

different compounds has resulted in the generation of significant hypersensitivity or inflammatory responses. For example, although transdermal delivery of arachalene (a compound that is useful in the treatment of Alzheimers disease) results in the sustained delivery of pharmacologically beneficial concentrations of the drug, it results in the generation of symptomatic contact hypersensitivity (CH) responses (Krueger, Pershing, and Roberts, personal communication). Furthermore, subsequent oral administration of this compound elicits a "memory" CH response. Thus, the induction of an immune response to a transdermally delivered compound may result in a condition in which it is no longer feasible to achieve delivery by conventional routes.

Historically, during the early development phases of transport systems, little attention was paid to the potential immunological consequences of transdermal drug delivery. A further complication of the issue is the reticence on the part of a number of companies and research groups to report the deleterious effects of transdermal transport systems in the scientific literature, thus, making systematic evaluation of many of the problems associated with transdermal delivery systems extremely difficult, if not impossible. This chapter will present an overview of the immunobiology of the skin and its interactions with systemic immune responses as an aid in consideration of the potential immunological ramifications of transdermal drug delivery systems. It is hoped that this will lead to development of rational approaches to obviate potentially deleterious side effects that may arise as a result of these delivery systems.

## II. STRUCTURE AND HISTOLOGICAL ORGANIZATION OF THE SKIN

Like other organs, the skin is well organized into histologically defined tissues to facilitate the performance of its various functions. The structural and functional relationships of the skin for its immunological role are discussed in the following:

The skin is divided into two main layers, the surface epithelium, termed *epidermis*, and the underlying connective tissue layer, termed the *dermis*. Beneath the dermis is the *hypodermis*, which is a layer of loose connective tissue consisting mainly of subcutaneous adipose tissue. The hypodermis is loosely connected to underlying deep fascia, aponeurosis, or periosteum. A schematic representation of the skin is presented in Figure 1.

The epidermis is a keratinizing, stratified squamous epithelium composed of several distinct cell populations. The keratinocytes represent more than 90% of the cells within the epidermis. These are the keratinizing squamous cells of the self-renewing epithelium