5 µm, makes it highly probable that cavitation could occur within it *in vivo* with medium-frequency ultrasound, but this is less probable with low-frequency ultrasound because of the greater size of the bubbles. The existence of dissolved gas at depth in living tissue can allow the development of cavitation bubbles (50). We demonstrated epidermal and dermal damage in mice using low-frequency ultrasound, including muscle and vessel necrosis highly suggestive of undesirable in-depth cavitation, using ultrasound parameters that are not far from those used in sonophoresis (2).

43.4.3 Miscellaneous

Independent of cavitation and heating, ultrasound waves provoke a rise in pressure in liquid medium in the donor compartment. The relative contribution of this flow has been estimated to represent 0.02% at 1 W/cm^2 and 2% at 100 W/cm^2 and is thus negligible (18). Phonophoresis of mannitol across pig skin *in vitro* was found to be the same when ultrasound was applied before application of mannitol or simultaneously, suggesting no significant effect of convection in ultrasound-induced transdermal transport (68). On the other hand, we did not evidence any changes in glucose blood levels of rats when ultrasound was applied before the application of insulin, while marked hypoglycemia was observed when ultrasound and insulin were applied simultaneously (8).

In conditions of negligible temperature rise and absence of cavitation, mechanical stress has shown evidence of intercellular widening induced by transverse (shear) waves (71, see Section 5.1).

The boundary layer of water immediately adjacent to membranes in studies carried out *in vitro* is less well mixed and constitutes an additional resistance to diffusion through the skin. This can be reduced by acoustic streaming (18).

43.5 BIOLOGICAL CONSEQUENCES OF ULTRASOUND APPLICATION ON SKIN

SC lipids are essential to skin barrier integrity. Hence, it is possible to hypothesize that ultrasound can affect lipid fluidity either by heating, shock waves, or microjets and moreover provokes partial removal of lipids from SC.

43.5.1 Removal or Modification of Stratum Corneum Lipids

In a model of lipid bilayers using low-frequency ultrasound, defects were observed using an atomic-force microscope, with diameters of 10 to 100 nanometers (72). Intercellular lipid content was measured in hairless rat skin *in vitro* after ultrasound exposure (150 kHz) in a surfactant solution (Tween 20). Lipid release from the skin was demonstrated, and this increased with length of time of exposure to 150-kHz ultrasound. Lipid release was correlated with increased skin conductivity and enhanced transport of polar molecules (73). Similarly, sebaceous gland debulking was demonstrated on histological sections of hairless rat skin exposed to low-intensity ultrasound (74). Moreover, removal of 30% of the total amount of SC lipids was demonstrated using 20-kHz ultrasound (15 W/cm^2, duty cycle 0.1 to 0.9 for 2 hours) in pigs, a species with less prominent sebaceous glands (45).

43.5.2 Imaging Pathway of Sonophoretic Transport

As seen in Section 4.2.2.1, pits secondary to cavitation on the skin surface have been shown with both medium- and low-frequency ultrasound (21, 41, 49). Nevertheless, whether these craterlike lesions are a possible pathway for transdermal transport remains uncertain. The following section will report on evidence for possible in-depth pathways.

43.5.2.1 High- and Medium-Frequency Ultrasound

The migration of a tracer (lanthanum) has been demonstrated between intercorneocyte spaces after exposure to high-frequency ultrasound (10 to 16 MHz) and the tracer reached the dermis (16).