THE ACTION OF DRUGS ON THE SKIN[1]

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The skin is more accessible to observation and treatment than any other part of the body, but our knowledge of its pharmacology is rather limited. Investigators in many different fields have used the skin for their experiments because it happened to be convenient—not because they were particularly interested in it. Reports of much of this work are scattered and not easily accessible, so that it seems useful to review some of it for pharmacologists as well as dermatologists. This article aims to survey a part of the field in detail; in many sections, however, space will only permit brief indications of where information is to be found. Special emphasis will be given to recent work and to human pharmacology. The literature on abnormal skin is not covered.

Methods of Applying Drugs Locally

A drug whose effects on the skin are to be studied may be applied in various ways. It may be merely placed on the intact skin, it may be rubbed in, driven in by iontophoresis, pricked in, or injected intradermally or intraarterially. The advantages and disadvantages of these various methods will be briefly discussed.

Contact and inunction.—These provide more uniform application to larger areas of skin than is possible with other methods. The dose of drug that actually enters the skin can only be determined by fairly elaborate methods [e.g., see Blank *et al.* (1); Gemmell & Morrison (2, 3); Griesemer *et al.* (4); Malkinson (5); Schulze & Reiff (6)]. The trauma of inunction, although usually slight, may in some circumstances be considered a disadvantage. For example, in patients with atopic dermatitis the unaffected skin tends to respond to mechanical stimuli by blanching, and this blanching after inunction of an ointment may be wrongly attributed to a constituent of the ointment [Reed, Kierland & Code (7)].

Iontophoresis.—Only electrolytes can be applied by iontophoresis. Theoretically the effects of the anionic and cationic constituents of a drug could be studied separately, but this is unlikely to be important. It is difficult to gauge the dose that enters the body and even more difficult to determine what proportion is in the skin, though attempts have been made, e.g., by Ghys (8). The passage of electric current may interfere with the effect of the drug. Iontophoresis requires relatively large amounts of drug.

Puncture or scarification, and intradermal injection.—The major limitation of these procedures is that drug effects can only be produced in a

[1] The survey of the literature pertaining to this review was concluded in August, 1960.

small area. Intradermal injection permits more accurate dosage and requires much less material than does puncture, but the latter is less traumatic. Much of the fluid introduced by puncture or scarification probably does not penetrate to the dermis in the first instance and acts predominantly on the epidermis; fluid introduced by superficial intradermal injection tends to lie more deeply, in the region of the dermoepidermal junction. That there may be an important difference between the two routes is illustrated by Broadbent's observations (9) on histamine-induced pruritus. Squire (10) matched histamine weals produced by puncture and by intradermal injection. He estimated from the results that the volume he introduced by a single prick was approximately 3×10^{-6} ml.

The technique of intradermal injection is important. Fine needles (diameter 0.45 mm.) are most often used. Whether short-bevel or long-bevel needles have any advantage is not certain. For injection into the most superficial layers of the skin the needle is inserted almost parallel to the skin surface, with the bevel facing upwards; having entered the skin, the needle is then advanced toward the skin surface until the bevel can be seen through the intact skin. With the needle in this position the fluid is injected. Most intradermal injections are made using tuberculin syringes graduated to 0.01 ml. Unfortunately many such syringes leak under pressure; therefore it is advisable to test syringes that are to be used for accurate work [Guld & Rud (11)]. Recently, however, a new type of syringe has become available in which the plunger is fitted with a small rubber ring; this syringe does not leak when tested by Guld & Rud's method (11a). Some other sources of error in the technique of intradermal injection, e.g., variation in depth, have been studied by Palmer & Edwards (12) and Guld (13) in connection with BCG vaccination and tuberculin testing.

Intraarterial injection or infusion.—These methods allow distribution of a drug to the skin of the distal part of a limb and do not entail any interference with the skin. However, the distribution of the drug to the skin is liable to be uneven because of differences in blood supply between different areas and tissues and because the injected solution may not mix uniformly with the blood flowing along the artery. A drug such as acetylcholine may be largely destroyed in the blood while it is passing from the site of injection to the skin vessels. These and other snags are discussed more fully by Duff *et al.* (14).

Skin Blood Flow

Recent reviews covering particular aspects of the cutaneous circulation are those by Furchgott on the pharmacology of vascular smooth muscle (15), and by Paton on vasodilator drugs (16). This section attempts to supplement these but excludes substances whose main action is indirect, i.e., at sites remote from the skin.

Most of the numerous methods that have been used to study skin circulation are described in *Methods in Medical Research* (17). Others are

those of Hensel & Bender (18), Bárány (19), Burch (20), and Fox & Wyatt (21). The multiplicity of methods is partly attributable to the difficulty of discriminating between the various parts of the skin circulation. There are important regional differences (e.g., in man between hand, forearm, and face) so that results obtained in one region do not necessarily apply in another. In addition, within each region the responses of different types of vessel often differ. Routine pharmacological studies of new compounds in animals frequently include observations on limb blood flow, but such data include skin and muscle blood flows and can give no reliable information about the skin.

Much of the quantitative work with drugs on skin blood flow has been done in man, using venous occlusion plethysmography of the hand. The hand contains about twice as much skin and subcutaneous tissue by volume as it does muscle [Abramson & Ferris (22)], so that the greater part of the hand blood flow is generally assumed to represent skin flow. The forearm contains several times more muscle than skin (22); the forearm blood flow is, therefore, an unreliable indicator of the blood flow in the forearm skin.

Sympathomimetic substances.—Epinephrine and norepinephrine have a powerful constrictor action on the vessels of the hand and foot [Barcroft & Swan (23)]. Glover *et al.* (24) have recently shown that both the prevenous resistance vessels and the capacity vessels, presumably mainly venous, are affected. Epinephrine is somewhat more potent than norepinephrine in reducing hand blood flow; this also seems to be true for skin vessels in other parts of the body (23). Isoprenaline (isoproterenol) infused into the brachial artery causes slight vasodilatation in the hand, or no change [Cobbold, Ginsburg & Paton (25)]; in the dog it increases the flow in the saphenous artery, which supplies only skin [Walters *et al.* (26)].

Adrenergic blocking agents.—Ergot alkaloids have a powerful direct constrictor action on skin vessels. For example, the dihydrogenated derivatives of the ergotoxine group (Hydergine) cause vasodilatation in the hand and foot by two distinct mechanisms, namely a local adrenergic blocking action and a central inhibition of vasoconstrictor tone [Barcroft, Konzett & Swan (27)]. Tolazoline and phentolamine have a direct vasodilator action in the skin as well as adrenergic blocking activity (28). Given by intraarterial infusion, phenoxybenzamine, which has a different mechanism of action, greatly reduces the constrictor response to epinephrine, norepinephrine, and to sympathetic stimuli; it also has a direct vasodilator action of its own [Duff & Ginsburg (29); Ginsburg & Duff (30)]. Bretylium tosylate is a different type of drug with a selective action on adrenergic nerves. In the perfused isolated rabbit ear it prevents the vasoconstriction caused by stimulation of sympathetic fibers but increases the vasoconstrictor effects of epinephrine and norepinephrine [Boura *et al.* (31)]. In man, intraarterial infusion produces moderate vasoconstriction [Blair *et al.* (32)], which may be followed by vasodilatation (31, 32). Reflex vasoconstrictor responses in the hand are reduced or abolished. Guanethidine appears to

have a similar mechanism of action [Maxwell, Mull & Plummer (33)]. The action of chlorpromazine has also been studied. This drug has a direct vasodilator action in the hand; in addition, it antagonizes norepinephrine specifically, but clear-cut antagonism to epinephrine could not be demonstrated [Ginsburg & Duff (34); Duff & Ginsburg (35)].

Hydrocortisone.—By itself, hydrocortisone infused intraarterially (total dose 0.6 to 1.2 mg.) does not affect hand blood flow, but epinephrine given immediately afterward causes a greater decrease in flow than in an untreated hand [Ginsburg & Duff (36)]. This potentiation does not occur with norepinephrine, and is difficult to explain.

Histamine, acetylcholine, and their antagonists.—Histamine and also acetylcholine cause a great increase in both the hand and the forearm blood flow when infused intraarterially [Duff *et al.* (14)]. Another interesting observation with a histamine analogue, 3-β-aminoethyl-1,2,4-triazole, has been made by Naftchi *et al.* (37). Blood pressure, mouth temperature, and finger blood flow were recorded before and at intervals after an oral dose of this substance. The drug caused flushing of the face and chest, and the fingers also showed vasodilatation; all the subjects felt chilly, and mouth temperatures fell. A striking fall in finger blood flow occurred in all subjects. Similar effects were observed after subcutaneous injection of histamine itself. The authors suggest that the heat loss following general capillary and venular vasodilatation caused reflex constriction of the digital arteriovenous anastomoses, thus decreasing the finger blood flow. A direct constrictor action of histamine or its analogue seems a less likely explanation.

Intraarterial atropine in doses that block the vasodilator effect of acetylcholine does not affect the hand blood flow [Gaskell (38); Allwood & Ginsburg (39)]. The flushing of the skin, particularly of the face, which often occurs after the systemic administration of atropine and similar drugs, does not appear to have been investigated, and its mechanism is unknown.

Serotonin (5-hydroxytryptamine).—The responses of the skin vessels to serotonin are complex. Roddie, Shepherd & Whelan (40) found that intraarterial infusion causes a decrease in hand blood flow accompanied by flushing of the skin and an increase in the volume of the part. This indicates constriction of the vessels mainly responsible for resistance to flow and dilatation of those responsible for the color of the skin. Reid (41) had previously shown that serotonin injected near a vein causes constriction. The ingenious observations of Glover *et al.* (24) have demonstrated that the low-pressure capacity vessels in the hand become less distensible when an intraarterial infusion of serotonin is given. These changes explain how the characteristic cyanotic flush is brought about. Intradermal doses of serotonin larger than those required to elicit these vascular reactions cause wealing; indirect evidence suggests that this may be caused by liberation of histamine [Möller & Rorsman (42); Demis, Davis & Lawler (43)].

It is not certain whether serotonin plays any part in the characteristic

attacks of flushing that occur in some patients with metastasizing carcinoid tumors. These tumors often contain large amounts of serotonin, and an abnormally high concentration may be present in the blood. Discussion of this problem [e.g., by Snow *et al.* (44); Smith *et al.* (45)] suggests that some substance other than serotonin may be responsible for the flushing. The discovery by Schneckloth *et al.* (46) and Peart *et al.* (47) that intravenous norepinephrine or epinephrine will provoke typical flushes in carcinoid patients should speed the search for such a substance.

Adenosine triphosphate (ATP).—This substance is of special interest because there is evidence that it may be the transmitter released from sensory nerve endings causing antidromic vasodilatation [Holton (48)]. In man, ATP is as powerful a vasodilator as histamine and acetylcholine [Duff, Patterson & Shepherd (49)]. Holton & Holton (50) compared the vasodilator activity of ATP with that of various substances related to it, using their denervated rabbit-ear preparation. The activities of adenosine, and of its di- and monophosphates, were of the same order as that of ATP; the other substances tested were much less active.

Peptides.—Vasopressin has long been known as a powerful constrictor of capillaries and arterioles [Goodman & Gilman (51); Kitchin (52)]. The circulatory effects of oxytocin in man have recently been investigated by Kitchin, Lloyd & Pickford (53). Given intravenously or intraarterially it causes considerable vasodilatation in the hand. Administration of one part of vasopressin together with 20 parts of oxytocin prevents this vasodilatation. Valyl[3]-oxytocin is about 1.5 to two times as active a vasodilator as the synthetic oxytocin, Syntocinon [Kitchin, Konzett & Pickford (54)], whereas it has about four times the oxytocic effect of Syntocinon on the human uterus [Smyth (55)].

Bock, Krecke & Kuhn (56) have studied the effects of intravenous and intraarterial administration of synthetic hypertensin II in man, using Hensel's heated thermocouple method to measure skin and muscle blood flow. Vasoconstriction occurred in both vascular beds but was more intense and lasted longer in the skin. The vasoconstriction in the skin was greater, while in muscle it was much less, than that produced by norepinephrine.

Bradykinin, which has recently become available in pure form, is a potent vasodilator in man and is about as active as histamine by intraarterial injection [Fox *et al.* (57)].

Rubefacients.—The term rubefacient embraces a heterogeneous collection of substances intended for local application to the skin. Many have a long history in therapeutics and have been little investigated. A number of these old-established rubefacients, such as mustard oil and cantharidin, cause inflammation, and this probably explains why they redden the skin. Some substances, e.g., capsaicin and camphor, stimulate certain sensory nerve endings; this may have something to do with their rubefacient activity. Histamine and histamine liberators such as ethylmorphine (Dionine)

constitute another group; these are very effective when applied by electrophoresis. The last and most recently introduced group consists of various esters of nicotinic acid.

Toh, Lee & Kiang (58) have studied the pharmacology of capsaicin, the main active principle of various species of *Capsicum,* and of several of its analogues, derivatives of vanillylamine. None of these substances had any direct action on the blood vessels of the perfused rabbit ear. This work has recently been extended by Crismon *et al.* (59) who found that inunction of 2 gm. of a water-miscible cream containing 0.1 per cent capsaicin into the skin of the forearm produced no definite increase in the forearm blood flow. After similar application of a cream containing 2.5 per cent benzyl nicotinate, the forearm blood flow was almost doubled. Reddening and a local sensation of warmth or burning were produced by both creams, the sensation being more marked and sustained after capsaicin and the reddening more marked after benzyl nicotinate. Block of the cutaneous nerves to the forearm skin before inunction of the nicotinic acid ester did not affect the vasodilatation, showing that the response does not depend on an intact nerve supply. Doerr & Heite (60) had earlier investigated a cream containing both 2.5 per cent benzyl nicotinate and 0.1 per cent capsaicin. The skin blood flow was measured calorimetrically and skin color photometrically. A substantial increase in blood flow occurred in all 50 subjects. In many the skin became redder, but the correlation between blood flow and color was low. It is interesting that the mean values for patients with atropic eczema did not differ significantly from those for normal subjects, because in atopic skin the superficial minute vessels are relatively unresponsive to dilator stimuli [for references see also Clendenning *et al.* (61)].

A different approach is that of Fulton *et al.* (62), who have studied the microcirculation in the cheek pouch of the hamster using a cinematographic technique. Four different esters of nicotinic acid, applied topically to vessels from a micropipette consistently produced vasodilatation in arterioles and precapillary arteriolar sphincters, but not in other vessels. The reaction was prompt and uniform, even at some distance, suggesting that the perivascular nerve plexus may be involved. This method may supply useful information about the action of rubefacients, though the vessels in the hamster's cheek pouch probably differ from those in human skin.

The nicotinic acid esters present several other interesting problems. Given by mouth or injected, nicotinic acid itself produces vasodilatation which is most prominent in the blush area and seems to be much less elsewhere. How is this vasodilator effect related to that of the esters? Some of the esters, thurfyl nicotinate (Trafuril, tetrahydrofurfuryl nicotinic acid) and benzyl nicotinate (63), frequently cause edema at the site of application. Pretreatment with antihistaminic drugs, either locally or systemically, appears to have no effect on this edema formation, suggesting that it is not caused by histamine release, but this point is far from settled.

In Great Britain alone at least eight different esters of nicotinic acid

are on sale in commercial rubefacient preparations, most of which contain other agents as well [Martindale (64)], and new ones continue to appear [e.g., Mombaerts (65)]. An objective comparison of these compounds is overdue.

Vascular Permeability

There is no evidence suggesting that the permeability of arterioles or of veins is important, and the subject has been little studied. Veins are permeable to some substances, for in man intravenous injection of histamine or of pethidine (meperidine), a histamine liberator, may cause linear wealing to appear in the skin overlying the vein. This is particularly marked when the flow of blood is obstructed. Mepyramine can apparently also pass through the vein wall [Finer & Partington (66)].

Substances that affect capillary permeability have recently been reviewed by Spector (67). Capillaries in the skin are normally impermeable to protein. Increased capillary permeability is demonstrated when plasma protein appears in the tissue fluid. It is harder to establish that foreign protein injected subcutaneously appears in the plasma before it appears in the thoracic duct lymph. A method that has been widely used in animals depends on the leakage of protein-bound dye, such as pontamine blue or Evans blue, from the plasma into the skin. The dye is injected intravenously, and the test substances intradermally. The size and intensity of the color of the lesion are used as a measure of capillary permeability. A few investigators have used Evans blue in this way in man [Demis *et al.* (45); Stewart & Bliss (68); Herxheimer & Schachter (69)]. Its only disadvantage seems to be that in some subjects the skin may show a faint greenish-grey tint for a few days. Sodium fluorescein has also been used [e.g., Möller & Rorsman (70), who give further references], but since it is incompletely bound to plasma protein its appearance in the skin does not necessarily indicate increased capillary permeability.

Miles & Miles (71) made extensive use of the dye method in the guinea pig, and their paper contains many important observations. With graded doses of histamine, the histamine liberator 48/80, and leukotaxine injected in a constant volume, the diameter of the lesion was proportional to the logarithmic dose of the drug. The measurements obtained when the dose was kept constant and the volume varied were used to measure the affinity of skin tissue for the substance injected. Histamine has a relatively low, and 48/80 a relatively high "affinity" for skin tissue. This partly explains why high doses of 48/80 produce smaller and more intensely blue lesions than do high doses of histamine. The same authors also studied the time course of the histamine effect, i.e., the rate of "fixation" of histamine in the tissue, the duration of increased permeability, and the duration of the immunity or refractoriness at injection sites to further doses of histamine or 48/80.

Various factors that influence the reactivity of guinea pig skin to his-

tamine were also examined (71). Important regional differences exist between the reactivity in the ear, the back or flank, and the abdomen near the midline. The explanation of these differences is not certain, but the greater vascularity of the ear may have something to do with it. The ventral skin of the trunk is thinner than dorsal skin, and fluid entering it probably spreads more easily. In general, factors that decrease intravascular pressure diminish the reactivity to histamine. Examples of such factors are lowered environmental temperature (10°C.), general anesthesia, shock produced by sublethal doses of *Escherichia coli* endotoxin or other means, and pretreatment with posterior pituitary extract. Such diminution of histamine bluing by pretreatment with a vasoconstrictor agent is the basis of Lockett & Jarman's (72) assay of the capillary action of flavanoid compounds in mice. Presumably, the method does not discriminate between any arteriolar constriction that may occur and capillary constriction. A raised environmental temperature (37°C) also diminishes reactivity to histamine in the guinea pig (71). Lewis & Grant (73), discussing a similar phenomenon in man, suggested that it may be caused by more rapid removal of histamine from the injection site.

A difference between the guinea pig and man which remains unexplained is that, in man, increased permeability of the minute vessels of the skin leads to weal formation, whereas in the guinea pig a definite weal can seldom be seen or felt. The dog and the horse are like man in this respect (74); most of the other common laboratory animals are like the guinea pig. This property of human skin has made it possible to study capillary permeability in man without the use of dyes, but until such methods have been tested directly against one of the dye techniques, one cannot exclude the possibility that they may give different
needs to be done.

Simple quantitative observations can be made by measuring the size of weals produced by injecting or puncturing the test substance into the skin. Since weals have depth as well as area it is logical to try to measure weal volume, but this has been attempted by only few investigators. Pfeiffer, Jenney & Williams (75) constructed a dermal plethysmograph for the purpose and made a few observations with it in man. Smith & Humphrey (76) and Humphrey (77) calculated the volume of local inflammatory edema in guinea pigs and rabbits from its depth and area. Many investigators have used weal area alone as a measure of effect [Squire (10); Bain, Hellier & Warin (78); Holti (79)]. Bain *et al.* (78) found that the weal area measured directly agreed closely with that calculated from the mean radius, as obtained from the average of the greatest diameter and the one at right angles to it. This approximation is reasonable when the difference between the two diameters is small, and offers a considerable saving of labor. A better approximation, however, which also holds when a weal is more elliptical in shape, is obtained by multiplying the product of the two diameters by $\pi/4$ [Engelhardt, Funk & Heite (80)].

Bain, Broadbent & Warin (81) found that the relationship between the

log of the dose of histamine and the weal area was rectilinear over a 300-fold range of dosage. This contrasts surprisingly with the findings of Miles & Miles (71) in the guinea pig that the diameter of the lesion is proportional to the log of the dose. They suggest that the difference may lie "in the modification of histamine spread or of weal diameter, by the copious exudation that occurs in man but not in the guinea pig." The contrast between the two types of response may, however, be more apparent than real, because in their assay Miles & Miles used only four doses, covering a thirty-fold range. Over such a restricted range, the line relating log of the dose to lesion diameter might be so slightly curved that it would appear as straight as the line relating log of the dose to area. The data of Bhoola, Calle & Schachter (82) lend some support to such an explanation, for these workers found the log dose/lesion-diameter line for histamine in the guinea pig to be curved. When their data are plotted using the square of the diameter instead of the diameter, the line appears straight.

In man, as in the guinea pig, many factors affect the local response to histamine. They are briefly reviewed by Engelhardt *et al.* (80), and only a few will be mentioned here. Wealing in response to other substances is also likely to be affected by these factors. Stüttgen *et al.* (83) compared 10 different sites in 34 subjects and found definite regional differences. The largest weals in response to a particular dose occurred on the anterior thigh, the smallest on the extensor surface of the forearm. In adults higher doses of histamine are required to elicit wealing with increasing age [Tuft *et al.* (84)]. Skin treated with x-rays [Shaffer (85)], histamine iontophoresis, or ultraviolet radiation [Holti (79)] shows a diminished wealing response, as well as impaired vasoconstrictor tone in the minute vessels. Such effects may persist for many months (79).

Information that has a bearing on capillary permeability, but is less directly related to it, is obtained from observations on the time taken for injection weals to disappear. The weal disappearance time is influenced not only by capillary blood flow and permeability, but also by the degree of "spreading" of fluid in the tissue, by the rate of reabsorption of fluid in the venous limb of the capillary, and by the patency of the lymphatics. Heite and his co-workers (86 to 89) have studied some of these problems by injecting solutions of fluorescein into the skin of the guinea pig and of man, and recording the weal disappearance time concurrently with the disappearance time of fluorescein staining. The combination of these two measures has helped greatly in the interpretation of the results. After intravenous calcium gluconate, for example, the injection weal disappeared more rapidly, while fluorescein staining persisted longer than normal, suggesting that reabsorption of fluid into the capillary was increased and that "rinsing" of the tissue spaces by capillary filtrate decreased (89). This is evidence against the traditional view that calcium decreases permeability along the whole length of the capillary, for if that were true the weal should have persisted longer than normal.

This is not the place for discussion of the complex problems of fluid

exchange between capillaries, tissue spaces, and lymphatics. They are fully dealt with in the excellent book on the lymphatic circulation by Rusznyák, Földi & Szabó (90) which has just appeared in an English version (91). This also contains much information on the effects and possible role of hyaluronidase.

Mention must now be made of some recent work on histamine, histamine release, mast cells and related topics, and peptides. Important studies on histamine in Kahlson's laboratory (92) have established that there is no correlation between the rate of histamine production in a tissue and its histamine content. The differences in histamine metabolism in the fetus and the adult are particularly striking [see also West (93)]. Another series of experiments has shown that healing of skin wounds in the rat can be accelerated or slowed respectively by increasing or decreasing the histamine-forming capacity [Kahlson *et al.* (94)]. Archer's observation (95) that eosinophil leukocytes in the skin of the horse respond chemotactically to histamine may possibly be relevant here.

Histamine liberators and the mechanism by which they act have been discussed by Paton (96) and Uvnäs (97), the physiopathological role of histamine and its liberation in man by Lecomte (98). Riley's monograph on mast cells (99) and West's review of tissue mast cells and tissue amines (100) both include material on histamine, serotonin, and their release. The mechanism of liberation of histamine and of a fat-soluble smooth muscle stimulating substance (SRS) in relation to mast cells in various tissues has been extensively studied in Uvnäs's laboratory (101). Parratt & West (102) have found that thyroxine greatly increases the sensitivity of the rat to histamine, serotonin, and substances which liberate them. Thyroxine appears to inhibit intestinal histaminase so that released histamine accumulates.

Halpern *et al.* (103) have compared the ability of promethazine, chlorpromazine, mepyramine, and *N,N*-diethyl-D-lysergamide to inhibit edema induced in the rat by histamine, serotonin, dextran, and histamine liberators 1935L and 48/80. Their effect on anaphylaxis in the guinea pig was also examined. Other workers have studied the inhibition in the rat of serotonin-induced edema by lysergic acid derivatives and antihistaminic drugs [Doepfner & Cerletti (104)], and of dextran-induced edema by various phenothiazine derivatives [Kató & Gözsy (105)], and by 2-deoxyglucose [Goth (106)].

The work of Bhoola, Calle & Schachter (82) has strengthened the suggestion that the release of kallidin and similar substances (e.g., bradykinin and pain-producing substance) from plasma by dilution, or by contact with glass, is a result of the activation of the enzyme kallikrein. The permeability-enhancing activity of the permeability globulins in fractionated plasma [Mill *et al.* (107)] and in inflammatory exudates [Spector (108)] may be attributable to kallikrein. Preliminary observations in man have shown that bradykinin, kallidin, and kallikrein have similar effects when

injected intradermally [Herxheimer & Schachter (69)]. The role of such substances in inflammation, pathological pain [Keele (109)], and certain forms of urticaria [Herxheimer (110)] is still obscure.

Sweating and Pilomotion

In 1955 Randall & Kimura (111) reviewed the pharmacology of sweating; other reviews have only covered limited aspects of the subject. Weiner & Hellmann (112), in their admirable review on the sweat glands, have discussed pharmacological observations bearing on the regulation of sweat secretion; in an article on the autonomic innervation of the skin, Herxheimer (113) has dealt with axon-reflex sweating and other axon reflexes in the skin.

Substances that inhibit sweating when applied locally to the skin have been reviewed by Sulzberger & Herrmann (114). These authors have also summarized the work on sweat suppression by mepacrine. Klarmann (115) has discussed chemical and bacteriological aspects of antiperspirants and deodorants. Of the substances effective when given systemically, atropine-like drugs are the most important. Many such drugs are available. All of them have other anticholinergic effects which limit their therapeutic use. The most troublesome in this respect are probably scopolamine, atropine itself (not atropine methylbromide), and methantheline, but there seems little to choose between other drugs of this group [for further discussion see Herxheimer (116)].

Only two interesting recent observations can be mentioned here. Hankiss (117) has reported experiments on a patient with diabetes insipidus which indicate that antidiuretic hormone can reduce the elimination of water in the sweat. Previous workers [e.g., Pearcy *et al.* (118)] have not been able to detect such an effect in normal subjects, and further work will have to clarify the conditions in which this response can be demonstrated.

Bernstein & Sonnenschein (119) have found that 5 per cent tetraethylammonium chloride injected intradermally produces local sweating and piloerection, apparently by potentiating central tonic impulses to the sweat glands and pilomotor muscles. This curious effect deserves to be studied further with a greater range of concentrations than were used by these authors.

Sensory Receptors, Itching, Pain

Gray & Diamond (120) reviewed the pharmacological properties of sensory receptors in 1957. Since then the main advance has been in the investigation of nonmyelinated C fibers [e.g., by Douglas & Ritchie (121) and Iggo (122)]. The recording of electrical activity in single sensory fibers may be expected to give important information about the actions of pain-producing substances and of substances such as menthol and capsicin which evoke other types of sensation.

Chemical causes of pain and itch have been reviewed by Keele (109).

More recently a study group at the Ciba Foundation (123) discussed the nervous mechanisms of pain and itch, and also chemical factors. Two main groups of substances are known to cause itching on local application to the skin: histamine or histamine liberators and various proteolytic enzymes. Histamine produces more itching when injected intradermally in a buffered solution than in 0.9 per cent sodium chloride. Direct application of the buffered solution to scarified skin causes more prolonged itching and shorter-lasting pain than intradermal injection of the same solution [Broadbent (93)]. Several factors may account for these differences (9) but their relative importance is not yet clear.

Shelley & Arthur (124, 125) discovered that various proteolytic enzymes can cause itching and implied that this itching is associated with proteolytic activity. Monash & Woessner (126) subsequently reported that heat-inactivated enzyme preparations could still produce itching, and that cowhage which had deteriorated after long exposure to moisture and no longer caused itching still showed proteolytic activity. Arthur & Shelley (123) have attempted to explain these findings, but the available information is vague, and much more detailed biochemical and pharmacological study of specific substances is necessary. The possibility that smaller molecules may be concerned in the production of pruritus also requires further investigation; bradykinin, for instance, appears to be pruritogenic [Cormia & Dougherty (127)].

Local applications used clinically to relieve itching fail to alleviate itching induced experimentally by histamine or cowhage [Melton & Shelley (128); Macris *et al.* (129)]. Such applications will therefore have to be assessed by well-controlled observations on pathological pruritus.

Moulton *et al.* (130) have reported an intriguing observation on xanthosine, which regularly produces pain on intradermal injection. About half their subjects reacted with a flare, whereas the others did not. There may be a genetic basis for this difference. The relationship of the flare to histamine release and to wealing remains obscure.

Antimicrobial Substances and the Skin

Disinfection of the skin.—A recent review, in which Price (131) has authoritatively discussed the choice of a local antiseptic for use on the skin, has in the last year or so been supplemented by a number of papers from Britain. Lowbury and his colleagues have investigated methods of disinfecting the hands of surgeons and nurses (132) and the skin of operation sites (133); their results suggest several improvements on current preoperative routines. The prevention of staphylococcal cross-infection (134, 135) and of self-reinfection in chronic furunculosis (136) has been studied by Gillespie and his collaborators. Much of this work brings out the great usefulness of hexachlorophene.

Toxicity to skin and antibacterial effect.—Lawrence (137) has compared

the toxicity of various antibiotics to the skin in tissue culture by measuring its oxygen consumption and by examining it histologically. He suggests that a concentration found toxic *in vitro* may well impede healing if used *in vivo*. Collier & Grimshaw (138) have studied the local action of antibacterial substances in intact guinea pig skin by a different method. Each drug was injected intradermally, either on its own, or into the site of injection of an inoculum of *Corynebacterium ovis,* which gives rise to circumscribed circular lesions in the skin. When the drug was injected alone, the relation of lesion diameter to dose indicated the toxicity of the drug; when the organisms were also present, the results for nontoxic doses were a measure of the antibacterial effect of the drug. As the authors point out, the results are difficult to relate to clinical practice, but further development of the method using organisms frequently met clinically may help to narrow the gap.

Griseofulvin.—Griseofulvin is the first drug to be effective by mouth in the treatment of fungus infections of the skin. Its discovery represents a major advance which has been celebrated by two international symposia, in Miami in October, 1959 (139) and in London in May, 1960 (140). An editorial in the *Lancet* (141) provides a good review of the present position.

Clinical Pharmacology

Dermatological treatment, particularly external treatment, is still dominated by tradition. Most of the local applications in use are prescribed because they were recommended by some authority in the past, not because objective evidence justifies their composition. Frazier & Blank (142) recognized this and compiled an admirably brief formulary for external therapy of the skin. They included only preparations logically based on current scientific knowledge or, when this was inadequate, on a critical appraisal of the evidence. However, most of the preparations in Frazier & Blank's formulary have not yet been subjected to controlled experimental testing in patients, and firm conclusions can only be based on such tests. Although lip service has often been paid to this experimental approach, it appears that only Siemens (143 to 146) has made extensive use of a satisfactory method. His "one side treatment" method can only be used on patients in hospital and is time consuming, but these are small disadvantages because the results are of great help in the treatment of the individual patient as well as of general importance. The method depends on repeated treatment comparisons within each patient; comparisons between skin patients (i.e., groups treated differently) require far greater numbers and can give misleading results. Siemens' papers should be compulsory reading for all dermatologists.

Somewhat more is known about the effects on the skin of drugs given systemically. The classical studies of Bain and his collaborators (78, 81,

147, 148) on antihistaminics are still the most important if not the only reliable source of information on the clinical pharmacology of these drugs, particularly their relative potency and duration of action. These workers have investigated at least eight (antazoline, chlorcyclizine, chlorpheniramine, mepyramine, promethazine, thonzylamine, triprolidine, and "compound 405") of the 40 or more antihistaminic drugs on the market. Adequate data are not available on the human pharmacology of the other drugs, but this has discouraged few physicians from using them. Although good methods of evaluating drugs given systemically have been used in many branches of medicine, their use in dermatology has so far been exceptional. One such exception has been the clinical trial of griseofulvin in the treatment of chronic ringworm of the skin and nails [Russell *et al.* (149)]. To mention only two examples, the use of chloroquine in discoid lupus erythematosus and of dapsone in dermatitis herpetiformis needs to be studied by similarly rigorous methods; current practice is insecurely founded on poorly controlled observations.

Other Topics

The effect of detergents on the skin has been compendiously reviewed in the monograph by Stüpel & Szakall (150). A recent article by Bettley (151) has dealt with the effects of soap. Some effects of carcinogenic substances on the skin have been discussed by Walpole and by Berenblum in a Ciba Foundation Symposium (152).

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