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# PERCUTANEOUS ABSORPTION OF DRUGS

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## *Introduction*

This is not an exhaustive review of the subject of percutaneous absorption because space is limited, but important studies related to the subjects in the text are noted in the bibliography. I try to concentrate on some clinical-basic science relationships in percutaneous absorption and show how our knowledge has been expanded and verified by clinical findings and bioassays.

When theoretical presentations of mathematical models, use of artificial membranes, and animal models are compared to what actually happens in vivo in human skin when drugs are applied topically, a great gap exists in our knowledge. For practical reasons we almost always need in the end to know what happens when drugs are applied to live human skin. Until we can accurately predict from theory or animal models, we must rely on direct systems of measuring penetration through human skin, preferably in vivo.

## *Drug Release from Vehicles*

A pharmacologically active agent must be released from its carrier (vehicle) before it can contact the epidermal surface and be available for penetration of the stratum corneum and lower layers of the skin.

The dynamics of drug release from its vehicle have been a subject of investigation for many years. Probably the most widely referenced works on glucocorticoids in relation to release from vehicles are those of Katz & Poulsen (1), Ostrenga et al (2, 3), and Poulsen et al (4). In vehicles containing propylene glycol, the highest release rate was found when the saturation of corticosteroid was at its highest level in the vehicle. These conclusions hold for the specific acceptor phase studied which was isopropyl myristate. However, there is still too little experience with corticosteroids and other



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vehicles and acceptor phases to be able to predict what will happen with any given vehicle and acceptor phase. This is particularly true with human skin as the acceptor phase. One apparently predictive general rule is that addition of propylene glycol to almost any vehicle will increase the release of the corticosteroid from that vehicle.

Theoretical considerations for vehicle release of pharmacologic agents are well outlined by Higuchi (5), but the laws seem to be distinguished more by the exceptions than the rule when related to in vivo use.

There are many practical applications of the fact that vehicles can greatly alter the biologic potency of the contained glucocorticosteroid, and I wish to outline these vehicle differences in some detail as they relate directly to the clinical use of these formulations.

The background for these discussions must include some information on the vasoconstrictor bioassay (6–12) of glucocorticoids and its direct correlation with the clinical potency of glucocorticoid formulations (12, 13). This bioassay has been used by many pharmaceutical companies to screen glucocorticoids and their vehicle formulations for guidelines on their potency in managing skin diseases.

Over 200 different glucocorticoid formulations are available for prescription use, and many of these have been compared in both the vasoconstrictor assay and clinical studies of skin disease. With few exceptions, the vasoconstrictor assay can be very accurate in predicting clinical potency (12, 13) and, at this time, must be one of the rare bioassays that will do this for any topical therapeutic drug.

Betamethasone dipropionate is a glucocorticoid that is present in the same concentration (0.05%) in six different vehicles available for prescription use under the names of Diprosone ® cream, Diprosone® ointment, Diprosone® lotion, Diprolene® cream, and Diprolene® ointment. There is a wide variance in biologic activity (potency) of these various vehicles containing 0.05% betamethasone dipropionate. Table 1 shows the class of these various formulations as they fit into the overall category of potency of topical gluco-

**Table 1** Potency of betamethasone dipropionate 0.05% in various vehicles

| Potency Class from Table 2 | Various formulations of betamethasone dipropionate 0.05% |
|---|---|
| Class I | Diprolene® ointment, Diprolene® cream |
| Class II | Diprosone® ointment |
| Class III | Diprosone® cream |
| Class VI | Diprosone® lotion |

**Table 2** Potency ranking of some commonly used brand name corticosteroids

| | | | |
|---|---|---|---|
| I[a] | Temovate cream 0.05% | IV | Cordran ointment 0.05% |
| | Temovate ointment 0.05% | | Elocon cream 0.1% |
| | Diprolene cream 0.05% | | Kenalog cream 0.1% |
| | Diprolene ointment 0.05% | | Synalar ointment 0.025% |
| | Psorcon ointment 0.05% | | Westcort ointment 0.2% |
| II[b] | Cyclocort ointment 0.1% | V | Cordran cream 0.05% |
| | Diprosone ointment 0.05% | | Diprosone lotion 0.05% |
| | Elocon ointment 0.1% | | Kenalog lotion 0.1% |
| | Florone ointment 0.05% | | Locoid cream 0.1% |
| | Halog cream 0.1% | | Synalar cream 0.025% |
| | Lidex cream 0.05% | | Valisone cream 0.1% |
| | Lidex gel 0.05% | | Westcort cream 0.2% |
| | Lidex ointment 0.05% | | |
| | Maxiflor ointment 0.05% | VI | Alcovate cream 0.05% |
| | Topicort cream 0.25% | | Alcovate ointment 0.05% |
| | Topicort gel 0.05% | | Locorten cream 0.03% |
| | Topicort ointment 0.25% | | Synalar solution 0.01% |
| | | | Synalar cream 0.01% |
| III | Aristocort A ointment 0.1% | | Tridesilone cream 0.05% |
| | Cyclocort cream 0.1% | | Valisone lotion 0.05% |
| | Cyclocort lotion 0.1% | | |
| | Diprosone cream 0.05% | VII | Topicals with hydrocortisone, |
| | Florone cream 0.05% | | dexamethasone, flumethalone, |
| | Lidex E cream 0.05% | | prednisolone, and methy- |
| | Halog ointment 0.1% | | prednisolone |
| | Maxiflor cream 0.05% | | |
| | Valisone ointment 0.1% | | |

[a]Group I is the super-potent category; potency descends with each group, to Group VII, which is least potent (II, III, potent steroids; IV, V, mid-strength steroids; VI, VII mild steroids).
[b]There is no significant difference between agents within Groups II through VII; the compounds are arranged alphabetically. In Group I Temovate cream or ointment is more potent than Diprolene cream or ointment and Psorcon ointment.

corticoids. Table 2 lists the different categories of potency of many topical glucocorticosteroids available in the United States.

This variation in biologic potency, which is determined by vehicles, can be seen with most of the glucocorticoids (14). Triamcinolone acetonide 0.1% (see Table 3) varies from Class III to Class VI depending on the vehicle. Betamethasone 17 valerate 0.1% (Table 4) varies from Class III to Class VI in different formulations; all of these are available for prescription use.

Another practical problem attributable to this enormous variation in clinical activity determined by the vehicle is in the area of generic substitution for brand name formulations. Changes in the social and political climate in the United States have allowed more generic substitutions of drugs in the past few

**Table 3** Bioavailability of the same concentration of triamcinolone acetonide (0.1%) from different vehicles

| Potency Class from Table 2 | Various formulations of triamcinolone acetonide 0.1% |
|---|---|
| Class III | Aristocort A® ointment |
| Class IV | Kenalog® cream |
| Class VI | Aristocort® cream |



years than for the preceding 30 years. Topical glucocorticoids are no exception, with over 40 generic substitutions for brand name topical glucocorticoids now available.

The first investigation of comparative activity of generic topical glucocorticoids versus the brand name products revealed many glaring differences in the biologic activity of the so-called equivalent formulations (15). Table 5 gives an example of these differences for 0.1% triamcinolone ointment. One hopes that this will be monitored more accurately in the future and that only topical glucocorticoid generics that are biologically equivalent will be allowed on the market in the United States.

Another area of concern is the relation of concentration of drug in the vehicle to amount of drug released over time. Again, the vasoconstrictor assay has been useful in obtaining information on the relation of concentration of glucocorticoid to penetration (14, 15). Many brand name glucocorticoids are available in different concentrations in the same vehicle. Kenalog® (triamcinolone acetonide) is available in 0.025%, 0.1%, and 0.5% concentrations in a cream vehicle. Table 6 shows that there is no difference in biologic activity between any of these three concentrations, which differ by 20-fold. The same is true for Aristocort® cream (triamcinolone acetonide) at concentrations of 0.025%, 0.1%, and 0.5% in the same vehicle (see table 7). Hydrocortisone at concentrations of 1.0% and 2.5% shows no difference in biologic potency

**Table 4** Bioavailability of the same concentration of betamethasone-17 valerate (0.1%) from different vehicles

| Potency Class from Table 2 | Various formulations of betamethasone-17 valerate |
|---|---|
| Class III | Valisone® ointment |
| Class V | Valisone® cream |
| Class VI | Valisone® lotion |

**Table 5** Bioavailability of the same concentration of triamcinolone acetonide 0.1% from generic and brand name ointments as measured by the vasoconstrictor assay

| Formulation | Vasoconstrictor score (30 subjects)[a] |
|---|---|
| Aristocort A®[b] | 74 |
| Generic (Goldline®) | 19 |
| Generic (Rugby®) | 35 |

[a]maximum score = 90
[b]Aristocort A® superior to generics $p < 0.05$



(Table 8). On the other hand, Table 9 shows that fluocinolone acetonide is available in concentrations of 0.01%, 0.025%, and 0.2% in Synalar® cream; statistically significant differences in these formulations exist as measured by the vasoconstrictor assay (R. B. Stoughton, unpublished observations). The least potent is 0.01% Synalar® cream. Synalar® cream 0.025% is more potent than 0.01% Synalar® cream ($p < 0.05$), and 0.2% Synalar® cream is more potent than 0.025% Synalar® cream ($p < 0.05$).

These relationships of concentration of the glucocorticoid to penetration were previously reviewed by Altmeyer & Zaun (16) for other glucocorticoids with similar conclusions. Scholtz & Dumas (17) previously reported no increase in potency on psoriatic lesions for fluocinolone acetonide cream when concentrations varied from 0.0025% to 0.01%.

## *Penetration Enhancers*

Many topically applied drugs have been shown to have beneficial effects on skin diseases. Examples are: glucocorticoids, anticholinergics, antibiotics (antifungals, antibacterials), antiseptic agents (benzoyl peroxide, chlorhexadine, hexachlorophene), anthralin, coal tar, salicylic acid, hydroxy acids, antiparasiticals (pyrethrins, benzoyl benzoate, malthion, thiobendazole), psoralens, and Vitamin A acid. This is an important, but certainly not a complete, list of drugs that can be therapeutic to skin.

Almost all these drugs are in conventional or slightly modified conven-

**Table 6** Bioavailability of different concentrations of triamcinolone acetonide from Kenalog® creams

| Formulation | Vasoconstrictor score (30 subjects)[a] |
|---|---|
| Kenalog® cream 0.025% | 54 |
| Kenalog® cream 0.1% | 57 |
| Kenalog® cream 0.5% | 54 |

[a]No significant difference between the 3 topical formulations

**Table 7** Bioavailability of different concentrations of triamcinolone acetonide from Aristocort A® creams

| Formulation | Vasoconstrictor score (30 subjects)[a] |
|---|---|
| Aristocort® cream 0.025% | 18 |
| Aristocort® cream 0.1% | 20 |
| Aristocort® cream 0.5% | 20 |

[a]No significant differences between the topical formulations



tional vehicles. The therapeutic effect in these vehicles is sometimes perfectly adequate, but partial rather than complete response is the usual observation in managing skin diseases. Therefore, efforts are being directed at improving delivery of the drugs we have, as well as discovering novel drugs.

Many theories have been developed with regard to mechanisms of action of penetration enhancers (16–22), but specific mechanisms are not well understood. A recent article discusses the effect of penetration enhancers on the kinetics of percutaneous absorption (23).

We have already discussed improvement in clinical activity of a given concentration glucocorticoid by a change in the vehicle. For the other therapeutic agents little has been done to prove enhanced therapeutic activity by altering the vehicle. This is surprising in that many penetration enhancers have been reported in the past 20 years. These include dimethylsulfoxide, dimethylacetamide, N methyl pyrrolidone, and Azone® (18–24), among many others. However, development of new, more effective formulations of known topical drugs with these powerful solvents and penetration enhancers has been practically nonexistent. When one views the obvious clinical advantages from developing glucocorticoid formulations that deliver more drug from the vehicle, it is hard to believe that this principle has not been applied to formulations of other drugs for skin diseases. For example, we know that the widely used topical antifungals are very effective against fungus infections of most areas of the body. However, these antifungals are practically useless in treating fungus infections of the nails, hair, and chronic involvement of the palms and soles. They are not effective in these areas because the topical antifungals are unable to penetrate the thick stratum corneum of these struc-

**Table 8** Bioavailability of different concentrations of hydrocortisone from Hytone® creams

| Formulation | Vasoconstrictor score (30 subjects)[a] |
|---|---|
| Hytone® cream 2.5% | 14 |
| Hytone® cream 1.0% | 13 |

[a]No significant difference between the two formulations

**Table 9** Bioavailability of different concentrations of fluocinolone acetonide from Synalar® cream

| Formulation | Vasoconstrictor score (30 subjects)[a] |
|---|---|
| Synalar® cream 0.01% | 28 |
| Synalar® cream 0.025% | 46 |
| Synalar® cream 0.2% | 71 |

[a]Synalar® cream 0.2% > Synalar® cream 0.025% ($p < 0.05$) > Synalar® cream 0.01% ($p < 0.05$)



ures to achieve the necessary concentrations to stop the growth of the organism. Logic would dictate a search for better vehicles to deliver the antifungals through these structures.

We have observed that some of these penetration enhancers are more effective in hairless mouse skin than in human skin, so one has to be careful to use human skin in penetration studies to determine the degree of enhancement of penetration.

There are important opportunities to enhance biologic effectiveness of topical drugs with known penetration enhancers, and this will surely be an important area for progress in treating skin diseases in the future.

## *The Stratum Corneum Barrier*

There is little doubt that the stratum corneum is the only important barrier to penetration of chemicals from the surface to the nucleated epidermis, the corium and areas beyond. Again, for a detailed review see the monograph of Schaefer et al (25). This comprehensive review of all aspects of percutaneous absorption is an excellent source for anyone working in this field.

Recent work has concentrated on the intracellular lipid bilayers that are thought to constitute the main barrier to penetration of chemicals through the stratum corneum (26–39). These barriers have an intracellular origin in membrane coating granules or Odland bodies, which are extruded into the intercellular spaces at the transition zone where the stratum corneum is beginning to form. The discs merge into lamellar sheets between the cells that constitude the stratum corneum. Linoleic acid-rich lipids, acylglucoscylceramide and acylceramide, seem to have an important function in the formation of these lipid, lamellar sheets (33, 39).

In vitro, formation of similar lamellar sheets can be induced by fusing liposomes made of ceramides, cholesterol, palmitic acid, and cholesteryl sulfate (27). Changes in these lamellar lipids can be detected in vivo by differential scanning calorimetry and infrared spectrometry. Thermal variance (35–80°C) can cause major alterations in these lipid structures (32) as do some penetration enhancers also (40).

Vickers showed that the stratum corneum acts as a significant reservoir for topically applied drugs (41). The biologic significance of this was emphasized when he demonstrated that topical glucocorticoids could be detected in the stratum corneum up to 30 days after a single topical application. He also showed that the vasoconstrictor response of human skin to topical glucocorticoid could be elicited 7–10 days after a single application followed by thorough washing of the surface of the skin. This vasoconstriction was redeveloped simply by occluding (hydrating) the same area with occlusive wrappings without any additional topical application of the steroid.

This reservoir for glucocorticoids in the stratum corneum is much greater when the stratum corneum is thoroughly hydrated. Without hydration with the initial application of glucocorticoid, the vasoconstrictor response on reapplication of occlusion will last only a day or two and will show minimal blanching at best. Percutaneous penetration enchancers such as dimethysulfoxide and dimethylacetamide also establish a much greater reservoir of the drug in the stratum corneum (42, 43).

The same principle can be easily illustrated by applying a fluorescent dye to the skin and finding the dye in lower layers of the stratum corneum for many days after the original application when it is immediately followed by washing of the surface (44, 45). More recently an antifungal has been shown to remain in the lower layers of the stratum corneum for several days after a single application (46). Another example of this reservoir effect appears in the Schaefer "minutes technique" of treating psoriasis with anthralin (47), where anthralin is applied topically and removed 30–60 min. later. This gives a good clinical response of the psoriatic lesions even with such a short period of exposure out of 24 hours.

In our laboratory we have recently shown that application of a potent topical glucocorticoid for 90 minutes followed by thorough washing will give a vasoconstrictor response in human skin that is equal to leaving the same glucocorticoid on the skin for 24 hours without washing (K. Wullich, R. Stoughton, unpublished observations).

The role of the stratum corneum as a "vehicle" for storage and delivery of a drug has not in the past been given the attention it deserves. Recent articles call attention to the relationships between the horny layer reservoir and percutaneous absorption in human, rat, and guinea pig (48–50). After 30 minute application times the amount in the stratum corneum determined how much would penetrate in the next 4 days and was consistent with different doses of the drug applied to the surface (49). Previous work (48) showed similar relationships for 10 different molecules, with the stratum corneum concentration determining the total amount of penetration through the stratum corneum. Another study showed a direct correlation of the amount of an

antiviral drug in the stratum corneum and the ability of the drug to prevent infection with the herpes simplex virus (50). This was determined for varied concentrations of iododeoxyuridine in dimethylsulfoxide, using guinea pig skin. Occlusion of the surface of the skin with thin impermeable films in vivo resulted in greatly increased penetration of most drugs applied to the skin. This was first dramatically demonstrated with glucocorticoids (51, 52). The increase in penetration is frequently over ten-fold higher than without occlusion. Many attempts have been made to develop polymer liquid films that contain glucocorticoids with the hope of easy application and increased activity. However, of the ten or more liquid films we have tested, the glucocorticoid gives very little increase in activity and frequently less than without the film, presumably due to binding of the glucocorticoid in the film and prevention of rapid release of the drug. Unlike the films, Cordran® tape, a solid occlusive tape with glucocorticoid in the sticky surface, is far more potent clinically than the same glucocorticoid at the same concentration, in lotion, cream, or ointment vehicles. Apparently the steroid is released adequately from the tape. Hydration enhances penetration, and any system that hydrates the stratum corneum will increase penetration.

More work is needed to measure the rates of disappearance of drugs from the stratum corneum in relation to the applied topical dose. Clinical use of topical drugs and application schedules are only guess work at this time. Such studies as those just discussed may bring some rational thought into dosage scheduling of topical drugs.

The major rate limiting step in percutaneous absorption is the stratum corneum (25, 53, 54). However, pure stratum corneum is very difficult to preserve intact without producing artifacts in its preparation for in vitro testing, that, in turn, provide variable and usually unreliable results compared to whole, intact skin of humans and animals. The results for measurements of penetration of given drugs and chemicals in the same animal range widely from one investigator to another, and from one species to another (55–58). This has led many investigators to experiment with artificial membranes (4, 59, 60). This entire area of varying measurements with different membranes leaves the field quite confused, and any conclusions regarding penetration in vivo drawn from in vitro data have to be seriously questioned. In vivo penetration data in various animals are not very reliable for predicting in vivo penetration of human skin. And, of course, different areas of human skin demonstrate wide ranges of variability in how they allow penetration of any given drug (61).

Some work has shown reasonably good correlation of in vitro and in vivo penetration of human skin with a variety of drugs (55, 62, 63). In vitro penetration of the drug seems to be greater than in vivo (53).

## *Penetration of Nails*

Nails are modified keratin structures that are quite different from stratum corneum or hair in many different ways (64). The nail contains only 1% lipid materials and absorbs less water than stratum corneum, which has a much larger amount of lipid derivatives (65, 66). One would therefore expect different permeation characteristics for the nail as compared to stratum corneum. Burch & Winsor (67) first reported water diffusion through the nail. Spruit (68) reported water transmission through the nail equal to that through the stratum corneum, with the rate of transmission for thicker nails less than that through thinner nails. Walters et al (65, 69, 70) report definite penetration of nails by a series of alkanols. They found no evidence of enhancement of nail penetration by alkanols when DMSO was added to the vehicle (65). Schaefer (71) found evidence of penetration of econozole into the nail with levels of $10^{-5}$–$10^{-4}$ M present in the inner layers of the nail. However, the radioactivity measured was not proved to be associated with econozole; this always raises the question whether the radioactivity was a breakdown product of the original radioactive drug, particularly when a very small percentage of the original radioactive drug is detected. Certainly, topical applications of such antifungals as Tinactin®, Haloprogin®, undecelynic acid, Lotrimin®, and Micatin® have not been known to influence the clinical course of onychomycosis (fungal infections of the nails) in humans.

In our laboratory we have recently developed two systems for detecting antifungal agents in toe nails after topical application in vitro for thirty days, using modified Franz cells (K. Wullich, R. Stoughton, unpublished observations). Diamond files 2–5 mm wide are used to file the nails. The filings are taken from five successive levels through the nail, starting at the top. Care is taken to prevent contamination from previously filed areas, and controls are done with the antifungal applied for only 30 min. and then filed as the nails with 30 day exposures were filed.

The filings are treated in two ways: they were (*a*) placed on a Sabouraud plate innoculated with *T. mentagrophytes* spores and (*b*) placed on a special tape that is then innoculated with *T. mentagrophytes* spores (Knight, 72). Zones of inhibition are determined for the Sabouraud plate, and the degree of inhibition of spores on the tape quantitated according to Knight's original method (72).

Using this system to measure penetration of nails by antifungals, we have found evidence of penetration of the entire toe nail by Loprox®, Griseoderm®, and oxiconazole. Antifungals showing no evidence for penetration of the entire nail with these bioassay systems are Haloprogin®, Lotrimin®, Micatin®, Tinactin®, undecylenic acid, and thiabendazole (Table 10). Because of their thickness, penetration through the entire nail may take many days for most drugs, and probably most will not go through the nail in

therapeutic concentrations over any time period. The encouraging results we have seen with antifungals suggests that further attempts to measure and improve penetration through the nails will be rewarding. To date no topical agent has been shown clinically, in careful double blind studies, to have significant therapeutic activity on diseases of the nail. Unfortunately there is an excess of anecdotal "evidence" in the literature of successful therapy of nail diseases with topical drugs.

## *Regional Differences in Penetration*

In the design of topical drugs and in their use, one must consider regional differences in penetration of human skin (73, 74). There are vastly different penetration rates between the skin of the sole of the foot and of the face, for example. There is practically no barrier to absorption through the scrotal skin. Mucous membranes offer little resistance to the penetration of most chemical agents (75), although the constant "washing" action of mucous rapidly removes applied agents from the surface. Thus topical steroids have little topical beneficial effect on inflammatory diseases of the mucous membranes of the mouth because of their rapid removal from the surface. Orabase® was designed as a thick sticky formulation to treat mucous membrane lesions. However, it has not proved very helpful in treating inflammatory diseases of the mucous membranes since the release rate of triamcinolone acetonide from this vehicle is very poor as measured by the vasoconstrictor assay (R. Stoughton, personal observations). By contrast local anesthetics are much more active on mucous membranes than on the cutaneous surface (76).

In management of psoriasis with topical glucocorticoids any given steroid formulation commonly results in a distinct grading of response of the psoriasis lesions based on region. The dorsa of the feet and hands, elbows and knees respond poorly, but better than the palms and soles, which rarely respond. Lesions on the upper thighs respond better than lesions on the lower

**Table 10** Toe nail penetration in vitro by various brand name antifungals topically applied[a]

| Formulation | Inhibition of *T. mentag.* on Sabouraud's | Inhibition of *T. mentag.* on tape |
|---|---|---|
| Micatin® cream | 0 | 0 |
| Haloprogin® cream | 0 | 0 |
| Tinactin® lotion | 0 | 0 |
| Lotrimin® lotion | 0 | 0 |
| Desenex® cream | 0 | 0 |
| Loprox® lotion | + | + |
| Griseoderm® lotion | + | + |

[a]Filings of nail taken from bottom 25% of the nail

legs: lesions on the chest better than those on the upper arms, and those on the face best of all. Thus the quantitative measurements of penetration of various regions correlate well with the clinical observations of regional response.

Other examples of specific penetration problems by region are the hair bulb, where the hair is made, and the sebaceous glands of human skin. *Tinea capitis* is a disease in which dermatophytes grow into the scalp hair. Topical antifungals are useless because they are unable to traverse the follicular canal from the surface. The penetration into the corium through the epidermis is sufficient to inhibit growth of organisms in the corium, according to an in vitro study (77), but, in vivo, any of the antifungal reaching the hair shaft is not in sufficiently high concentrations to inhibit the organisms, probably because of rapid diffusion into the vascular rivulets where the antifungal is carried away from the local site.

In *alopecia totalis*, topical low strength glucocorticoid under occlusion will cause regrowth of hair, but not even the strongest topical glucocorticoid will cause regrowth of hair when the surface is not occluded with an impermeable wrap (14).

I do not know of any evidence for change in sebaceous gland function due to direct topical application of a drug. Any effect is always due to systemic activity of the drug. Retinoids such as *cis*-retinoic acid are a good example of systemic dosage giving a precipitous fall in sebaceous gland function, while local application has no effect. The same can be said for all the anti-andogens that have been tried locally to influence sebaceous gland function.

Sweat glands show a diminishing response to anticholinergics with depth in the corium (78).

These regional differences in penetration are important to the clinician who treats disease and to toxicologists in predicting both topical and systemic reactions to topical exposure in relation to the areas exposed.

## *Summary*

Some practical applications of basic information in percutaneous absorption have been reviewed. Drug release from vehicles is discussed in relation to glucocorticosteroids. Penetration enhancers are reviewed with emphasis on the need for further investigations and applications of enhancers for clinical use. The role of the stratum corneum as a barrier to and a reservoir for drugs is discussed. Special problems in penetration as presented by regional anatomic variations, nails, and follicles are mentioned. Overall, we review some practical problems existing in the penetration of drugs through human skin.

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