PHARMACEUTICAL FORMULATION IN SKIN MEDICATION

By J. W. Hadgraft, F.P.S., F.R.I.C.

*Pharmaceutical Department, Royal Free Hospital, London, W.C.*1

Numerous criteria have been listed as ideal properties of dermatological bases (Mumford, 1940, Chamings, 1943) but no one substance or preparation will meet all requirements. It is now possible to formulate a range of preparations from which the dermatologist can make a selection for the particular need he has in mind. A skin preparation should not contain ingredients likely to irritate the skin or aggravate the condition under treatment. The vehicle should not interfere with the activity of the medicament or with normal skin function unless the condition under treatment requires that there should be some modifying influence. The preparation should be pharmaceutically compatible, cosmetically acceptable, easily applied to the skin surface, stable under normal conditions of storage and should not support the growth of micro-organisms. The formulation should be kept as simple as possible since the fewer ingredients present, the less likelihood there is of introducing potentially skin sensitising substances or of interfering with the activity of the medicament.

The pharmaceutical aspects of dermatology have recently been discussed by Van Abbe (1959) who drew attention to the need for more precise knowledge of the effects of topically applied preparations and for better correlation of the physicochemical properties of the materials used in formulation and skin physiology. Many preparations commonly used are traditional and, although the broad requirements for the different types of vehicles are defined, there are no clear clinical indications for the more subtle variations which can be achieved by pharmaceutical formulation.

In the acute inflammatory stages of disease, simple aqueous lotions may be used in the form of wet dressings. They have a cooling effect on the skin, do not impede drainage and are useful in the removal of crusts and debris. Lotions containing an insoluble solid, which may be of value in the treatment of subacute conditions, combine the cooling effects of an aqueous solution with the protective effects of a powder which remains on the skin surface.

Ointments are useful for the application of insoluble and oil-soluble medicaments. They leave a greasy film on the skin, inhibiting the loss of moisture and encouraging hydration of the keratin layer. They may be of value for dry scaly lesions in which there is a need to improve the suppleness of the skin. Pastes contain a high proportion of powder dispersed in a fatty base. They combine the properties of powders, absorbing exudate, and ointments, providing a greasy protective film on the skin.

Creams combine the characteristics of the lotions and ointments. They contain water which evaporates to produce a cooling effect and the greasy film remaining on the skin surface possesses the properties of ointments.

It is the purpose of this paper to describe some of the materials used to formulate dermatological preparations and to deal with a few of the pharmaceutical problems encountered in their use.

Lotions

Lotions are usually simple aqueous solutions or suspensions which present little difficulty in formulation. Water-soluble medicaments are probably best applied to the skin in this form but it may be necessary to add other ingredients to modify the behaviour of the lotion on the skin. Methylcellulose or sodium carboxymethylcellulose together with glycerol may be added to form a water-soluble plasticised film which will help to localise the effects of the lotion and hold the active medicament in contact with the affected area.

Solubility problems may arise in the formulation of lotions. Hydrocortisone, for example, may be formulated in liquid preparations using a combination of cetomacrogol and self-emulsifying monostearin as the suspending agent. If, however, it is required in true solution this can be achieved by using a water-miscible vehicle such as liquid macrogol (Collard, 1961).

Suspending agents are used to promote the dispersion of insoluble powders in lotions. Bentonite is used for this purpose in calamine lotion but may produce thixotropic suspensions which are difficult to pour and froth excessively on shaking. Armstrong and Fenton (1954) have suggested the addition of sodium citrate to overcome these difficulties.

More investigations of suspending agents for this kind of lotion are needed. They compare badly with many cosmetic preparations of a similar character. A new concept has recently been advanced by Meyer and Cohen (1959) who have related suspending ability to the rheological characteristics of the aqueous phase. Most hydrophilic colloids (macrogols, sodium carboxymethylcellulose and methylcellulose) exhibit pseudoplastic properties and prevent the settling out of suspended particles by increasing the viscosity of the continuous phase. Substances which exhibit plasticity and show a critical yield-value when examined in a rotating cylinder viscometer may produce permanent suspensions, irrespective of their apparent viscosity. Two hydrophilic colloids have been found to have such characteristics. Tragacanth mucilage, prepared by homogenization in which it is exposed to high shear, exhibits a critical yield-value and produces permanent suspensions. A synthetic carboxyvinyl-polymer (Carbopol 934) possesses similar properties. Meyer and Cohen have suggested that materials for preparing suspensions should be selected by determining the ratio of yield-value : apparent viscosity and point out that if this value is high, permanent suspensions with maximal flow properties may be formulated.

Reviewing the factors influencing the performance of gums in cosmetic formulations, Levy (1959) also deals with the effect of homogenisation on tragacanth solutions and points out that it produces a rapid hydration of the gum. By controlled homogenisation, tragacanth solutions possessing a range of stability characteristics may be obtained.

Other ingredients in the preparation may influence the performance of suspending agents. Levy and Schwarz (1958) have found that sorbitol and glycerol lower the gel point of methylcellulose so that preparations combining these substances may become cloudy under warm conditions and change from fluid, easily-pourable liquids into opaque, semi-solid gels. Propylene glycol, on the other hand, raises the gel point of methylcellulose. Bolliger and Muenzel (1958) have also found that the addition of polyhydric alcohols to solutions of hydrophilic gums increases their viscosity and, if the concentration is sufficiently high, interferes with hydration of the gum, and an otherwise pseudoplastic system may become plastic.

Ointments

The division of ointment bases into emollient and protective types can no longer be maintained in the light of the recent findings of Blank (1952, 1955) and of Peck and Glick (1956). Oils and waxes do not soften callous tissue and the effect of ointments on the pliability of the skin depends upon their ability to form a water-insoluble film on the stratum corneum thus reducing the rate of loss of moisture from the skin. Hydration of the keratin layer by moisture from the underlying tissues is thus encouraged and it is for this reason that the skin is rendered more pliable.

Comparative studies by Powers and Fox (1957, 1959) of the effect of lotions and cosmetic creams on the water content of the skin have indicated that soft paraffin produces the greatest reduction in loss of moisture whilst anhydrous wool fat is the next most efficient. A number of surface-active agents actually increase the rate of moisture loss from the skin but this would not necessarily apply when they are combined with fatty materials in ointment bases. Glycerol, a traditional emollient, and propylene glycol also increase the loss of moisture from the skin. But the formation of an occlusive film may cause an excessive retention of water in the keratin layer and have other undesirable effects. Blockage of the hair follicles may provoke an inflammatory reaction causing folliculitis and an occlusive film may produce localised heating of the affected area.

Mineral Oils

Mineral oils such as soft paraffin and liquid paraffin are bland, inert preparations which are not absorbed by the skin (Harry, 1941). They have the advantages of chemical stability and do not react with the substances incorporated into ointments.

According to Meyer (1935), soft paraffin consists of a colloidal system containing mineral oil dispersed in a solid wax, the dispersion being stabilised by the presence of an amorphous constituent. The composition cannot be clearly defined and varies in consistency. Hard paraffin is a mixture of solid hydrocarbons with a crystalline structure which renders it difficult to incorporate with oils, unless melted and vigorously stirred during the cooling process. The effect of the variable consistency of soft paraffin may be minimised by combining it with liquid paraffin and hard paraffin as in paraffin ointment.

A range of proprietary mineral waxes are now available which have distinct advantages over hard paraffin. They have been described as "microcrystalline" or "amorphous" waxes and because of their internal structure they are superior to hard paraffin as blending agents. They produce homogeneous mixtures with mineral and vegetable oils and with synthetic esters of fatty acids (Hadgraft and Wolpert, 1960). To produce a satisfactory gel with liquid paraffin it is necessary to have a crystalline wax like hard paraffin combined with an amorphous wax, thus simulating the composition of soft paraffin. Such combinations exhibit thixotropic properties, the viscosity being reduced if the mixture is subjected to milling at high pressure (Mutimer, Riffkin, Hill and Cyr, 1956).

Polyethylene-Mineral Oil Combinations

Examination of the properties of wax-thickened mineral oils has suggested the use of hydrocarbon polymers as gelling agents for mineral oil. A proprietary base, developed on this principle, is prepared by dissolving polyethylene in mineral oil and rapidly cooling the solution by pouring on to a water-cooled metal surface. Under these conditions, supercooling occurs and the polyethylene is very rapidly precipitated in a colloidal form. The ratio of crystalline to amorphous resin produced in the final gel depends upon the molecular weight of the polymer (21,000) and the rate of cooling (about 10° per second). The ointment bases obtained are non-reactive, have reliable consistency and show little variation in viscosity over a range of temperature from 5° to 45°. Although available in America, these bases are unobtainable in this country except in proprietary ointments (U.S. Patents 2,627,938; 2,628,187; 2,628,205).

Wool Fat and Derivatives

Wool fat is more readily absorbed by the skin than are the paraffins and may be used in ointments when deeper penetration is desired. It shows freedom from rancidity and readily absorbs water to form stable water-in-oil emulsions. Its main disadvantages are its odour, stickiness on the skin and liability to show surface disolouration. Some of these disadvantages are overcome by combining wool fat with the paraffins as in simple ointment.

The use of wool-alcohols was discussed at the first Symposium Session of this Conference in 1947 (Hadgraft, 1947) and it need be mentioned only briefly here. Wool-alcohols may be combined with the paraffins to produce hydrophilic bases like ointment of wool-alcohols. But it has a number of disadvantages since it is a mixture of uncertain composition and is not readily standardised. On storage, it is liable to surface oxidation with resultant loss of its emulsifying power. The autoxidation of wool alcohols during storage at room temperature has been investigated by Clark and Kitchen (1960a) who have shown that it may be effectively inhibited by the addition of 500 p.p.m. of butylated hydroxyanisole.

In recent years, other derivatives of wool fat have become available. Hydrogenation produces a white solid wax melting at about 50° and containing hydrogenated methylsterols with dihydrocholesterol and

saturated alcohols. Hydrogenated wool fat may be combined with mineral oils and an ointment base containing 70 per cent of the wool fat preparation with 30 per cent of liquid paraffin has been suggested (Fayaud, 1953). It spreads smoothly on the skin surface, producing a less greasy film than unmodified wool fat.

Reaction between wool fat and ethylene oxide produces a water soluble wax, melting at about 40°. It is a non-ionic surface-active agent which promotes the formation of oil-in-water emulsions and is also capable of acting as a solubilising agent. It could be useful in dermatological preparations since it combines some of the characteristics of wool fat with complete solubility in water.

Vegetable Oils and Related Substances

The vegetable oils have penetrating properties which are intermediate between those of the mineral oils and the animal fats (Harry, 1941). They are liable to become rancid on storage and this may be overcome by the inclusion of an antoxidant (Shotton, 1954). When used in dermatological vehicles, the possibility of these substances having skin sensitising properties must not be overlooked. Propyl gallate (0·05 to 0·15 per cent), tocopherol and butylated hydroxytoluene appear to be satisfactory but sensitivity reactions to hydroquinone have been reported (Lapin, 1942).

The acetoglycerides are a group of modified natural oils and fats obtained by substituting acetate groups in place of one or more of the fatty acid groups in the triglycerides (Newman, 1957). Any triglyceride may be modified by conversion to the mono- or diacetate and in the manufacturing process mixtures are obtained. Depending upon the nature of the raw materials and the conditions of the process, acetoglycerides are obtained ranging from mobile oily liquids to solid waxes.*

Acetoglycerides have a microcrystalline structure and produce thixotropic mixtures when blended with waxes and oils. Such mixtures retain their consistency over a wide range of temperatures. The acetoglycerides are stable to heat but can oxidise and commercial grades contain an antoxidant.

Skin penetration tests on the acetoglycerides have not been reported yet but their chemical nature suggests that they would penetrate the skin as readily as the natural oils and fats from which they are derived. They produce a film on the skin which is less greasy and occlusive than the mineral oils and wool fat.

Synthetic esters of fatty acids have also been used in the cosmetic industry to replace the natural vegetable oils. They have the advantages of more constant composition, lower acid values and they become less readily rancid than the natural oils. Isopropyl myristate (Hadgraft and Wolpert, 1960) is a clear, colourless, odourless liquid which is less viscous than arachis oil. In combination with the paraffins, it reduces their viscosity and increases the ease and rate with which they spread on the skin. Isopropyl palmitate and isopropyl palmitate-stearate are more viscous esters which give more "body" to the base.

* A. Boake Roberts & Co. Ltd.

The pharmacopoeial bases have been criticised by Howard (1960) who finds them unpleasant to use, coating the skin with a thick, greasy and occlusive residual film. He suggests that paraffin ointment could be improved if it were modified by the inclusion of acetoglyceride L/C or isopropyl myristate. A similar modification is suggested for simple ointment in which some of the soft paraffin should be replaced with isopropyl myristate. These modifications produce ointment bases which are pleasanter to use, less occlusive and do not interfere with the normal transport of water at the skin surface.

Emulsified Bases

Emulsified bases may be either water-in-oil emulsions (oily creams) or oil-in-water emulsions (aqueous creams). They are cosmetically superior to the older fatty type of base and are less likely to interfere with normal skin functions. They have a cooling effect from the evaporation of the water which they contain and are miscible with exudates, thus permitting drainage. Many emulsified bases contain surface-active agents which assist in bringing the active medicament into intimate contact with the skin surface.

Emulsification of an oil does not appear to enhance its ability to penetrate the skin (Harry, 1941). When a cream is applied to the skin, the aqueous phase evaporates leaving a film of oil, the penetration of which depends upon the nature of the oil phase and does not differ significantly from that obtained when the oil is applied alone. Creams containing mineral oils produce films which remain on the skin surface whereas those containing vegetable oils or wool fat produce films which slowly penetrate the skin. It should be noted that the concentration of active medicaments is greater in the residual film than in the original preparation. This needs to be taken into consideration in determining the strength and may possibly explain the greater efficiency of emulsified as opposed to oily preparations.

The rate of release of medicaments from emulsified bases is affected by the particular phase in which they are soluble. Oil-soluble medicaments incorporated into oily creams are dissolved in the external phase and come into immediate contact with the skin surface. Water-soluble medicaments are dissolved in the internal aqueous phase and are less immediately released. The release of drugs from aqueous creams follows a reverse order. Water-soluble substances are more immediately released from aqueous creams than from oily creams.

Oily Creams

The only official base of this type is oily cream which was discussed at the Symposium Session of this Conference in 1947 (Hadgraft). Its poor stability, particularly when combined with a number of commonly used medicaments, leaves a need which at present is not completely filled by an official preparation. The stability of oily cream has been shown by Clark and Kitchen (1960b) to be affected by the amount of autoxidation in the wool alcohols used in making the cream and by the method of

preparation. These authors have found that autoxidation is greatly reduced if the wool alcohols is stored as a mixture with liquid paraffin. Greater stability may also be obtained if Liquid Lanolin "60" is used as an auxiliary emulsifier.

Dr. Jarrett has referred to the possible role of zinc in keratin formation and it may be for this reason that zinc cream is frequently used as the vehicle for other dermatological medicaments. It is often combined with ichthammol with which it shows only poor stability. For this reason, a higher proportion of wool fat is included in zinc and ichthammol cream but even with this formulation, separation may occur on storage.

The fatty acid esters of the anhydrides of polyhydric alcohols may be of value in the formulation of stable oily creams. Many such substances are commercially available but they consist of mixtures which are not readily standardised and none are yet described in standard publications. Sorbitan mono-oleate and sorbitan sesqui-oleate are typical representatives which are soluble in vegetable and mineral oils and dispersible in water. They are free from irritant properties when applied to the skin (Dodd, Hartman and Ward, 1946) and can be combined with soft paraffin and wool fat to form oily creams which are stable in the presence of resorcinol, sulphur, ammoniated mercury, solution of coal tar and salicylic and benzoic acids.

Aqueous Creams

Surface-active agents for the formulation of aqueous creams can be divided into three main groups: (i) anionic, (ii) cationic and (iii) non-ionic compounds. A fourth group, the amphoteric surface-active agents (Moore, 1960) have not yet been used in dermatological preparations. For the production of stable emulsions, surface-active agents must be combined with an auxiliary material capable of forming a stable, close-packed, interfacial film (Schulman and Cockbain, 1940) and cetostearyl alcohol is commonly used for this purpose.

Anionic and cationic emulsifying agents such as self-emulsifying monostearin (Soulsby, 1940), emulsifying wax (Gunn, 1960; Hadgraft, 1947; Silcock and Chamings, 1939; Soulsby, 1940) and cetrimide emulsifying wax (Gunn, 1960) are incompatible with electrolytes in high concentration and with organic ions bearing a charge of opposite sign to the surface-active compound because neutralisation of the charged oil droplets interferes with the stability of the emulsion and the activity of the medicament may be reduced.

Non-ionic emulsifying agents possess both hydrophilic and lipophilic groups. The hydrophilic group is usually an ethylene oxide chain which can be combined with numerous lipophilic radicals. Compounds of this type may be polyethylene glycol ethers of fatty alcohols (Hadgraft, 1954) such as cetomacrogol 1000 or esters of polyethylene glycol and a fatty acid such as the macrogol stearates (Johnson and Thomas, 1955). They are incompatible with phenolic compounds with which they probably form compounds by hydrogen bonding (Mulley and Metcalf, 1956). Although non-ionic they possess a residual negative charge and may

inactivate cationic medicaments such as the quaternary ammonium compounds.

A third type of non-ionic emulsifying agent consists of the polyethyleneglycol derivatives of the esters of fatty acids and the anhydrides of polyhydric alcohols. In the formulation of aqueous creams, a mixture of sorbitan monostearate and sorbitan monostearate polyoxyethylene derivative is used. By varying the proportions of oil-soluble and water-soluble derivatives in mixtures of this type a range of emulsifying agents of varying hydrophile-lipophile balance may be obtained. To facilitate the selection of an emulsifying agent for a particular purpose, an empirical number (HLB value) has been ascribed to compounds of this type representing their hydrophile-lipophile balance (Griffin, 1949). Maximal stability is achieved at a specific HLB value characteristic of the oil phase concerned and the HLB values for emulsifying a range of commonly used oils and waxes may be obtained by reference to tables which have been compiled by Griffin.

More recently a linear relation between HLB values and spreading coefficients has been established (Becher, 1960). For stability in an oil-in-water emulsion, a negative spreading coefficient between the oil phase and an aqueous solution of the emulsifying agent is necessary to prevent oil globules from rising in the emulsion and spreading on the surface to form a separate phase. This is limited by the requirement that a low interfacial tension is also a necessary condition for emulsion stability. The emulsifying agent selected, therefore, must provide the most negative spreading coefficient consistent with a low interfacial tension. This can be determined by a simple practical method in which the oil phase is dropped on to a series of dishes containing solutions of emulsifiers of varying HLB values. The emulsifying agent having the highest HLB value which permits no spreading of the oil phase is selected. This method might profitably be extended to the investigation of incompatibilities encountered in the formulation of dermatological creams. For example, the incorporation of water-soluble substances such as ichthammol often produces creams of poor stability and the selection of an emulsifying agent which provides the most negative spreading coefficient for the oil phase in the presence of the medicament might indicate a more stable formulation.

Preservation of Aqueous Creams

Aqueous creams often support the growth of moulds and bacteria and a preservative may be required to prevent contamination during storage. Creams containing anionic or cationic emulsifying agents may be preserved with chlorocresol or the esters of hydroxybenzoic acid. Aqueous creams containing the non-ionic emulsifying agents present greater difficulties.

Much evidence indicates that non-ionic surface-active agents are capable of interaction with preservatives thus reducing their activity (Beckett and Robinson, 1958; Bolle and Mirimanoff, 1950; Navarre, 1957). However, the performance of methyl and propyl hydroxybenzoates in aqueous creams is sometimes better than is indicated by their activity

in the presence of a non-ionic compound in a liquid culture medium (Charles and Carter, 1959). Alternative preservatives which have been suggested are sorbic acid and a combination of sorbic acid and hexylene glycol (Barr and Tice, 1957).

A synergistic effect has been found to exist between the hydroxybenzoates and polyhydric alcohols such as propylene glycol, 1,3-propanediol and 1,4-butanediol (Poprzan and Navarre, 1959). It has been suggested that this arises from the interference with the compound formed between the preservative and the non-ionic agent. Aqueous creams containing non-ionic emulsifying agents may be preserved with the hydroxybenzoates, providing the formulation contains at least 10 per cent of propylene glycol.

More recently, the view has been advanced (Hibbott and Monks, 1960) that the performance of methyl hydroxybenzoate in aqueous creams depends upon its partition between the oil and the aqueous phase and to be effective, it must be present in the aqueous phase in adequate concentration. This is consistent with the finding that methyl hydroxybenzoate is more effective in a cream containing mineral oil, in which it is poorly soluble, than in one containing isopropyl myristate, in which the ester is appreciably soluble. When non-ionic emulsifying agents are present, the ester is partitioned not only between the oil and the aqueous phase but its effective concentration is further reduced owing to its solubility in the emulsifying agent. The addition of propylene glycol and similar substances increases the solubility of the preservative in the aqueous phase and this may account for its greater efficiency in such formulations.

Water-Soluble Ointments

The macrogols, two of which have been included in the B.P.C., are simple polyethylene glycols which are used in the formulation of water-soluble ointment bases. The higher members of the series such as hard macrogol are unique substances in combining complete solubility in water with a wax-like consistency. A number of authors have reported on their use in the formulation of ointments (Hopkins, 1946; Landon and Zopf, 1943; McClelland and Bateman, 1949; Meyers Nadkarni and Zopf, 1950) and they have been shown to be relatively free from skin sensitising properties. However, two instances of demonstrable sensitivity to the polyethylene glycols have been reported (Strauss, 1950).

There is some evidence that medicaments may be more readily absorbed from macrogol bases than from paraffin bases (Meyers, Nadkarni and Zopf, 1949) and it may be necessary to reduce the concentration if macrogol ointment is substituted for a paraffin base. Moreover, it has also been reported that the macrogols may increase the possibility of sensitivity reactions of diseased skin to the active medicament in ointments (Sulzberger and Baer, 1953). Ointment bases containing the macrogols are hygroscopic and the surface may become moist on storage. They have only a limited use in the formulation of dermatological preparations but may be of particular value when it is desired to wash the preparations from the skin.

Pressurised Aerosols

Pressurised containers have recently been used for the application of medicaments to the skin. The formulation of such preparations is outside the scope of this review and has been the subject of a number of articles (Briston, 1958; P.A.S.R., 1957; Root, 1956; Sciarra, Tinney and Feely, 1960; Streatfield, 1955). Only those aspects which affect the performance of the preparation on the skin will be discussed here.

A propellant is used which is usually a liquified gas of the fluorinated hydrocarbon series or a mixture of these. The most commonly used propellants are Arcton 11 (trichlorofluoromethane), Arcton 12 (dichlorodifluoromethane) and Arcton 114 (dichlorotetrafluoroethane). Carbon dioxide and nitrogen may also be used. In one kind of formulation the medicament is dissolved in a solvent which may be miscible or immiscible with the propellant. For this purpose, ethanol, isopropanol, propylene glycol and the liquid macrogols have been used. The solution is discharged from the container in the form of a fine mist and the propellant is assumed to be completely vaporised before the preparation reaches the skin. Even so, the possibility of sensitivity reactions to the propellant needs to be considered. A more serious possibility is the risk of reactions to the solvent in which the medicament is dissolved. There have been reports of a burning sensation from isopropanol (Thorne, 1959) and of irritation from propylene glycol (*Prescribers J.*, 1961). These are hazards which apply to the same substances when used in any other form of topical application.

In another kind of formulation, the medicament is dispersed in the propellant and is delivered to the skin surface as a fine powder. Such preparations may be of particular value in the application of antibiotics to infected areas.

Emulsified preparations may also be dispensed in pressurised containers but at present no dermatological preparations of this kind are available. The possibility of some propellant remaining in the preparation after application to the skin and a consequent increased risk of sensitivity reactions would need to be carefully considered. Carbon dioxide or nitrogen may be used as alternative propellants but have the disadvantage that the pressure falls as the container is emptied. About 10 per cent of the product may not be discharged and it would be a wasteful method for dispensing an expensive medicament. Creams which are passed through pressurised containers acquire foam characteristics since they are aerated by the propellant and homogenised by the valve. Consequently, they possess very good cosmetic properties.

Aerosol formulations have a number of advantages for skin medication. The preparation may be kept sterile and out of contact with air until the time of use. The medicament is applied directly to the skin surface by a no-touch technique and this may be of particular value in the treatment of conditions which are susceptible to secondary infection. The efficiency of distribution may also be important in covering a large area of the skin with the minimal amount of medicament in a finely divided form. But doubt has been expressed whether significant amounts of hydrocortisone

are absorbed when applied by spraying (*Prescribers J.*, 1961) and the precise value of such formulations must await further clinical assessment.

Skin Penetration and Absorption

In the treatment of skin diseases, it is seldom necessary for the medicament to be absorbed percutaneously, but penetration of the preparation to the deeper layers may be necessary. In such circumstances, the possibility of systemic absorption may be an undesired hazard (Snyder, 1960).

Percutaneous absorption has been the subject of a number of reviews (Blank, 1960; Gemmell and Morrison, 1957; Griesemer, 1960; Hadgraft and Somers, 1956). The main route by which substances pass through the skin is by the hair follicles, although autoradiographic studies have recently demonstrated that the corticosteroids are capable of true transepidermal penetration. The sweat glands may also play a part in the absorption of medicaments through the skin.

In general, lipid-soluble substances penetrate the skin more readily than water-soluble substances. If lipid-solubility is combined with water-solubility, the substance is likely to be absorbed at the base of the hair follicle. The vehicle in which the medicament is formulated may have a modifying influence on the amount absorbed (Gemmell and Morrison, 1958, a, b). The most important factor concerned is the physicochemical nature of the drug and it is doubtful whether pharmaceutical formulation is capable of promoting the absorption of a substance which is not alone capable of being absorbed. Some substances are very readily absorbed by the skin and occasionally this may form a useful route for the administration of drugs. Ditophal, which is used in the treatment of leprosy, is rapidly and completely absorbed by the skin and releases ethyl-mercaptan in the tissues.

The corticosteroids are extensively used in topical preparations and the possibilities of percutaneous absorption are of particular importance in this group of substances. Hydrocortisone is absorbed percutaneously through both the transepidermal and pilosebaceous routes. The amount absorbed is small and is about 1 per cent of the total dose applied to normal skin. Absorption from inflammatory sites is greater and may be as high as 15 per cent of the dose applied to the skin. Fludocortisone is also absorbed percutaneously and since its systemic effects are produced by small doses, it is the only analogue of cortisone known to be capable of eliciting systemic effects after the use of topical preparations (Malkinson, [sic]1960).

Conclusion

Preparations formulated for skin medication should be kept as simple as possible. Water-soluble medicaments are probably best applied to the skin in aqueous solution. Ease of application and localisation of effect may be achieved either by the addition of hydrophilic colloids such as sodium carboxymethylcellulose or by emulsification with an oil to form an aqueous cream. The nature of the oil phase will depend upon the condition under treatment but the materials added to assist pharmaceutical

formulation should be kept to a minimum to avoid adding materials which are likely to interfere with the activity of the medicament or to produce sensitivity reactions. The chosen emulsifying agent will depend upon the active medicament but there are now available anionic, cationic and non-ionic emulsifying agents which permit the formulation of creams suitable for all kinds of medicaments.

Oil-soluble medicaments are best applied in oily creams but at the present there is no entirely satisfactory official preparation for this purpose. Oil-soluble medicaments may also be incorporated in anhydrous bases.

The water-soluble bases such as macrogol ointment have only a limited use since they do not appear to be free from irritant effects.

The effects of pharmaceutical formulation on the activity of topically applied medicaments has not been fully assessed clinically. Probably, the most that can be achieved is to present the medicament in a form which enables it to exert its maximal activity in a preparation which is cosmetically as acceptable as possible. For this purpose, additional materials which are in use in the cosmetic industry are applicable to the formulation of dermatological preparations.

References

Abbe, J. Van (1959). *Pharm. J.*, **183**, 111–115.
Armstrong, J. and Fenton, A. H. (1954). *Ibid.*, **173**, 8–13.
Barr, M. and Tice, L. F. (1957). *J. Amer. pharm. Ass. Sci. Ed.*, **46**, 445–451.
Becher, P. (1960). *J. Soc. cosmetic Chem.*, **11**, 325–332.
Beckett, A. H. and Robinson, A. E. (1958). *Soap, Perf. and Cosmetics*, **31**, 454–459.
Blank, I. H. (1952). *J. invest. Dermatol.*, **18**, 433–440.
Blank, I. H. (1955). *Proc. Sci. Sect. Toilet Goods Assoc.*, **23**, 19.
Blank, I. H. (1960). *J. Soc. cosmetic Chem.*, **11**, 59–68.
Bolle, A. and Mirimanoff, A. (1950). *J. Pharm. Pharmacol.*, **2**, 685–691.
Bolliger, R. and Muenzel, K. (1958). *Pharm. Acta. Helvet.*, **33**, 141–155.
Briston, J. H. (1958). *Pharm. J.*, **180**, 65–66.
Chamings, A. R. G. (1943). *Ibid.*, **151**, 203.
Charles, R. D. and Carter, P. J. (1959). *J. Soc. cosmetic Chem.*, **10**, 383–394.
Clark, E. W. and Kitchen, G. F. (1960a). *J. Pharm. Pharmacol.*, **12**, 233–236.
Clark, E. W. and Kitchen, G. F. (1960b). *Ibid.*, **12**, 227–232.
Collard, R. E. (1961). *Pharm. J.*, **186**, 113–117.
Dodd, M. C., Hartmann, F. W., and Ward, W. C. (1946). *J. Amer. pharm. Ass. Sci. Ed.*, **35**, 33–41.
Fayaud, A. (1953). *Soap, Perf. and Cosmetics*, **26**, 1247–1248.
Gemmell, D. H. O. and Morrison, J. C. (1957). *J. Pharm. Pharmacol.*, **9**, 641–655.
Gemmell, D. H. O. and Morrison, J. C. (1958a). *Ibid.*, **10**, *Suppl.* 210*T*–211*T*.
Gemmell, D. H. O. and Morrison, J. C. (1958b). *Ibid.*, **10**, 553–560.
Griesemer, R. D. (1960). *J. Soc. cosmetic Chem.*, **11**, 79–85.
Griffin, W. C. (1949). *Ibid.*, **1**, 311–326.
Gunn, C. (1960). *Pharm. J.*, **184**, 25–26.
Hadgraft, J. W. and Wolpert, R. (1960). *Ibid.*, **184**, 509–510.
Hadgraft, J. W. (1947). *Quart. J. Pharm.*, **20**, 484–491.
Hadgraft, J. W. (1954). *J. Pharm. Pharmacol.*, **6**, 816–827.
Hadgraft, J. W. and Somers, G. F. (1956). *Ibid.*, **8**, 625–633.
Harry, R. G. (1941). *Brit. J. Dermatol.*, **53**, 65–96.
Hibbott, H. W. and Monks, J. (1960). *Conference of Society of Cosmetic Chemists, August.*
Hopkins, J. G. (1946). *J. invest. Dermatol.*, **7**, 171–174.
Howard, G. M. (1960). *Perf. essent. Oil. Rec.*, **51**, 613–619.
Johnson, C. A. and Thomas, J. A. (1955). *Pharm. J.*, **175**, 51–54.
Landon, F. W. and Zopf, L. C. (1943). *J. Amer. pharm. Ass., pract. Pharm. Ed.*, **4**, 251–253.
Lapin, J. H. (1942). *Amer. J. Dis. Child*, **63**, 89–91.
Levy, G. (1959). *J. Soc. cosmetic Chem.*, **10**, 395–401.

Levy, G. and Schwarz, T. W. (1958). *J. Amer. pharm. Ass. Sci. Ed.*, **47**, 44–46.
Malkinson, F. D. (1960). *J. Soc. cosmetic Chem.*, **11**, 146–159.
McClelland, C. P. and Bateman, R. L. (1949). *J. Amer. pharm. Ass., pract. Pharm. Ed.*, **10**, 30–33.
Meyer, E. (1935). *J. Amer. pharm. Ass. Sci. Ed.*, **24**, 319–325.
Meyer, R. J. and Cohen, L. (1959). *J. Soc. cosmetic Chem.*, **10**, 143–154.
Meyers, D. B., Nadkarni, M. V. and Zopf, L. C. (1949). *J. Amer. pharm. Ass. Sci. Ed.*, **38**, 231–234.
Meyers, D. B., Nadkarni, M. V. and Zopf, L. C. (1950). *J. Amer. pharm. Ass., pract. Pharm. Ed.*, **11**, 32–35.
Moore, C. D. (1960). *J. Soc. cosmetic Chem.*, **11**, 13–25.
Mulley, B. A. and Metcalf, A. D. (1956). *J. Pharm. Pharmacol.*, **8**, 774–779.
Mumford, P. B. (1940). *Practitioner*, **145**, 258–262.
Mutimer, M. N., Riffkin, C., Hill, J. A. and Cyr, G. N. (1956). *J. Amer. pharm. Ass. Sci. Ed.*, **75**, 101–105.
Navarre, M. G. de (1957). *J. Soc. cosmetic Chem.*, **8**, 68–75.
Newman, H. G. (1957). *Ibid.*, **8**, 44–54.
Peck, S. M. and Glick, A. W. (1956). *J. Soc. cosmetic Chem.*, **7**, 530–540.
Pharmaceutical Aerosol Symposium Report (1957). *Drug and Cosmetic Ind.*, **81**, 302–303.
Poprzan, J. and Navarre, G. M. de (1959). *J. Soc. cosmetic Chem.*, **10**, 81–87.
Powers, D. H. and Fox, C. (1957). *Proc. Sci. Sect. Toilet Goods Assoc.* **28**, 21–26.
Powers, D. H. and Fox, C. (1959). *J. Soc. cosmetic Chem.*, **10**, 109–116.
Prescribers J. (1961). **1**, 7.
Root, M. J. (1956). *Drug and Cosmetic Ind.*, **79**, 473–474, 571–573.
Rubin, S. H. (1960). *J. Soc. cosmetic Chem.*, **11**, 160–169.
Schulman, J. H. and Cockbain, E. G. (1940). *Trans. Farad. Soc.*, **36**, 651–668.
Sciarra, J. J., Tinney, F. J. and Feely, W. J. (1960). *Aerosol Age*, **5**, 63–68.
Shotton, E. (1954). *Pharm. J.*, **173**, 297–298.
Silcock, F. A. E. and Chamings, A. R. G. (1939). *Brit. med. J.*, **2**, 691.
Snyder, F. H. (1960). *J. Soc. cosmetic Chem.*, **11**, 117–127.
Soulsby, J. (1940). *Brit. J. Dermatol.*, **52**, 25–35.
Strauss, M. J. (1950). *Arch. Derm. Syph., Chicago*, **61**, 420–425.
Streatfield, H. (1956). *Soap, Perf. and Cosmetics*, **29**, 67–71.
Sulzberger, M. B. and Baer, R. L. (1953). *Yearbook of Dermatology and Sypholology* 19.
Thorne, N. (1959). *Lancet*, **1**, 786.

Discussion

The following points arose out of the discussion.

Despite newer techniques and materials, the formulation of skin medicaments relied much on empiricism. Laboratory tests, such as the FDA cup plate method, could give useful information about the release of medicaments from bases. Although animal studies helped in assessing absorption and penetration and the sensitising and irritant properties of bases and medicaments, it was not easy to draw firm conclusions from them. Radioactive materials were valuable in the study of how absorption into the skin was affected by dermatological conditions but the techniques were very sensitive and there was a danger of over-optimistic interpretation of the results. Although propylene glycol had been found to be a sensitising agent, this was not the experience of all dermatologists; selenium sulphide was similar in this respect. Psychological disturbances could make an established skin disease worse but were not usually the causative agents: tranquilising drugs were of limited value in dermatology. Goose-grease still compared favourably with modern bases. Many modern

medicaments were available in both greasy and non-greasy bases. Since greasy bases encouraged hydration of the keratin layer, there were grounds for using this type of base. Some substances could penetrate the skin by different routes: it was necessary to distinguish between trans-epidermal penetration and passage through the hair follicles and glands. The azo dyes were now seldom used in dermatology.