens plus UVA experimental groups, no cataracts were seen in any animals of this study.

Preliminary Experiments: Dose Parameters

Compared to humans, the skin of the rabbits was much less sensitive to orally-administered methoxsalen and UVA exposure. Using methoxsalen doses from 0.1 mg/kg to 24 mg/kg it was not possible to see evidence of delayed erythema or edema with UVA doses up to 30 J/cm².

A single exposure of 50 J/cm² of UVA alone never elicited any delayed erythema on the shaved, unpigmented skin of Dutch-belted rabbits and 100 J/cm² caused minimally perceptible delayed erythema in only four of eight animals tested at that dose. However, when 12 mg/kg of methoxsalen was administered to 8 animals 1 hr before onset of a single exposure of UVA, 50 J/cm² caused delayed redness in 3 animals, 2 of which had 2+ erythema with slight edema. Delayed pigmentation after this dose of PUVA occurred in all 8 of the animals and was in every case more intense than that seen after twice the dose (100 J/cm²) of UVA alone.

When examined at 24 hr intervals, the delayed erythema response of Dutch-belted rabbits to a single PUVA administration is maximum when observed 48 hr after exposure. The most intense response can be produced when the irradiation is initiated within the first hour after methoxsalen administration, but responses produced by the same exposure initiated 90-240 min after intubation are only slightly less intense.

It was concluded from these and other preliminary experiments that: (1) a single intubated dose of 12 mg/kg of methoxsalen and subsequent exposure one hour later to 20-60 J/cm² of polychromatic UVA causes mild but definite transient phototoxicity in the Dutch-belted rabbit; (2) considerable variation of phototoxic responses exist between individual rabbits; (3) in the Dutch-belted rabbit, delayed hyperpigmentation in exposed sites is a more sensitive indicator of methoxsalen phototoxicity than is delayed erythema; and (4) after intubation of methoxsalen, the UVA exposure dose necessary to induce delayed edema is only slightly higher than that necessary to induce delayed erythema in the rabbit.

Experimental Animals

Thirty-six animals died or were euthanized during the 18-mo experiment, and these animals were evenly distributed among the 5 experimental groups. The cause of death was infectious agents commonly occurring in rabbit colonies; 9 of the 36 rabbits not completing the study died or were euthanized during the first month of the experiment. The attrition rate thereafter remained relatively constant, usually 0-3 rabbits per month, for the remainder of the experiment.

UVA Dose Ranges

Video tape and direct observations showed that the movement of the rabbits about the cage during UVA exposure was random and that the animals kept their eyes open during the exposure. Depending on the position of the rabbit in the cage, upper and lower limits of the calculated daily exposure dose to the rabbit eye for the 2 hr condition was 4.2-32.4 J/cm² and for the 8 hr condition was 17.2-129.6 J/cm². Estimated average daily exposure dose was 15-20 J/cm² for the 2 hr group and 60-80 J/cm² for the 8 hr group.

Skin Evaluation

The ears were most sensitive to phototoxicity, and erythema, scaling, thickening, induration and epidermal thinning were most marked in the margin of the ears. Occasionally rabbits also had erythema and scaling of the nose. The peripheral parts of the ear pigmented more quickly and more deeply than did the central inner concave aspects of the external ear.

Ophthalmoscopic Evaluation

During the course of the experiments, the only change noted in the lens was a variation with age in the slit-lamp appearance of the posterior suture which, in some animals, showed increasing tortuosity. This sutural change and its adjacent cortical haze, did not constitute a lens opacity; these were not visible with direct ophthalmoscopy or slit-lamp biomicroscopy against the red fundus reflex. The occurrence of these sutural variations, whether normal or artifactual, was the same in all experimental groups and the same as those seen in the satellite colony examined at Dutchland Laboratories, Inc.

Stereophotographic study of the excised lens allows one to locate lens opacities which might have been obscured by the iris even when the pupil is maximally dilated and permits evaluation of the degree to which the sutural changes constituted lens opacities. Using this examination, there were no significant differences in the prevalence of nuclear haze, cortical/nuclear ring or cortical haze among the five experimental groups.

Histologic examination of the lens of all rabbits showed no abnormalities. Occasionally swollen cells seen in the posterior suture zone were considered normal variation, as this occurred equally in all groups.

Laboratory and Histologic Examination

Analysis of the hematologic and serum chemical data failed to reveal any evidence of toxicity that could be related to administration of the psoralen compound, the prolonged exposure to the specific wavelength of ultraviolet radiation used in this study or to the combination of the above 2 treatments. Most of the abnormal values could be explained by the presence of a spontaneously or naturally-occurring disease process detected either in the gross or microscopic examination of the tissues of the individual animals.

Similarly, gross and microscopic examinations of the major organs and tissues aside from skin from these rabbits failed to reveal evidence of cytoxicity of the psoralen compound. One neoplasia was encountered in the animals administered psoralen; this was an adenocarcinoma of bile ducts (cholangiocarcinoma). It was a solitary 2.0 mm mass in the caudate lobe of the liver of a rabbit in Group A. This type of neoplasm has been described as the fourth most common spontaneously occurring
neoplasms in the rabbits [22] and its presence in this animal probably represents a spontaneous rather than an experimentally-induced lesion. One animal in Group A had a gastric ulcer and one animal in Group C had submucosal edema of the gastric mucosa. The remainder of the lesions encountered in this study were regarded as incidental or spontaneously occurring lesions of rabbits and occurred in all experimental groups.

**DISCUSSION**

While the cornea absorbs ultraviolet radiation of wavelengths shorter than 310 nm, UVA is absorbed primarily by the lens [4]. This absorption may damage lens tissue by thermal and/or photochemical mechanisms [4,6-8,23]. UVA may induce cataracts by changing soluble, lower-molecular-weight crystallin proteins to insoluble, higher-molecular-weight crystallins, which cause light-scattering within the lens (cataract). Ultraviolet radiation may photochemically alter proteins or specific amino acids to create new chromophores or pigments which absorb visible light. Tryptophan and its photoproducts may act as endogenous photosensitizers for this process [4,23,24]. In guinea pigs, rabbits, and monkeys, corneal opacity and permanent lenticular cataracts have been produced by single exposures to UVB (280-320 nm) or UVA [4-9]. In albino mice, cataracts may be produced by multiple daily UVA exposures (320-400 nm) that are below the single-exposure threshold dose of observable corneal damage [25]. There is evidence that long-term daily UVA exposure also damages the photoreceptor cells of retina of dogfish [26] and mice [27].Experimental evidence documenting UVA effects on the eye has recently been summarized [4]. Epidemiologic studies suggest that certain human cataracts may be related to solar ultraviolet [10,11,28].

Certain photosensitizing agents increase UVA-induced damage to both the cornea and the lens. Phototoxic keratoconjunctivitis is seen in roofers exposed simultaneously to coal-tar pitch volatiles and sunlight. The same substances produce conjunctivitis in rabbits exposed to artificial UVA (F400 nm). This maximum photosensitization of the eyes (primarily corneal injury) was found between 320 and 340 nm, and no effect was noted for wavelengths longer than 380 nm. Guinea pigs were found to be particularly sensitive to UVA after 6 to 12 weeks of daily oral (0.5 g/kg diet) or intraperitoneal (0.4 mg/mouse) administration of methoxsalen and subsequent exposure of UVA radiation. Scarc tissue formed around the ears, eyes, and face and almost all the animals showed corneal opacities and cataract formation. Cloud, Hakim, and Griffin [16] found extensive damage to cornea, lenses and lenses after oral (80 mg/kg) administration of methoxsalen to albino and pigmented guinea pigs exposed to UVA continuously for 24 hr. In another experiment [17] mice received 10 min/day of UVA (Sylvania BLB, 320-400 nm) exposure 1 hr after intraperitoneal injection of 4 mg (160 mg/kg) of methoxsalen 6 days a week for 5 months and were then observed for an additional 5 mo. Phototoxic reactions were severe; 50% of the mice receiving 8-methoxypsoralen died. Of the 28 mice that lived 10 weeks, 89% developed cataracts, 64% of which were anterior cortical cataracts.

When the seeds of the Ammi majus, a plant from which methoxsalen is extracted, were fed to dandelions exposed to the sun for 4-5 hr each day, conjunctivitis was observed within 2-3 days [48]. Although no cataracts were observed within one month, birds developed mydriasis and severe pigmentary retinopathy [49].

Kremlev and Troll [18] determined an action spectrum for eye damage in guinea pigs and rabbits receiving oral methoxsalen (88 mg/kg). Eyes were examined 72 hr after a single ultraviolet exposure (xenon arc and grating monochromator, 10 nm spectral intervals) given 1 hr after oral methoxsalen. The maximum photosensitization of the eyes (primarily corneal injury) was found between 320 and 340 nm, and no effect was noted for wavelengths longer than 380 nm. Guinea pigs were found to be more susceptible than were rabbits. Rats given repeated large doses of methoxsalen by oral intubation (100 mg/kg) and subsequently exposed to UVA from above the cages (500 ml/cm²) develop corneal opacities which gradually disappear after exposures are discontinued. However, 4 to 6 weeks later cuneiform opacities appear in the inferior equator of the lens [50].

Methoxsalen and UVA doses not leading to signs of acute or chronic cutaneous phototoxicity do not appear to alter the lens. Guinea pigs given repeated doses of methoxsalen and UVA comparable to doses used to treat human skin disease did not develop erythema of skin or eye abnormalities [18]. Daily intraperitoneal methoxsalen (0.5 mg/kg) and exposure for 10 hr to fluorescent UVA (P40 BLB) lamps at a distance of 10 inches, resulted in no gross ophthalmoscopic, slit lamp, or histologic manifestations of ocular injury after 13 mo. Two human studies are available but the number of subjects in the first is small
and the follow-up time of the second is short compared to the life span of the species. Eleven vitiligo patients treated with psoralens and sunlight for 3-12 yr showed no evidence of eye abnormalities [51]. In a prospective study, after 2 yr of observations of over 1000 psoriatic patients treated with PUVA there is no apparent increase in the incidence of cataracts (R. Stern: personal communication).

Because of marked species variation in susceptibility to the photosensitizing properties of methoxsalen, dose comparisons of drug and radiation are difficult. A more reasonable comparison may be based on equivalent photosensitizing potential. We elected to study the maximum dose of drug and radiation which could be tolerated by the skin over a long period of time. Based on many dose-response studies, we chose doses which were clearly phototoxic, but also allowed the animals to tolerate many months of daily exposure. The methoxsalen dose used is 20 times that used in humans. The rabbits were treated 5 days per week. The average UVA dose for each rabbit was 60-80 J/cm² for the 8 hr exposure and 15-20 J/cm² for the 2 hr exposure. Skin tolerance was increased by using smaller UVA doses during the first days of the experiment, reaching maximum levels after 2-4 weeks. Therapeutic exposure doses in humans range from 0.5 J/cm² to 20 J/cm². The maximal daily UVA exposure from sunlight could be an additional 15 to 35 J/cm² during the observation period.

Treatments are usually twice weekly.

Levels after 2-4 weeks. Therapeutic exposure doses in humans we attempt to employ drug and radiation doses slightly less than those causing obvious acute or chronic phototoxicity. Treatments are usually twice weekly.

Doses of methoxsalen and UVA which caused acute and chronic skin changes in rabbits did not cause abnormalities in hematologic or chemical parameters, induced no microscopic or macroscopic post-mortem changes and led to no pathologic changes in the eye. However, this study design and drug doses used are not appropriate to utilize the anatomic and functional investigations of tissue and organs as an acceptable chronic toxicity study.

The observations regarding absence of eye toxicity help to put the magnitude of the eye hazard of oral psoralen phototherapy in some perspective. In one species the daily dose of methoxsalen and UVA required to induce tolerable acute and chronic cutaneous photosensitization is lower than the dose required to induce cataracts during an 18-mo observation period. It is inadvisable to extrapolate this to the human eye as evidence of such a relationship exists in patients being treated with oral methoxsalen phototheraphy. Because of the serious nature of cataracts and because of the ease of shielding the eye from UVA we recommend the use of occlusive, ultraviolet opaque goggles during treatment and appropriate well-fitting sunglasses during courses of oral methoxsalen phototheraphy.

We are grateful to R. Rox Anderson of the Photobiology Unit, Harvard Medical School for his critical review of this manuscript and to Dr. Burton Whitestone of Consulting Services, Inc., and to Dr. Robert Levin, of GTE Sylvania Lighting Products Group, designed the experimental system and periodically performed radiometric measurements.

REFERENCES


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38. References

Announcement

A dermatopathology workshop, approved for 8 hr category I credit towards the physician’s recognition award of the A.M.A. will be held this fall on Friday, October 5, 1979, at the University of Massachusetts Medical School, Worcester, Mass. The workshop will include the study of 50 unknown microscopic slides, using multiple choice questions, followed by discussion of those 50 unknown cases by the faculty. Microscopes and printed material will be provided. For further information contact, Jag Bhawan, M.D. U. Mass. Med. School, Worcester, MA 01605; (617) 856-2412.