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LITERATURE SURVEY

Drug Delivery to Local Subcutaneous Structures Following Topical Administration

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This article brings together a collection of results and observations which demonstrate the achievement of significant drug delivery to local subcutaneous structures following topical administration. It is probably no exaggeration to say that the concept of using the transdermal route to advantageously reach lower tissue, such as the muscle beneath the subcutaneous fat, goes directly against conventional thought. Indeed, the cutaneous microvasculature has long been offered as an excellent example of a classical "sink" phenomenon; that is, following penetration through the stratum corneum, epidermis, and upper dermis, it has been held that the permeating species will then pass into one of the small blood vessels forming the microcapillary network and hence be systemically diluted in the circulatory system. The argument seems totally reasonable: the stratum corneum is an excellent barrier to the passage into the body of many substances that contact with the skin. Thus, in the large majority of cases, drug arrival beneath the stratum corneum is slow such that the concentration of material at this point is invariably very much less than that present on the skin surface. These conditions are precisely those implicit in a "sink" situation and, coupled with the extensive dermal capillary matrix, it is not surprising that further penetration into the tissue has been considered unlikely.

On closer perusal of the literature, however, it becomes apparent that a small but significant number of reports exist which show that deeper penetration can take place and that subcutaneous drug levels can be achieved following topical application which cannot be reached after parenteral or oral administration of the active agent. This brief review gathers the results available in the (admittedly) diverse sources to reanalyze conventional thought and to stimulate inquiry into this important aspect of drug input *via* the skin.

SUBCUTANEOUS DRUG DELIVERY: EXPERIMENTAL OBSERVATIONS

Over the last 15 years, there have appeared several communications which address the question of local subcutaneous drug delivery following topical dosing. These encompass a diverse array of chemical substances such as dimethyl sulfoxide, a salicylate derivative, steroids, and commonly used organophosphorous pesticides. In almost all cases, the studies have involved animal models since excision of tissue and its analysis is possible. However, evidence has been found that the same deeper penetration from the skin surface occurs in humans; further, *a priori*, there is no reason to suggest that the animal experiments performed are not good qualitative predictors, at least of the behavior expected in humans. It is believed, therefore, that the following discussion provides tantalizing and somewhat novel information on the potential of the topical route for the delivery of chemotherapeutic agents.

In 1968, Gorog and Kovacs (1) studied the anti-inflammatory properties of dimethyl sulfoxide (DMSO) in rats. It was found that carrageenan-induced rat paw edema was improved by both oral and topical DMSO therapy. Furthermore, and of greater relevance, arthritis induced by Mycobacterium adjuvant was inhibited to a greater degree by topical, rather than oral, DMSO administration. In the same way, DMSO applied to the skin of rats had an inhibitory effect on arthritis produced experimentally by 6-sulfanilamidazole. These early data, therefore, argue strongly for local deep penetration of the solvent.

A more detailed investigation on the disposition of topically applied ^{3}H-labeled escin was performed in mice and rats by Lang (2). The radioactive compound was ap-

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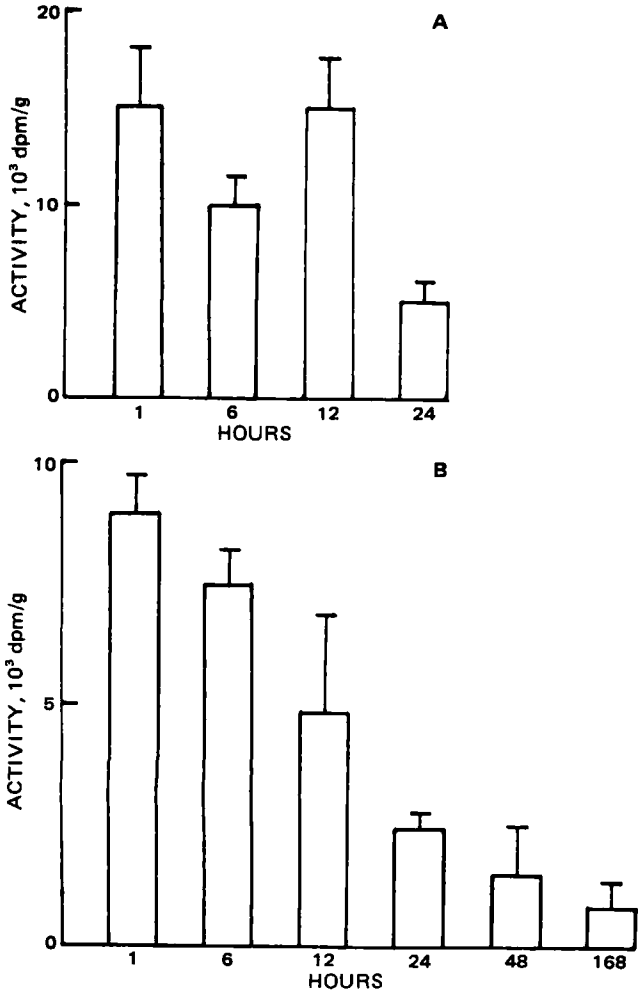

Figure 1—*Radioactivity in mouse (A) and rat (B) back muscles at various times after cutaneous application of [^{3}H]escin. (Data taken from Ref. 2.)*

plied to the backs of animals, and tissue distribution was subsequently evaluated at various times by organ dissection after sacrifice. The tissues monitored were the back muscles, blood, liver, kidney, heart, lungs, spleen, testes, brain, leg muscle, femur, and stomach lining. In the mouse the amount of activity detected in the back muscle beneath the skin application site exceeded by 20–100 times the amount detected in any of the other regions. A similar pattern of behavior, though less pronounced (10–30 times greater in the back muscle) was observed in the rat. The time course of disposition to the back muscle in the two species is shown in Fig. 1. It is apparent that significant levels of escin are present in the deeper local tissue over prolonged periods of time. A further observation reported in this paper (and elsewhere) also implies that all material penetrating the upper skin layers is not immediately subjected to a sink condition. Measurements were made of activity residing in the skin beneath the application site and in several skin strips 0.5 cm wide at distances of 1–5 cm from the center of the application zone. The data (Fig. 2) for the mouse clearly show that radial movement of drug within the skin is an additional transport pathway to the expected capillary uptake process. It should be pointed out that implied radial movement within the skin has been reported on other occasions. It is a common observation

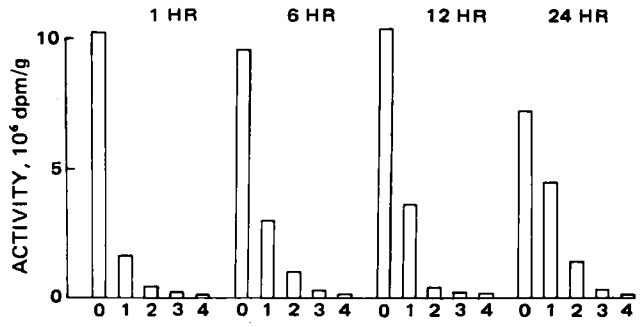

Figure 2—*Radioactivity located in several skin areas at various times after cutaneous application of [^{3}H]escin to the mouse. Column 0 corresponds to skin directly under the application site. Columns 1, 2, 3, and 4 refer to skin strips at 0.5-cm intervals away from the contact zone. (Data taken from Ref. 2.)*

that topical vasodilators capable of producing visible erythema induce a redness on the skin surface that expands with time beyond the region of application (3). As an example, the work by Fountain *et al.* (4) with the methyl ester of nicotinic acid may be cited (Fig. 3); recently, this line of investigation has been pursued in a more quantitative sense (5), and the radial transport of methyl nicotinate absorbed into the skin has been measured as a function of drug concentration and time (Table I). The rapidity of the outward movement implies that passive diffusion cannot be the mechanism involved, and it has been suggested that the cutaneous vasculature must participate. However, it is evident, whatever the mechanism, that the role of the microcirculation in this case is not merely depletive. It is also true that radial movement within the skin as assessed by visual detection of a pharmacological response is not limited to vasodilation, but has also been witnessed with the opposite effect produced by corticosteroids (6). Thus, the evidence for lateral transport prior to removal by dermal capillaries seems quite firm.

The most extensive study of local subcutaneous delivery of chemical substances was by Marty *et al.* (7–11) who

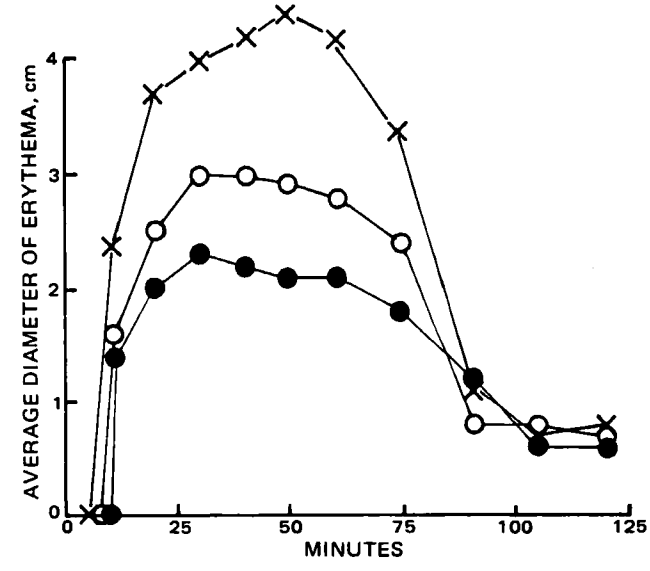

Figure 3—*Lateral movement of methyl nicotinate in the skin as assessed by erythematous area. The drug was applied in aqueous solution at ambient temperature (25°). Each data point is the average of five readings from various sites. Key: methyl nicotinate concentration (×) 1.0%; (○) 0.5%; (●) 0.25%. (Data from ref. 5.)*

Table I—Radial Transport of Methyl Nicotinate in the Dermis as a Function of Time (t) for Two Topically Applied Concentrations (C) with Various Application Durations (t_1)[a]

Erythematous Reaction to Methyl Nicotinate[b]					
C = 997 mM			C = 100 mM		
t_1, sec	t, min	A, cm^2	t_1, sec	t, min	A, cm^2
15	2.25	1.4	120	2.5	1.4
	4	7.5		6	2.7
	7	13.9		9.5	5.9
	10	18.4		15	7.1
30	2.75	3.5	600	4	2.4
	4	5.5		7	4.6
	5	11.4		11	8.7
	6	14.4		16	11.2
	7	15.7	1200	6	2.6
	10.5	18.8		8	7.7
60	2	4.5		12	11.6
	3	7.7		18	14.7
	5	15.4		23	19.1
	8	23.1			
	14	25.8			

[a] Data taken from Ref. 5. Methyl nicotinate was applied in aqueous solution to a skin surface area of 0.79 cm^2. [b] A = area of erythema.

attempted to explain the localized and deep therapeutic effect of certain dermatological preparations. These authors demonstrated, in each case, that percutaneous absorption was accompanied by diffusion and retention in the connective and muscle tissues located beneath the administration area. Alcoholic or propylene glycol solutions of radiolabeled thyroxine, triiodothyronine, estradiol, dexamethasone, and diisopropyl fluorophosphate were applied to the shorn abdomen or back of Sprague–Dawley rats, and the contact zones were protected and covered for periods of between 0.5 and 6 hr (7). At the end of the test the rat was killed and blood was drawn from the carotid artery. The site of skin application was dissected and fragments of subcutaneous tissue, muscle, and brown interscapular fat were removed from below the contact area. Samples of liver, kidneys, and part of the muscle from a rear paw were also collected and weighed.

Liquid scintillation counting was used to determine the radioactive concentrations in the various organs; the results were converted to amounts of drug present in nanograms per gram of tissue (Table II). For thyroxine, after 1 hr, the levels in plasma, liver, kidneys, and skeletal muscle were not significantly different. Beneath the application area, the radioactive concentration was 100 times greater in the subcutaneous tissue than in the plasma. The subjacent muscle showed the same phenomenon though of less intensity. The ratio (concentration in muscle below the application zone/concentration in paw muscle) increased substantially with time (4.2 at 30 min, 8.6 at 60 min, and 14.3 at 2 hr). Triiodothyronine gave similar results with considerable retention in the subcutaneous region and deeper muscle. Liver and kidney levels matched the plasma concentration. Estradiol showed the greatest retention in the subcutis and muscle below the application area (20 and 40 times the plasma level, respectively). The ratio of the skin muscle concentration to the paw muscle concentration was 17. Dexamethasone showed the lowest penetration rate, and enhanced drug delivery to the subjacent tissue was barely significant. Absorption of diisopropyl fluorophosphate was greatest, on the other hand, but resulted in little local muscle retention over that found elsewhere. In general, however, the authors showed accumulation in local skin muscle under the application zone.

It was suggested that this enhancement corresponded to molecular diffusion in the deep direction independent of the level of vascular perfusion (the latter being anatomically distinct for the regions of viable epidermis, dermis, and subjacent muscle). Further, the authors implied that, contrary to accepted concepts (12), the blood supply to the dermis is *not* capable of resorbing certain chemicals proportionately to their penetration through the epidermis. Thus, the substrate accumulates with time and is able to diffuse to deeper tissue. To support their hypothesis, Marty *et al.* (7) drew attention to the fact that both dexamethasone (a poorly absorbed substance with low solubility in water) and diisopropyl fluorophosphate (soluble in water and oil) show little accumulation, suggesting that the blood supply is able to transport these substances away in solution relatively efficiently. Conversely, the poorly water soluble thyroxine, triiodothyronine, and estradiol show much diminished resorption by the microvasculature and establish significant levels further into the tissue with increasing contact time.

In two subsequent reports (8, 9), the disposition of tritiated dexamethasone in mice and rats following topical application was compared with oral administration. Pro-

Table II—Distribution of Various Substances in Different Tissues in the Rat after Application to the Skin[a]

Penetrating Species/Amount Deposited, μg	Experiment Duration, hr	Tissue Concentration, ng/g						Significance of Difference Between A and B
		Plasma	Liver	Kidneys	Subcutaneous Tissue[b]	Muscle under Application Zone (A)	Paw Muscle (B)	
[^{125}I]Thyroxine/400 (N = 7, 6, 5)	0.5	0.7 ± 0.2	1.1 ± 0.4	2.1 ± 0.6	55 ± 11	3.8 ± 1.0	1.0 ± 0.5	$p < 0.05$
	1	1.60 ± 0.5	2.9 ± 1.2	2.6 ± 0.7	132 ± 42	8.0 ± 2.4	1.5 ± 0.6	$p < 0.05$
	2	4.0 ± 0.9	3.9 ± 1.8	5.6 ± 0.7	178 ± 45	23 ± 2.3	1.6 ± 0.2	$p < 0.01$
[^{125}I]Triiodothyronine/400 (N = 6,6)	1	2.5 ± 0.2	3.6 ± 0.7	5 ± 1	111 ± 15	10 ± 3	2.5 ± 0.9	$p < 0.05$
	2	3.9 ± 0.3	5 ± 1	8.3 ± 2.2	240 ± 70	23 ± 4.4	2.0 ± 0.4	$p < 0.01$
[^{3}H]Estradiol/110 (N = 6)	2	1.0 ± 0.3	4 ± 1.5	2.2 ± 0.4	370 ± 87	42 ± 15	2.4 ± 0.6	$p < 0.01$
[^{3}H]Dexamethasone/100 (N = 12, 5, 5)	2	0.19 ± 0.06	1.05 ± 0.33	0.65 ± 0.14	8.1 ± 2.1	0.75 ± 0.14	0.27 ± 0.08	$p < 0.05$
	4	0.19 ± 0.03	1.52 ± 0.30	0.67 ± 0.20	5.2 ± 0.9	0.7 ± 0.3	0.25 ± 0.01	$p = 0.05$
	6	0.34 ± 0.10	1.0 ± 0.1	1.44 ± 0.60	4.8 ± 0.6	1.6 ± 0.6	0.42 ± 0.15	N.S.
[^{3}H]Diisopropyl fluorophosphate/20,000 (N = 7)	3	1210 ± 114	3100 ± 640	8500 ± 2400	35800 ± 15000	2450 ± 1000	590 ± 150	$p < 0.05$

[a] Data taken from Ref. 7. [b] All values significantly different from those in plasma, $p < 0.01$.

Table III—Percutaneous Absorption of [^{3}H]Dexamethasone in Mice [a]

Application Duration, hr [b]	Tissue Concentration, ng/g: Subcutaneous Tissue	Abdominal Muscle	Homogenized Mouse
1	49 ± 19 [c]	4.1 ± 1.3 [c]	0.90 ± 0.14
2	69 ± 10 [c]	12 ± 3.5 [c]	2.6 ± 1.7
4	97 ± 30 [c]	29 ± 13 [d]	3.3 ± 1.0

[a] Data taken from Refs. 8 and 9. Dose applied = 19 μg/cm^2. [b] N = 5 at 1 hr; N = 6 at 2 and 4 hr. [c] Significance of difference between tissue and homogenized mouse, $p < 0.05$. [d] Significance of difference between tissue and homogenized mouse, $p < 0.01$.

cedures similar to those described in the previous study (7) were used; Tables III and IV summarize the results. It is plain that observations consistent with those of the earlier work were found; for example, in mice, under the area of topical application, the levels of radioactivity in subcutaneous tissue and in the lower muscle were 30 and 10 times higher, respectively, than in other tissues. Levels and distribution were quite different following oral administration; the plasma concentration was higher and large amounts were located in liver and kidney. Such a pattern of behavior (topical *versus* oral) was intimated to be of potential importance in terms of the metabolic inactivation of the administered chemical.

Further investigation into the fixation of topically applied materials in the superficial structures of the skin, and its importance in problems of decontamination and bioavailability, was then conducted (10, 11). The materials studied were diisopropyl fluorophosphate, malathion, parathion, estradiol, and progesterone. Comparable methodology was employed in the rat and mouse animal models (Tables V, VI, and VII). In the mouse, the amount of diisopropyl fluorophosphate found in the abdominal muscle under the application region and in the local vicinity represented ~28% (105 μg) of the total quantity absorbed; the remaining 72% was diluted in almost the entire animal. Malathion produced similar observations with 36% of the absorbed chemical being located in subcutaneous tissue at or near to the application zone. The subjacent tissue showed malathion levels of the order of 1000 μg/g compared with the animal carcass concentration

Table VII—Distribution of Diisopropyl Fluorophosphate, Malathion, and Parathion in Rat Tissues after Percutaneous Application [a]

Tissue	Tissue Concentration, μg/g: Diisopropyl Fluorophosphate	Malathion	Parathion
Subcutaneous tissue	130 ± 25 [b]	145 ± 20 [b]	155 ± 60 [b]
Muscle beneath zone	14 ± 2 [b]	2.5 ± 0.6	1.45 ± 0.45 [c]
Paw muscle	4.0 ± 1.5	1.7 ± 0.6	—[d]
Blood	1.3 ± 0.3	3.6 ± 0.6	0.4 ± 0.1
Liver	4.1 ± 0.5 [b]	1.4 ± 0.2	0.10 ± 0.02 [c]
Plasma	2.3 ± 0.7	—[d]	—[d]
Kidney	8.9 ± 1.5 [b]	2.3 ± 0.7	0.20 ± 0.03

[a] Data taken from Ref. 10; 100 μl was applied over a surface area of 5 cm^2 for 3 hr. N = 7 for diisopropyl fluorophosphate, N = 8 for malathion and parathion. [b] Significance of the difference between blood and tissue concentrations, $p < 0.01$. [c] Significance of the difference between blood and tissue concentrations, $p < 0.05$. [d] —, Not detectable.

Table IV—Tissue Concentrations of [^{3}H]Dexamethasone Following Topical and Oral Administration to Rats [a]

Route	Time, hr [b]	Tissue Concentration, ng/g: Plasma	Subcutaneous Tissue	Abdominal Muscle	Leg Muscle	Liver	Kidneys
Topical	2	0.19 ± 0.06	8.1 ± 2.1 [c]	0.77 ± 0.14 [c]	0.27 ± 0.08	1.05 ± 0.30	0.65 ± 0.14
	4	0.19 ± 0.03	5.2 ± 0.9 [c]	0.68 ± 0.30 [d]	0.25 ± 0.04	1.52 ± 0.30	0.67 ± 0.20
	6	0.34 ± 0.10	4.9 ± 0.5 [c]	1.6 ± 0.6 [c]	0.43 ± 0.15	0.99 ± 0.10	1.44 ± 0.50
Oral	1	22 ± 1	13 ± 2	11.5 ± 1.3	11.6 ± 1.7	145 ± 9	44 ± 6
	4	19 ± 0.5	8.1 ± 1.6	8.9 ± 0.4	9.5 ± 0.7	168 ± 27	36 ± 3
	24	2.7 ± 0.4	1.6 ± 0.5	1.50 ± 0.35	1.5 ± 0.3	11 ± 1.6	3.6 ± 0.6

[a] Data taken from Refs. 8 and 9. The topical dose was 19 μg/cm^2; the oral dose was 40 μg/kg. N = 5 for all times except t = 2 hr (topical) for which N = 12. [b] Time = duration of application (topical) or survival time (oral). [c] Significance of difference between tissue and plasma, $p < 0.05$. [d] Significance of difference between tissue and plasma, $p < 0.01$.

Table V—Percutaneous Absorption of [^{3}H]Diisopropyl Fluorophosphate, [^{35}S]Malathion, and [^{35}S]Parathion in the Mouse [a]

Penetrating Species [b]	Quantities of the Applied Dose Found in Tissues: Muscle Under and Circumscribed at Application Area, μg	%	Mouse Carcass, μg	%	Overall Absorption, μg	%
Diisopropyl fluorophosphate	105 ± 10	1.05 ± 0.10	250 ± 60	2.5 ± 0.6	355 ± 70	3.5 ± 0.7
Malathion	60 ± 10	0.50 ± 0.08	110 ± 25	0.9 ± 0.2	170 ± 40	1.4 ± 0.3
Parathion	50 ± 8	0.40 ± 0.06	130 ± 25	1.0 ± 0.2	180 ± 20	1.4 ± 0.2

[a] Data taken from Ref. 10; 10 μl was applied over a surface area of 1 cm^2 for 1 hr. [b] N = 6 for diisopropyl fluorophosphate and parathion, N = 7 for malathion.

Table VI—Tissue Concentrations of Diisopropyl Fluorophosphate, Malathion, and Parathion after Absorption in the Mouse [a]

Penetrating Species [b]	Tissue Concentration, μg/g: Muscle Under Application Area (M_1)	Circumscribed Muscle (M_2)	Carcass (B)	M_1/B	M_2/B
Diisopropyl fluorophosphate	3920 ± 520	1610 ± 610 [c]	11 ± 3.5	355	145
Malathion	1880 ± 570	650 ± 200 [d]	3.4 ± 0.8	550	190
Parathion	2140 ± 730	530 ± 180 [e]	4.0 ± 0.7	535	130

[a] Data taken from Ref. 10; 10 μl was applied over a surface area of 1 cm^2 for 1 hr. [b] N = 6 for diisopropyl fluorophosphate and parathion, N = 7 for malathion. [c] Significance of the difference between M_1 and M_2 (by the paired series method), $p < 0.001$. [d] Significance of the difference between M_1 and M_2 (by the paired series method), $p < 0.02$. [e] Significance of the difference between M_1 and M_2 (by the paired series method), $p < 0.05$.

Table VIII—Skin Absorption of Estradiol and Progesterone in the Mouse [a]

Steroid	Concentration, μg/g	Conc. in Tissue Under Application Zone, ng/g		Conc. in Whole Crushed Mouse, ng/g
		Subcutaneous	Muscle	
Estradiol	600	1695 ± 350	804 ± 191	43 ± 8
Progesterone	5000	43,600 ± 1100	9350 ± 2900	342 ± 52

[a] Data taken from Ref. 11.

Table IX—Local Concentrations of Steroids in Subcutaneous Tissue Beneath the Application Zone on the Skin after 2 hr [a]

Species	Steroid/Conc., %	Reference Conc.[b] (S), ng/g	Concentration Ratio (Tissue/S)	
			Subcutaneous	Muscle
Mouse	Estradiol/0.06	43 ± 8	39	19
Rat[c]	Estradiol/0.06	1.93 ± 0.18	75	11
Mouse	Progesterone/0.5	342 ± 52	125	27
Rat	Progesterone/0.5	15.1 ± 1.1	200	19

[a] Data taken from Ref. 11. [b] The reference concentration for the mouse is that in the whole crushed carcass after local excision; for the rat, the reference is plasma concentration. [c] After subcutaneous injection (10 μg/kg), S = 0.88 ± 0.05 and tissue/S = 2 (subcutaneous) and 0.75 (muscle).

of <5 μg/g. The data for parathion paralleled those for malathion quite closely. With the same substances in the rat, essentially the same pattern of behavior was found (Table VII). It is apparent, therefore, that the organophosphorous pesticides represent another class of compound for which subcutaneous fixation takes place.

For the steroids estradiol and progesterone (11) (Tables VIII and IX), accumulation was again found in the connective tissue of the abdominal muscle in the region under application. The effect was not seen after subcutaneous administration (Table IX). As before, the authors argued that the results demonstrate slow exchanges between blood and tissue such that the steroids are not removed efficiently as they diffuse in the intercellular fluids. Their observations were emphasized to be distinct from the classic "reservoir" effect noted for this class of compound (13–15), but it was suggested that the latter would mean that the likelihood of deeper penetration was increased. It was concluded that the data constitute pharmacokinetic proof contributing to the confirmation of local subcutaneous pharmacological effects of topically administered hormones.

Finally, in a recent paper (16) Rabinowitz *et al.* have studied the local, articular, and systemic absorption of oral and topical salicylates in dogs and humans using radioisotope techniques. Specifically, tissue disposition following oral [^{14}C]aspirin was compared with that after topical administration of triethanolamine [^{14}C]salicylate. In the canine model, one group of five beagles received per os a 500-mg capsule of [^{14}C]aspirin; a second group received 10 g of ^{14}C-labeled triethanolamine salicylate cream applied to the shaved right knee. Urine and blood samples were taken at 30 and 60 min, and the animals were then killed and tissue samples were analyzed. In the human model, six subjects with seropositive adult-onset rheumatoid arthritis and active knee synovitis were studied. Each subject was dosed, on separate occasions, orally with a [^{14}C]aspirin capsule and topically with 10 g of triethanolamine [^{14}C]salicylate cream to one knee; 2–6 weeks elapsed between the two administrations. Blood and urine samples were taken pretreatment and at 60 and 120 min postdose. At 120 min a synovial fluid aspiration was performed, taking care to avoid sample contamination from the application site. Patients were also asked to rate their subjective pain relief after the two medications.

Table X—[^{14}C]Salicylate Tissue Concentrations after Oral and Topical Salicylate Administration to Dogs [a]

Tissue	[^{14}C]Salicylate Concentration, μg/g	
	Oral	Topical
Blood		
30 min	34.80 ± 2.33	2.60 ± 0.02
60 min	30.60 ± 0.24	0.22 ± 0.02
Urine	12.57 ± 5.16	0.16 ± 0.09
Skin	0.64 ± 0.09	312.20 ± 40.80
Muscle	1.76 ± 0.16	38.20 ± 5.16
Fascia	1.04 ± 0.28	16.40 ± 1.96
Fat pad	1.00 ± 0.10	5.60 ± 1.20
Tendon	0.20 ± 0.03	3.00 ± 0.44
Ligament	0.50 ± 0.16	2.00 ± 0.20
Cartilage	0.43 ± 0.03	1.62 ± 0.49
Synovial fluid	1.00 ± 0.10	0.80 ± 0.12
Synovium	0.62 ± 0.10	0.74 ± 0.12

[a] Data taken from Ref. 16; all values are mean ± *SEM*.

Blood levels achieved in dogs after topical dosing were 10–100 times lower than those after oral administration of an equimolecular quantity of salicylate (Table X). However, the topical route resulted in higher local salicylate levels: the skin level was, expectedly, highest, but superior levels were seen in all local deeper tissues (ligament, tendon, cartilage, fascia, fat). The adjacent muscle showed 20 times more radioactivity after topical than oral administration.

Despite blood level differences spanning orders of magnitude (oral ≫ topical), topical dosing in humans produced 60% of the salicylate level in synovial fluid found after oral aspirin administration (Table XI). Subjective improvement was reported by two-thirds of the study group for both salicylate administration routes. Hence, once again, topical delivery is seen to produce high local subcutaneous levels of drug despite appreciably reduced blood concentrations. Direct deep penetration is thus the mechanism implicated. The authors of this study concluded that the lipid solubility of triethanolamine salicylate permits it to remain localized and to be slowly absorbed into the blood. This suggested a desirable feature for providing pain relief of local discomfort without systemic side effects. Parenthetically, a study[1] performed in the rabbit using two commercial preparations[2] of triethanolamine salicylate found as much salicylate in the muscle beneath the application site as in the same tissue

[1] A. Fujii, L. G. Nutine, and E. S. Cook, personal communication.
[2] Asperheat and Aspercreme; Thompson Medical Co., Inc., New York, N.Y.

Table XI—[^{14}C]Salicylate Concentrations in Blood, Urine, and Synovial Fluid 1 and 2 hr after Oral and Topical Salicylate Administration to Humans [a]

Tissue	[^{14}C]Salicylate Concentration, μg/ml			
	Oral		Topical	
	1 hr	2 hr	1 hr	2 hr
Blood	10.27 ± 1.04	10.33 ± 1.06	0.03 ± 0.00	0.08 ± 0.01
Urine	0.64 ± 0.13	1.45 ± 0.27	0.02 ± 0.01	0.18 ± 0.06
Synovial fluid	0.29 ± 0.03	0.40 ± 0.08	0.16 ± 0.02	0.25 ± 0.04

[a] Data taken from Ref. 16. All values are mean ± *SEM*; $N = 6$ for $t = 1$ hr, $N = 4$ for $t = 2$ hr.

following oral dosing of aspirin. Also, a double-blind investigation carried out by Golden (17) using similar salicylate preparations[2] on 40 patients again indicated that equally effective subjective pain relief could be attained using topical triethanolamine salicylate as with oral aspirin. The topical delivery route was suggested to offer a superior alternative in the alleviation of certain rheumatic conditions.

CONCLUSIONS

The experimental work summarized in this survey leaves little doubt that the principle of subcutaneous delivery of topically applied substances is established. Together with the observations of lateral movement of penetrating materials within the dermis, it is apparent that the vascular supply of the skin is not always a perfect "sink." The limited data available is teasing and implies that deeper penetration may be a far more ubiquitous phenomenon than had ever been thought possible; in a sense, the behavior has rarely been seen (and hence assumed not to exist) because few have bothered to look for it. As with all research, additional studies will provide further clarification and delineation of these issues. For example, further kinetic information and, hence, the residence times of various penetrating species as a function of depth into the tissue, and the quantity of material present subcutaneously, await clearer assessment. More information is required about the amount of applied substance absorbed and what fraction of that amount is localized in the deeper tissues. In terms of a complete overview of percutaneous absorption as a drug delivery process, it is important that the aspects discussed here are not ignored. As for practical applications, the clinical one is self-evident and, even on the basis of the results reviewed here, has been repeatedly alluded to by the workers involved: deeper penetration can concentrate more active compound in local affected muscular tissue than can practical alternative administration routes. Better (or at least equivalent) therapy is possible, therefore, without systemic distribution of the drug, *i.e.*, significant blood levels, and possible side effects. The ramifications of this potential in terms of pharmacology and pharmacokinetics warrant further study.

ADDENDUM

Since the submission of this article two further examples of local deep penetration after topical administration have been brought to our attention. Areh (Ph.D. thesis, Massachusetts College of Pharmacy and Allied Health Science, 1982) prepared a number of salicylate derivatives and demonstrated, in rabbits, that therapeutic levels could be achieved in local muscle tissue after transdermal delivery. Wada *et al.* [*J. Pharm. Pharmacol.*, **34**, 467 (1982)] considered the percutaneous absorption and anti-inflammatory activity of indomethacin administered in a topical ointment to rats. They found that the drug concentration in the muscle of the treated paw was very high and ~10 times that in the tissue of any other paw and 7 times that in the blood.

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