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Mid-Infrared Laser Ablation of Stratum Corneum Enhances In Vitro Percutaneous Transport of Drugs

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The precise removal of stratum corneum from cadaveric swine skin by a mid-infrared erbium : yttrium scandium gallium garnet laser ($\lambda = 2.79$ μm; 250 μsec pulse width) was assessed by electrical resistance measurements and documented by histology. The effects of stratum corneum removal by laser ablation and by adhesive tape-stripping on the in vitro penetration of ^{3}H-hydrocortisone and ^{125}I-γ-interferon were determined. Excised swine skin was irradiated with laser (1 J/cm^2; 31 mJ/pulse; 1 Hz; 2 mm spot diameter). For skin penetration studies, laser pulses were delivered to discrete 2-mm areas to ablate up to 12.6% of the total 3-cm^2 stratum corneum diffusional area. Franz in vitro skin penetration chambers were used to measure the cumulative 48-h penetration of ^{3}H-hydrocortisone and ^{125}I-γ-interferon in laser-treated and tape-stripped skin. Electrical resistance measurements and histologic studies demonstrated that 10–14 laser pulses at the above energy density were required to abolish skin resistance and selectively ablate stratum corneum without damage to adjacent dermal structures. Laser ablation of 12.6% of the surface area of stratum corneum produced a 2.8 and 2.1-times increase in permeability constant (k_p) for ^{3}H-hydrocortisone and ^{125}I-γ-interferon, respectively. These studies demonstrate that a pulsed mid-infrared laser can reliably and precisely remove the stratum corneum, facilitating penetration of large molecules such as ^{125}I-γ-interferon that cannot penetrate intact skin. This new technique may be useful for basic and clinical investigation of skin barrier properties. *J Invest Dermatol 97:874–879, 1991*

The stratum corneum provides the principal barrier that limits the percutaneous penetration of topical drugs. This barrier can be partially overcome by removal of the stratum corneum, as in tape-stripping [1]; heating the stratum corneum, as in CO_2 gas monitoring [2]; and enhancement of permeability by solvents, such as dimethylsulfoxide and laurocapram [3].

Lasers are new tools that can be used for the ablation or removal of cutaneous tissues. However, lasers currently used by dermatologic surgeons remove tissue by a photothermal process leading to varying degrees of damage to adjacent structures. For very thin, delicate skin lesions, the ideal approach would be a precise elimination of diseased structures with sparing of remaining tissues. This objective requires an extremely high absorption of laser energy, thereby confining the volume of photoexcitation to a thin layer at the irradiated surface. There are two optical wavelength regions where absorption is adequate to meet this objective: 1) in the very short wavelength ultraviolet where there is strong absorption by tissue proteins [4]; and 2) in the mid-infrared where there is strong absorption by tissue water [5]. These absorption characteristics have stimulated interest in both the excimer and mid-infrared lasers with regard to their potential usefulness in skin surgery.

The excimer [argon fluoride (ArF) 193 nm] laser has been suggested for the controlled removal of the stratum corneum of human skin [6] to enhance percutaneous transport of ^{3}H-H_2O. The precise control offered by the excimer laser allows a stepwise removal of 1 μm stratum corneum per pulse by a photochemical breaking of molecular bonds. However, excimer laser radiation has been shown to induce DNA damage throughout a zone of cells surrounding the ablated area, thus bearing a potential for mutagenesis [7]. The short nanosecond pulses of the excimer laser have also been shown to cause significant photoacoustic injury to epidermal and dermal tissue structures due to the pressure waves induced by the sudden ejection of ablated material [8].

The mid-infrared erbium laser has recently been shown to cut effectively a variety of tissues, with minimal injury to adjacent structures [9–15]. Furthermore, thermal modeling has suggested that this laser emitting at the absorption maximum of tissue water should ablate skin with only minimal thermal damage [16,17]. For clinical use, the major advantages of mid-infrared radiation over ultraviolet (UV) excimer laser radiation are 1) no known mutagenic or carcinogenic effects of mid-infrared radiation, 2) probably less photoacoustic injury due to the longer pulse duration of the mid-infrared laser than the excimer laser, and 3) the solid-state mid-infrared laser is less expensive, more compact, highly reliable, requires less maintenance, and is inherently simpler to operate than excimer laser systems. However, to date, there has been no attempt to use the

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Abbreviations:

ArF: argon fluoride
^{3}H: tritium
^{125}I: iodine-125
k_p: permeability constant
UV: ultraviolet
YSGG: yttrium scandium gallium garnet

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mid-infrared erbium laser for the controlled removal of stratum corneum.

The purpose of the present in vitro study is twofold: 1) to determine if it is possible to ablate, reliably and precisely, stratum corneum without damage to adjacent dermal structures, and to measure the penetration enhancement of ^{3}H-hydrocortisone and ^{125}I-γ-interferon after laser removal of stratum corneum.

MATERIALS AND METHODS

Skin Samples Frozen (−20°C) full-thickness, excised dorsal miniature swine skin was obtained from Charles River, Wilmington, MA. Immediately prior to laser irradiation, skin samples were thawed, hair was carefully removed with curved surgical scissors, and subcutaneous adipose tissue dissected free.

Laser Ablation A Schwartz Electro-Optics (Orlando, FL) Laser 1-2-3 with an erbium:yttrium scandium gallium garnet (YSGG) crystal-emitting mid-infrared photons at a wavelength of 2.79 μm with a pulse width of 250 μsec was used. The laser beam was deflected down to an operating stage using a front surface mirror and focused with a 50-mm focal length calcium fluoride lens to a spot diameter of 5 mm. The intensity profile of the light was determined by scanning a 10-μm slit across the laser beam at the focal point. An aperture was placed to select the central 2-mm region, which was found to have a flat field (±10%), with an energy density of 1 J/cm^2. This 2-mm spot diameter was subsequently used throughout the experiment.

In vitro irradiations were performed with a laser energy density of 1 J/cm^2 (31 mJ/pulse) at a repetition rate of 1 Hz. These laser parameters were predetermined based on histologic studies that documented no zone of tissue damage immediately adjacent to the irradiated spot. Laser irradiation was monitored with a Gentec (Plattsburgh, NY) PRJ-D energy meter before and after treatment.

Electrical Resistance Measurements The gel electrodes were fabricated by first electroplating a layer of AgCl on a 0.25-mm diameter silver wire in a beaker filled with 0.1 N HCl using an electrical current of 0.4 mA. The treated wire was then inserted into a micropipette tip containing 2% agar in normal saline. Electrodes were ready to use once the agar solidified into a gel.

The skin resistance was measured using a voltage divider configuration. A signal generator (Wavetek, San Diego, CA) was placed in series with a 100-kΩ potentiometer, the gel electrode, and the swine skin sample to be measured. The latter was placed on an agar gel that was formed on the top of a silicone rubber sheet glued to the bottom of a petri dish. The ground electrode consisted of wire braid that was placed in the agar gel as it cooled. The gel electrode was held by a clamp while positioned over, and in physical contact with, the ablation site, which was kept fully hydrated by placing a few drops of saline on it 10 min before the measurements were made. A lock-in amplifier (Stanford Research Systems, Sunnyvale, CA), using the signal generator as a reference, measured the peak-to-peak voltage across the skin and the potentiometer. The signal generator was set at approximately 1 V peak-to-peak at 100 Hz. The resistance of the skin was then calculated by taking the ratio of the skin voltage to the voltage across the potentiometer and multiplying by the potentiometer resistance.

Skin resistance measurements were made before and after each successive laser pulse, normalized to the 2-mm area of the ablation site and expressed in kΩ-cm^2 [equal to the measured resistance (Ω) times the gel electrode area (cm^2)]. It is known that when the skin resistance values drop below 30 kΩ-cm^2, there is high confidence that the stratum corneum has been completely removed [6].

Histology Skin samples received from 1 to 50 pulses at the laser irradiation parameters described above. Tissue was immediately fixed in 3% glutaraldehyde:5% formaldehyde in phosphate buffer (pH 7.4). Samples were then dehydrated in graded alcohols, cleared in xylene, and embedded in paraffin. Six-micrometer sections were cut, stained with hematoxylin and eosin, cleared of paraffin in xylene, and dried. Sections were examined with an Olympus microscope and photographed with Panatomic-X film (Eastman Kodak Co., Rochester, NY). Histology studies were correlated with electrical resistance measurements.

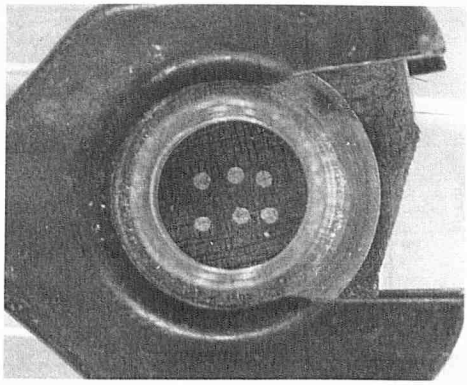


Figure 1. Laser-ablated sites (2 mm) on excised pig skin.

Other skin samples received from 1 to 50 pulses at the laser irradiation parameters described above and were processed for scanning electron microscopy. Those specimens were immediately post-fixed in 1% osmium tetroxide, dehydrated in acetone, critical point dried, and sputter coated with gold on a PAC-1 evaporating system (Pelco, Redding, CA). Photomicrographs were taken on a Philips 515 (Manwah, NJ) scanning electron microscope.

In Vitro Diffusion Studies The total diffusional surface area of skin sample in the Franz chamber was 3 cm^2. Therefore, the ablation of 3.1%, 6.3%, 9.4%, and 12.6% of the surface area, using a 2-mm spot diameter (Fig 1), required a total of 3, 6, 9, and 12 spots, respectively. Three different skin specimens were examined at each percentage level. For each spot, skin resistance measurements were made before and after successive laser pulses. The endpoint of laser irradiation at each spot occurred when the skin resistance value dropped below 30 kΩ-cm^2.

The in vitro penetrations of 1% ^{3}H-hydrocortisone (50 Ci/mmol) and ^{125}I-γ-interferon (690 Ci/mmol) (Amersham, Arlington Heights, IL) were measured using Franz diffusion cells [18,19]. Drugs were dissolved in ethanol:water (60:40). A volume of 200 μl (^{3}H-hydrocortisone or ^{125}I-γ-interferon) was applied to the stratum corneum surface (area 3 cm^2) of swine skin. The stratum corneum of the skin specimens was either intact, or had been removed immediately prior by either stripping 25 times with adhesive tape or by laser ablation as described above. The lower reservoir contained isotonic saline and 4% bovine serum albumin. Diffusion cells were incubated with constant stirring at 37°C. Three diffusion cells were run for each percentage level of total surface area ablation. One-milliliter aliquots were removed from the reservoir solution at each time point and assayed by liquid scintillation counting to measure cumulative penetration. The permeability constant k_p was calculated in units of cm/h: $k_p = J/dC$, where J (flux) was calculated from the slope of penetration during the initial 8 h and dC is the concentration.

RESULTS

Electrical Resistance Measurements The electrical resistances of the swine skin samples were measured prior to the in vitro diffusion experiments with ^{3}H-hydrocortisone and ^{125}I-γ-interferon. The correlation between the number of pulses delivered and skin electrical resistance is shown in Fig 2. As the superficial layers of the stratum corneum were removed, there was a slow gradual drop in the resistance of the skin. However, the electrical resistance dropped

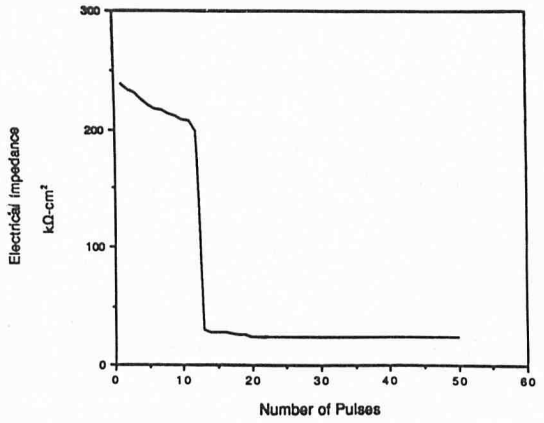


Figure 2. Effect of erbium:YSGG laser pulse on skin resistance. $\lambda = 2.79\ \mu m$; fluence = 1 J/cm²; 2 mm spot size.

suddenly from greater than 200 kΩ-cm² to below 30 kΩ-cm² with a single pulse delivered in the range of 10–14 pulses per irradiated spot.

Histology Histologic studies demonstrated that laser ablation can achieve both partial and complete removal of stratum corneum and viable epidermis (Fig 3). Five laser pulses resulted in partial ablation of the outermost layers of stratum corneum (Fig 3*B*). There was no histologic evidence of charring or carbonaceous material seen at, or immediately adjacent to, the irradiation site. This conclusion was based on the histologic examination of all swine skin specimens within the defined laser parameters, regardless of the way in which the sections were cut. A range of 10–14 laser pulses selectively removed the entire stratum corneum, sparing the underlying epidermis (Fig 3*C*), and correlated with the precipitous drop seen in electrical resistance; 35–45 laser pulses ablated both stratum corneum and epidermis (Fig 3*D*). Removal of stratum corneum was also achieved by repetitively stripping (25 times) with adhesive tape to achieve glistening of the exposed skin surface (Fig 3*E*).

Scanning electron microscopic images (Fig 4) of skin samples, ablated with successive laser pulses until the skin electrical resistance values dropped to less than 30 kΩ-cm², showed disruption with "ridging" of the surface layers of tissue at the irradiation site. There were no associated swelling or other textural changes observed in the region of laser exposure.

In Vitro Diffusion Studies The ablation of stratum corneum by laser enhanced the percutaneous transport of both ^{3}H-hydrocortisone (Fig 5) and ^{125}I-γ-interferon (Fig 6). The increase in surface area ablated (3.1% to 12.6%) resulted in an increase in the permeability constant, k_p (Table I). Ablation of 12.6% of the surface area produced 2.8-times and 2.1-times increases in k_p for ^{3}H-hydrocortisone and ^{125}I-γ-interferon, respectively, compared with controls. Removal of 100% of the stratum corneum by tape-stripping produced a 3.2-times and 1.5-times increase in k_p, for ^{3}H-hydrocortisone ^{125}I-γ-interferon, respectively (Table I).

DISCUSSION

During mid-infrared erbium:YSGG laser irradiation, the photon energy initially absorbed by water as electronic excitation is rapidly converted to vibrational heating of the substrate [20]. As energy is added, the water in the substrate is raised to its boiling point. Internal vapor pressure builds up until a microexplosion occurs (Fig 7). The rapid expansion created by this excitation gives rise to the actual ejection of microscopic tissue fragments at high velocities or the ablation phenomenon. Because most of the energy of the laser pulse goes into the thermal phase change associated with tissue vaporization, ablated fragments ejected from the tissue surface carry most of the energy with them, leaving little energy in the form of heat to damage the surrounding material. Therefore, ablation of the exposed material can, in principle, be performed more precisely. This phenomenon should prevent undesirable melting or carbonization of remaining biologic tissues, a problem that exists when light irradiation from conventional laser systems is used. Further-

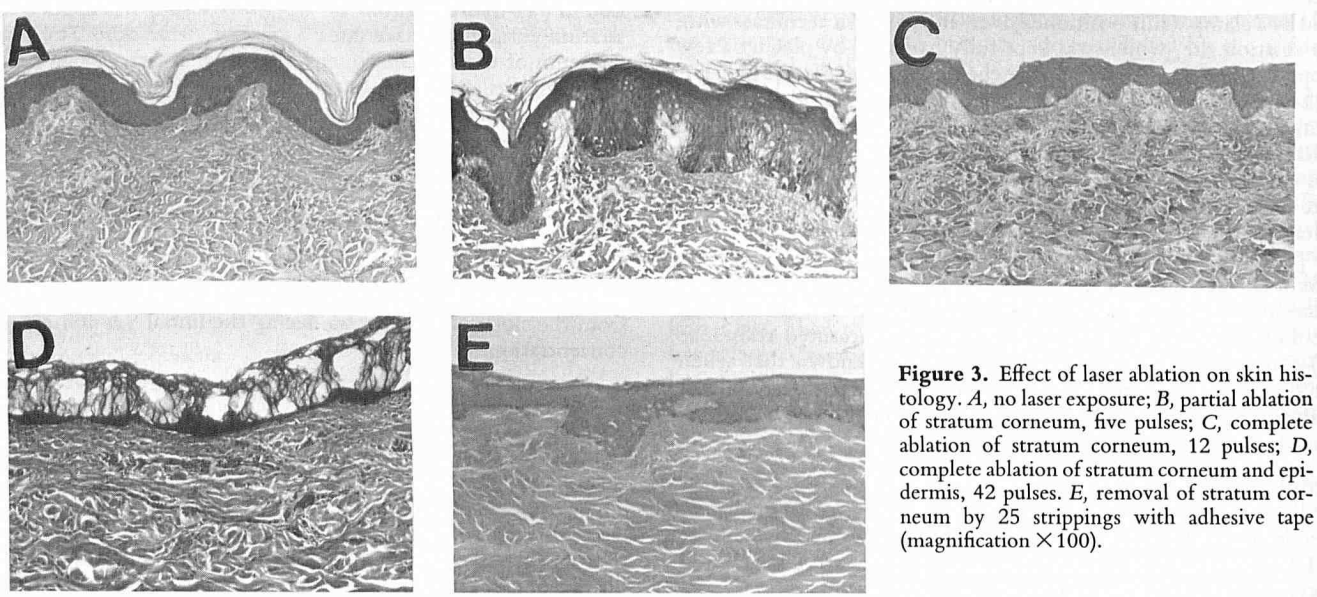
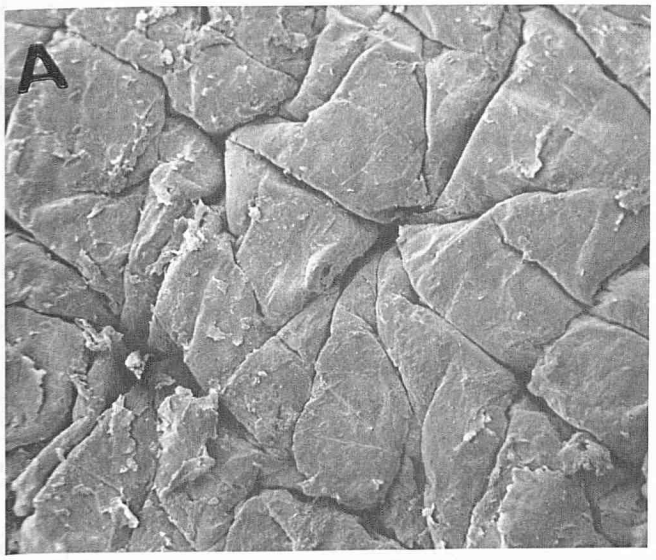
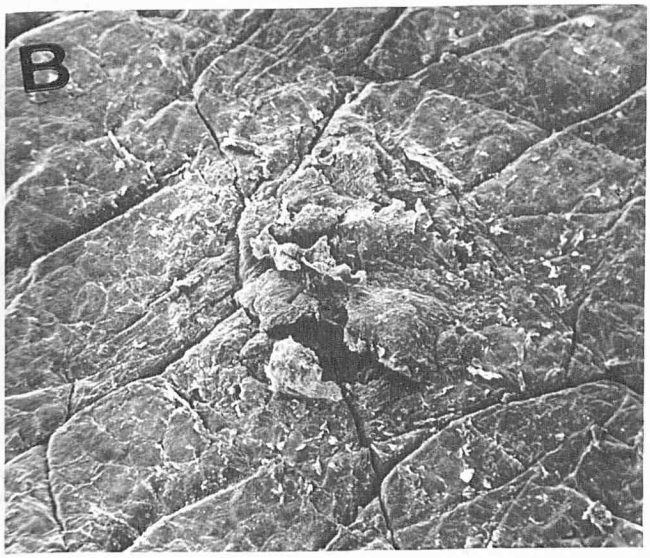


Figure 3. Effect of laser ablation on skin histology. *A*, no laser exposure; *B*, partial ablation of stratum corneum, five pulses; *C*, complete ablation of stratum corneum, 12 pulses; *D*, complete ablation of stratum corneum and epidermis, 42 pulses. *E*, removal of stratum corneum by 25 strippings with adhesive tape (magnification ×100).





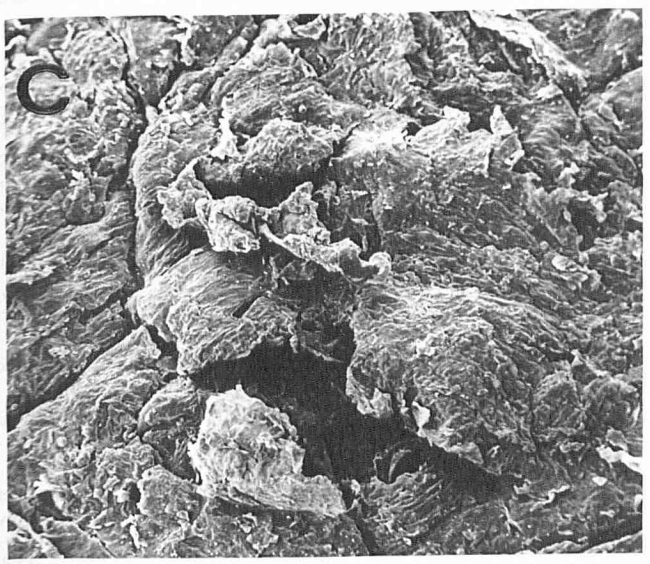


Figure 4. Scanning electron micrographs of swine skin. *A*, control (no laser exposure); *B*, after 10 pulses of laser irradiation; *C*, higher power magnification of *(B)* illustrating disruption with "ridging" of superficial layers of tissue (magnification: *A,B* ×38; *C* ×72).

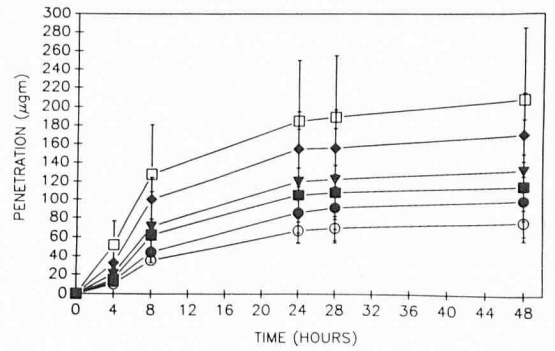


Figure 5. Effect of stratum corneum removal by laser ablation versus tape-stripping on the in vitro percutaneous penetration of ^{3}H-hydrocortisone. Untreated control ○; tape-stripped □; percent of stratum corneum surface area ablated by laser: 3.1%, ●; 6.3%, ■; 9.4%, ▼; 12.6%, ◆.

more, the depth of substrate removal is precisely controllable because, for a fixed energy density per pulse, there is a linear relationship between etched depth and the number of pulses delivered.

The erbium:YSGG laser's emission wavelength at 2.79 μm is maximally absorbed by water, which has an absorption coefficient (μ_a) of 7700 cm^{-1} [21]. A hydrated piece of skin tissue, which is typically 75% water, is estimated to have an μ_a of 5800 cm^{-1}. Therefore, the optical penetration depth, $1/\mu_a$, is approximately 1.7 μm. However, because the laser pulse is 250 μsec long, there is time for laser energy to diffuse as thermal energy into the tissue during the pulse. We used a one-dimensional thermal diffusion model to map the thermal energy distribution at the end of a single 1 J/cm^2 250 μsec pulse of an erbium:YSGG laser (data not shown). The spatial distribution of thermal energy (J/cc) versus depth was one half of a Gaussian distribution, which was quite closely approximated by a simple exponential function with a maximum energy density of 1550 J/cc at the skin surface and a 1/e depth of 1/1550 cm or 6.5 μm. In other words, the 250-μsec laser pulse deposits energy as if the tissue absorption was effectively 1550 cm^{-1}. About 12 laser pulses were required to achieve complete removal of the stratum corneum, as indicated by the electrical resistance measurements. Because hydrated stratum corneum is about 27 μm thick [6], a first-order estimate of the removal per pulse is 27/12, or 2.2 μm per pulse.

The present study demonstrated in vitro that the stratum cor-

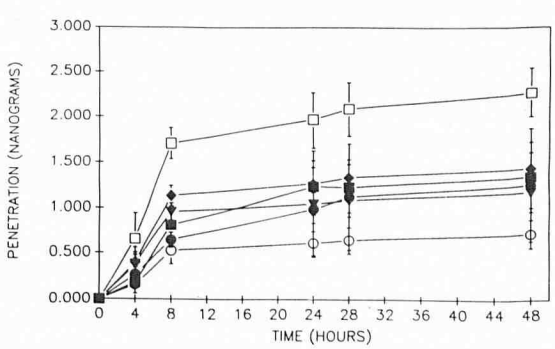


Figure 6. Effect of stratum corneum removal by laser ablation versus tape-stripping on the in vitro percutaneous penetration of ^{125}I-γ-interferon. Untreated control ○; tape-stripped □; percent of stratum corneum surface area ablated by laser: 3.1%, ●; 6.3%, ■; 9.4%, ▼; 12.6%, ◆.

Table I. Enhancement of Hydrocortisone and γ-Interferon Flux after Stratum Corneum Removal

Treatment	Ablation (%)	k_p (cm/h × 10^{-5})[a] Hydrocortisone	γ-Interferon
Control	0	1.46	43.8
Tape-Stripped	100	5.32	142
	3.1	1.85	53.4
	6.3	2.59	67.4
Laser Ablation	9.4	2.95	80.1
	12.6	4.17	94.4

[a] The permeability constant k_p was calculated in units of cm/h: $k_p = J/dC$, where J (flux) was calculated from the slope of penetration during the initial 8 h and dC is the concentration.

neum can be ablated reliably, without visible damage to the adjacent viable epidermal structures, with a mid-infrared erbium:YSGG laser at the defined irradiation parameters. Furthermore, using electrical resistance measurements, stratum corneum removal with this laser can be precisely controlled to a single pulse, and may offer a distinct advantage over tape-stripping, which is both macroscopic, and to some extent, unpredictable. Efficient ablation enables small steps of tissue removal per laser pulse, which confers control over the ablation process. Ablation with 12 small steps is easier to control than one big ablative step.

This new technique offers both basic and clinical research applications. Selective ablation of the stratum corneum will facilitate studies on the barrier function of the various skin layers, as well as provide information on skin renewal kinetics. Selective epidermal ablation will also provide a useful pathophysiologic model to study wounding mechanisms and repair.

The present study has shown that laser ablation of limited areas of stratum corneum, up to 12.6% of the surface area, increases percutaneous absorption of both ^{3}H-hydrocortisone and ^{125}I-γ-interferon. If the permeability constant (k_p) data of the laser-irradiated area is extrapolated to an area of 100% ablation, this gives a k_p value of 22 for ^{3}H-hydrocortisone and 449 for ^{125}I-γ-interferon. Consequently, 100% ablation by laser increases skin permeability by 4.1 for ^{3}H-hydrocortisone and 3.1 for ^{125}I-γ-interferon, relative to total stratum corneum removal by tape-stripping. This suggests that laser damages deeper skin layers, although this is not seen in the photomicrographs. An explanation for the increased penetration of ^{3}H-hydrocortisone and ^{125}I-γ-interferon relative to the 100% tape-stripped control may be due to a photomechanical acoustic effect similar to that described for the Q-switched and mode-locked Nd:YAG laser photodisruption of pathologic lesions in the eye [22]. During erbium:YSGG laser irradiation of stratum corneum an audible snap is heard, which could represent a laser-induced rapidly expanding acoustic shock wave. Local propagation of the acoustic shock wave may cause "cracking" of the upper layers of the epidermis that may not be evident on conventional light microscopy. This cracking of the epidermis could lead to more drug penetration across the skin than a simple model would predict. However, the potential role of this process during ablation with the erbium:YSGG laser has yet to be fully evaluated.

Laser ablation of stratum corneum allows for the percutaneous transport of large molecules, such as ^{125}I-γ-interferon, which do not penetrate intact skin. Current techniques that employ penetration enhancers have not been effective in delivery of such large molecules as γ-interferon [23]. Ablation of the stratum corneum also has the potential to increase percutaneous transport in applications such as cutaneous patch testing and percutaneous blood gas monitoring. Additional studies are required to determine the biologic effects of cutaneous laser ablation and the resultant barrier epidermal renewal kinetics.

Figure 7. Removal of stratum corneum by pulsed mid-infrared erbium:YSGG laser is an explosive event. The ablated stratum corneum appears as a plume of particulate matter above the skin surface (photograph courtesy of Gary Gofstein, University of Texas).

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