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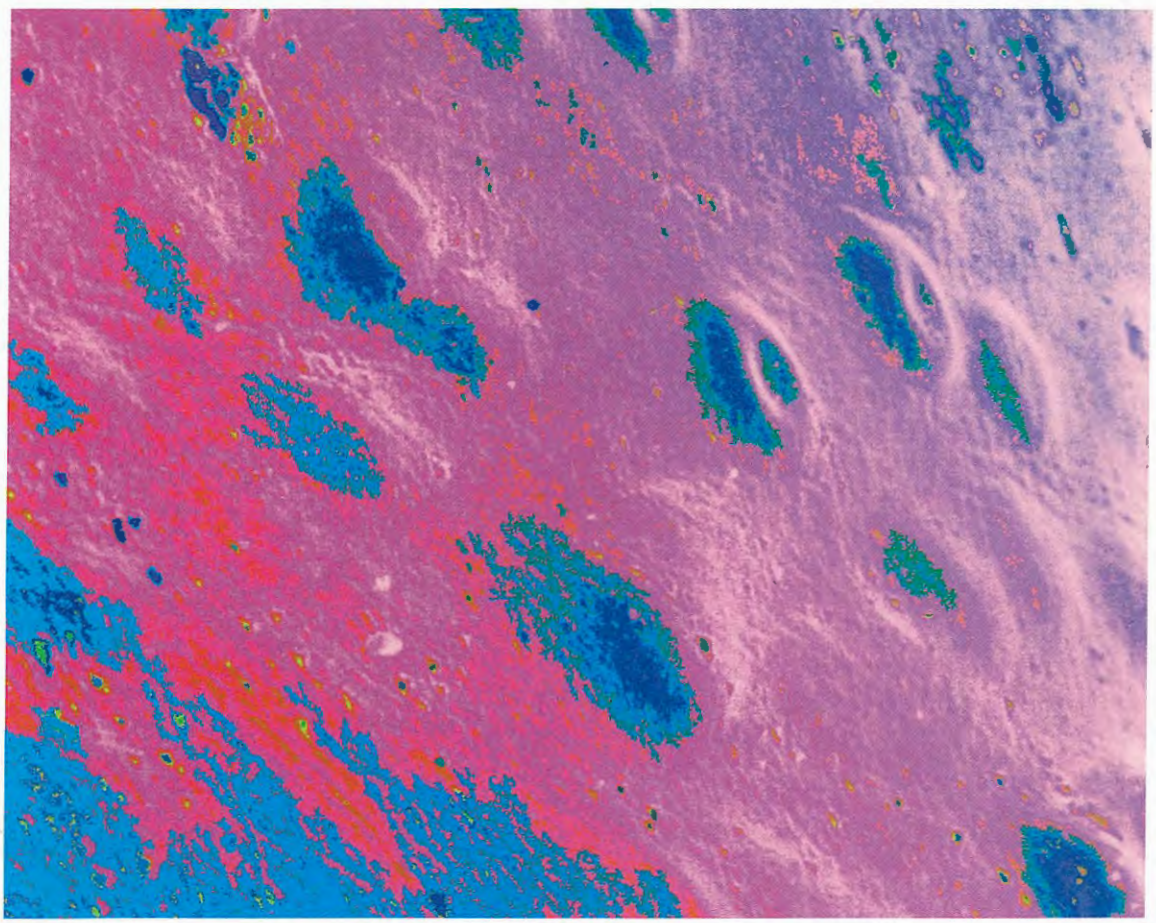

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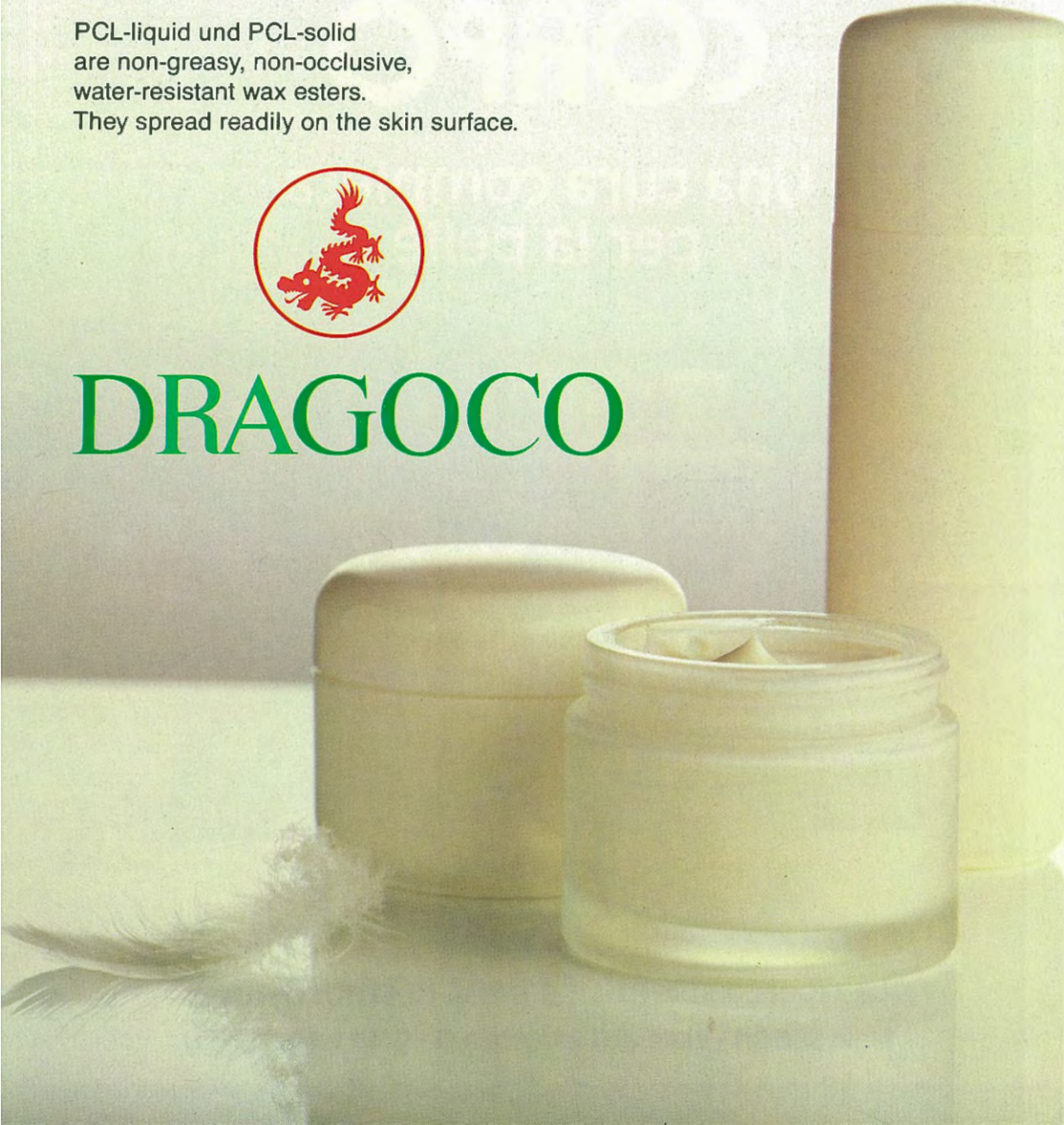

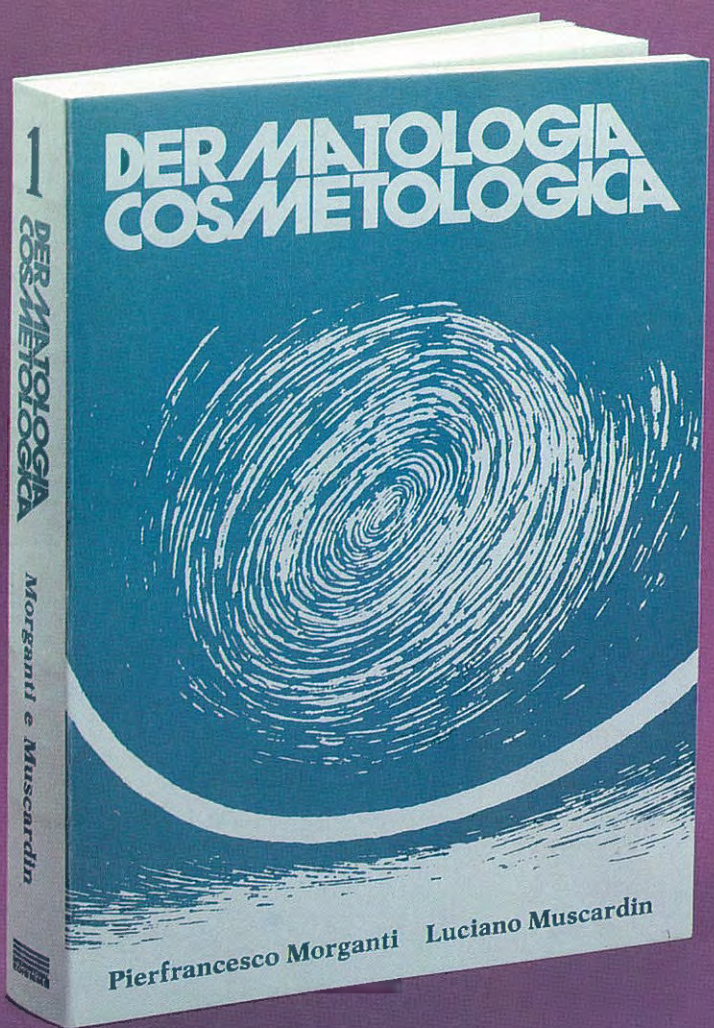

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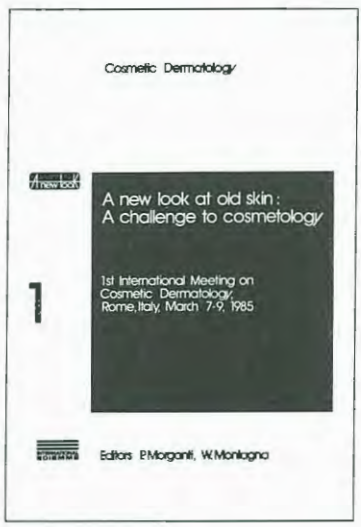
A new look at old skin: A challenge to cosmetology

1st International Meeting on Cosmetic Dermatology, Rome, Italy, March 7-9, 1985

Editors: P. Morganti, W. Montagna



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Contents

General Articles

Original Laboratory Studies

J. Appl. Cosmetol. 9, 1-7 (January - March 1991)

USE AND EFFICACY OF UREA IN DERMATOLOGICAL PREPARATIONS

W. Wohlrab
Department of Dermatology, Martin-Luther-University, PSF 302-D-4010 Halle

Received: *October 26, 1989; Presented at at 3rd International Congress on Cosmetic Dermatology "Progress in Cosmetic Dermatology" - 27 - 29th October 1989, Wien*

Key words: *Urea; Penetration; Water-binding capacity; Topical therapy.*

Synopsis

The basis of the effects of urea on the human skin is its penetration kinetics into different skin layers. A strong vehicle dependence can be estabilished. Therefore wide differences are found in the duration and intensity of increased water-binding capacity after application of different urea containing emulsions. For therapy to increase the hydration and water-binding capacity in the horny layer of diseased skin preparations with 10% urea are more suitable than those containing 2% or 5% urea. For cosmetic preparations, the higher concentrations of urea are inappropriate, lower ones are sufficient. By altering the functional structure of the horny layer and increasing of drug liberation from ointment bases, urea is one of the most effective penetration promoters. An increased penetration rate of some corticosteroids, dithranol and other drugs in human skin. The resulting penetration has two possible implications for topical therapy:
- an increased therapeutic effect for any given concentration of an active constituent
- the attainment of a given therapeutic effect with a reduced concentration of the active ingredient.

Riassunto

Gli effetti esplicati dall'urea sono connessi alla sua penetrazione attraverso i differenti strati dell'epidermide e, quindi, direttamente dipendenti dal tipo di veicolo utilizzato. Per questi motivi sono state riscontrate differenze nella durata e nella intensità della capacità del prodotto di legare acqua in dipendenza del tipo di emulsione. Per incrementare l'idratazione cutanea e la capacità di legare acqua della cute affetta da patologie si sono dimostrate più efficaci concentrazioni di urea del 10% rispetto a concentrazioni del 2 o del 5%. Per uso cosmetico sono più adatte e sufficienti concentrazioni basse di urea.
L'urea può essere considerata una delle sostanze più attive nel promuovere la liberazione dei farmaci dai veicoli e, quindi, il loro assorbimento. Facilita, perciò, l'attività dei corticosteroidi, del ditranolo e di molti altri farmaci.
Queste sue caratteristiche ne consigliano l'uso terapeutico in due direzioni diverse:
-per incrementare l'effetto terapeutico di una data concentrazione di farmaci resi per questi motivi ugualmente attivi a concentrazioni più basse.

The use of urea in topical therapy and in cosmetics has undergone a revival in recent years (1, 3, 4, 11 and others).
Some reasons for this can be listed as follows:

1. By intensive basic research many properties of urea have been discovered and precisely defined. At the same time, the conditions for the therapeutic utilization of these properties e.g. problems of stabilization, have been delineated.

2. In topical therapy increasing use is made of pharmacokinetic information. The equal significance of the properties of the active substances and of the vehicle, the condition of the skin, and their mutual interactions, are not only recognized but also increasingly utilized a basic for overall therapeutic activity. Pharmaceutical formulations are selected and optimized in such a way that a desirable concentration/time profile is achieved for the substance in the appropriate skin layer.

3. The properties of urea itself make it ideal for external use, as it is a natural moisturizer and is well tolerated. As a physiological substance it is the end product of protein metabolism. In human skin its concentration is 1% and it is excreted in sweat in considerable quantities. After external or systemic administration it is not metabolized. No side effects, in particular non cases of sensitization or photosensitization, have so far been reported under therapeutic conditions.

Principles of the action of urea on skin

The penetration kinetics of urea, i.e. how much urea, in relation to exposure time, penetrates into individual skin layers after external application, are of decisive importance to the achievement of its effects. In relation to the vehicle, the penetration kinetics of urea show fundamental differences between w/o and o/w emulsions (7), and these yield different therapeutic effects.
Urea penetrates the horny layer of human skin more quickly from o/w emulsions than from w/o emulsions (Fig. 1). It should be noted that, at about 80%, the bulk of the urea which has penetrated is found in the upper horny layers.

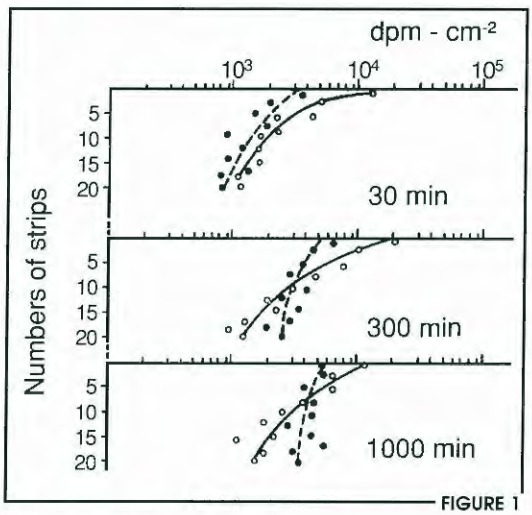

FIGURE 1

Distribution of urea in the horny layer of human skin after external application of 10% urea containing preparations.

•- - -• w/o-emulsion (Ungt. Alcohol. Lanae aquosum, Pharmacopoea GDR)
o — o o/w-emulsion (Ungt. emulsificans aquosum, Pharmacopoea GDR)

The steep concentration gradient is largely maintained when o/w emulsious are used, even after as long as 1000 min.
In contrast, the penetration of urea from w/o emulsions is noticeably smaller after short exposure. The concentration gradient within the horny layer decreases so that after 1000 min approximately equal urea concentrations can be measured throughout the stratum corneum.
This results in different urea concentrations in the epidermis and dermis (Fig. 2), which are appreciably higher for w/o emulsions. Overall, however, the penetration of the lower epidermis and dermis are small in comparison with that of the horny layer, regardless of the emulsion used.

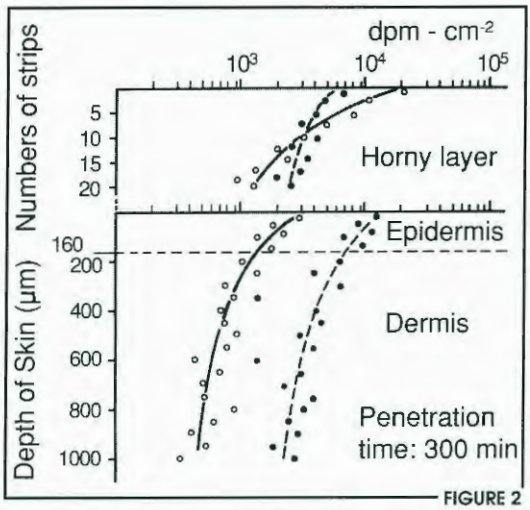

FIGURE 2

Distribution of urea in human skin after external application of 10% urea containing preparations.

•- - -• w/o-emulsion (Ungt. Alcohol. Lanae aquosum, Pharmacopoea GDR)
o — o o/w-emulsion (Ungt. emulsificans aquosum, Pharmacopoea GDR)

These differences in the course of penetration and hence in the concentration/time profile of urea in the individual skin layer provide for different degrees of efficacy. Different emulsions can be used according to whether the urea is to act on the functional skin structure (e.g. hydration and water-binding capacity, keratolysis, inhibition of proliferation, alleviation of itching, etc.) or to aid penetration by other products.

What is the necessary concentration of urea in the vehicle?

From the findings so far discussed, it is clear that the decisive factor in therapeutic activity is not the concentration of urea in the applied vehicle but rather the quantity of urea which penetrates into the individual skin layers, i.e. the concentration/time profile achieved. It has be

Table I

CONCENTRATION OF UREA PENETRATING TO THE STRATUM CORNEUM (SC) OF HUMAN SKIN IN RELATION TO THE CONCENTRATION OF UREA IN THE VEHICLE (9)

Vehicle: W/O-emulsion (Ungt. Alcohol. Lanae aquosum AB-DDR)

Penetration Period (min)	Urea Concentration (%) applied	Urea concentration (mm) in the sc
30	2	29,9
	5	103,1
	10	212,6
300	2	48,3
	5	145,7
	10	449,9
1000	2	95,8
	5	231,6
	10	602,9

noted that, at around 80%, the bulk of the urea which penetrates is situated in the outer horny layers (Tab. 1). When vehicles containing 2% or 5% are used the urea concentration necessary for normal human stratum corneum cannot be reached. To increase the water-binding capacity in the horny layer of diseased skin products containing 10% of urea are more suitable from the therapeutic point of view (9). High urea concentrations (over 2-3%) are not, however suitable for cosmetic use without medical supervision.

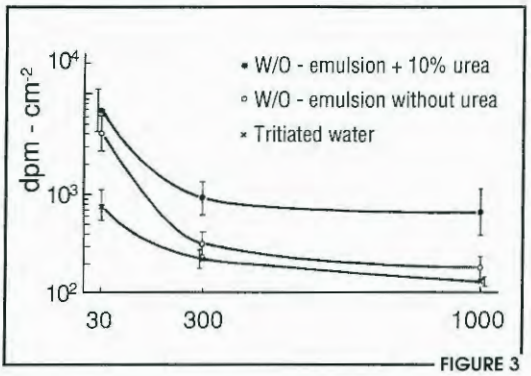

FIGURE 3

Influence of urea on the water-binding capacity of the human horny layer (10).
Vehicle: w/o-emulsion (Ungt. Alcohol. Lanae aquosum, Pharmacopoea GDR) labeled with tritiated water.

Influence of the vehicle on the water-binding capacity due to urea.

Corresponding to the described differences in penetration, depending on the vehicle and the urea concentrations used, there are also variations in the effectiveness of the urea-containing basic skin products to increase the water-binding capacity of the stratum corneum (5, 6). When the urea is used in o/w emulsions or lotions, a high degree of hydration is quickly reached (immediate effect), but this fairly quickly declines (Fig. 3).
In contrast, with w/o emulsions there is a more market and longer-lasting increase in water-binding capacity.

Table II

WATER-BINDING CAPACITY OF HUMAN HORNY LAYER AFTER APPLICATION OF UREA CONTAINING PREPARATIONS (10).
Application: 10 mg of urea containing preparation labeled with 5 µCi tritiated water at 4 cm² skin surface.

preparation	urea concentration (%)	Horny layer dpm/cm2 after 30	300	1000 min
Basodexan (R) Ointment	10	5422 ± 521	2478 ± 205	902 ± 51
Basodexan (R) Cremé	10	8104 ± 514	1386 ± 169	472 ± 34
Basodexan (R) Soft	10	10606 ± 678	542 ± 98	185 ± 22
Carbamid-Cremé(R)	12	8666 ± 426	1214 ± 100	475 ± 28
Elacutan-F(R)	10	3968 ± 275	994 ± 63	678 ± 74
Elacutan-W(R)	10	7185 ± 376	426 ± 72	183 ± 19
Excipial(R)-U-Lotio	2	6804 ± 248	388 ± 26	126 ± 24
HTH(R)	10	12011 ± 528	568 ± 59	223 ± 63

If one examines these basic mechanism in relation to the various commercial urea-containing basic skin products, large differences are found in the action on the water-binding capacity of the stratum corneum (Tab. 2). These differences are evidently not primarily dependent on the urea concentration used but on the vehicle (10).

Influence of urea on the penetration of other products

Urea promotes the release of various drugs from their base, and in addition it is a very effective promoter of penetration of various active substances (1, 3, 4, 11). Essentially, the promotion of drug penetration by urea can be exploited in two ways (8):

1. to improve therapeutic efficacy at the same concentration of active substance and
2. to achieve the same therapeutic efficacy with a considerably lower concentration (Fig. 4).

The optimization of the therapeutic efficacy of other drugs by urea has been demonstrated above all with glucocorticoids (e.g. Hydrodexan (R), Hycozon (R), Alphaderm (R), etc.) and dithranol (e.g. Psoradexan (R)), with impressive evidence from numerous clinical studies.

With respect to hydrocortisone, it has been shown that when low concentrations of urea are used enhancement of penetration is barely apparent, whereas with a urea content of between 5% and 10% there is a particular increase (Fig. 5).

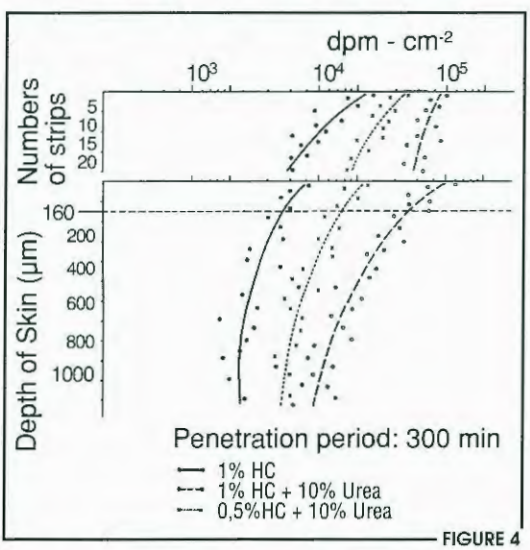

FIGURE 4

Distribution of hydrocortisone (HC) in human skin after external application (8).

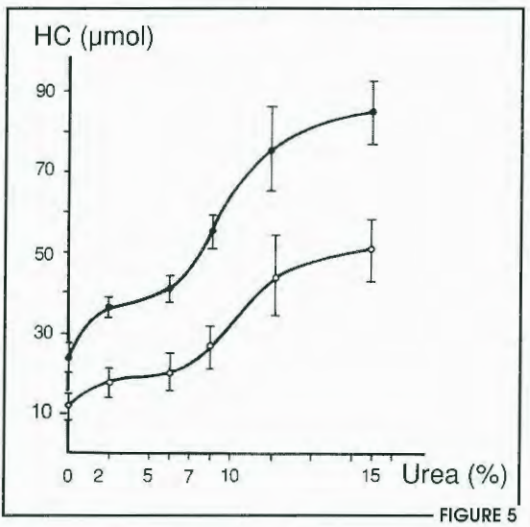

FIGURE 5

Dependence of hydrocortisone penetration into epidermis of human skin on urea concentration and used vehicle.
Penetration time: 300 min.
Hydrocortisone concentration: 1%
•- - -• w/o-emulsion (Ungt. Alcohol. Lanae aquosum, Pharmacopoea GDR)
o o o/w-emulsion (Ungt. emulsificans aquosum, Pharmacopoeia GDR)

When the urea concentrations are raised further, no further decisive changes are detectable. In this connection o/w emulsions and w/o emulsions basically act in the same direction, but w/o emulsions have a considerably greater penetration-promoting effect.

On the basis of these data hydrocortisone, the determination of the penetration kinetics of the glucocorticoid and of the urea in each vehicle is indispensable for making use of the penetration-promoting action of urea in the development of

glucocorticoids for external use (8). The urea and glucocorticoid concentrations can then be optimized.

Less attention has so far been paid to the possibility of using the penetration-promoting action of urea to achieve a particular therapeutic efficacy with a considerably reduced quantity of glucorticoid. One reason is very probably the widely practised dilution of proprietary glucocorticoid formulations. In 1984 Müller (2) summarized the reasons for this procedure and its problems and risks in a very informative review. The example of hydrocortisone shows very clearly that after reduction to 0,5% the quantity which penetrates e.g. into the epidermis can be reduced by 75-80% (Tab. 3). In contrast, when various quantities of urea are added, a concentration-dependent promotion of penetration is detectable, so that the formulation becomes identical in efficacy with a 1% hydrocortisone product in which there is no urea.

Viewing this subject as a whole, we still know too little about the pharmacological properties of urea fot external use. Automatic procedures in the application of urea in external therapy and examination of the properties of urea in isolation therefore promise little success and should be avoided.

Table III

INFLUENCE OF UREA ON THE PENETRATION OF REDUCED HYDROCORTISONE CONCENTRATIONS INTO HUMAN SKIN (12).

Vehicle: W/O-emulsion (Ungt. Alcohol. Lanae aquosum, Pharmacopea GDR)
HC = hydrocortisone; U^+ = Urea.

Preparation	penetration time (min)	
	30	300
horny layer (mmol)		
1,0% HC	13,9	16,1
0,5% HC	2,9	3,9
0,5% HC + 5% U^+	8,5	10,0
O,5% HC + 10% U^+	12,5	13,8
0,5% HC + 15% U^+	12,8	14,0
epidermis (µmol)		
1,0% HC	12,8	23,2
0,5% HC	2,1	5,7
0,5%HC + 5% U^+	6,8	11,0
0,5% HC + 10% U^+	10,2	19,9
0,5% HC + 15% U^+	11,9	20,7

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UREA FROM THE CHEMIST'S POINT OF VIEW

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Key words: *Urea; Chemistry; Manufacture; Decomposition; Stabilization; Recommended Concentrations*

Synopsis

Urea is a colourless and odourless tetragonal crystal. Due to its molecular structure (dipolaric) it can easily be dissolved in water, whereas it is almost insoluble in nonpolar substances such as chloroform or ether. In solution, urea undergoes a decomposition to carbon dioxide and ammonia. A so-called "sand paper effect" may occur, especially in preparations containing higher urea concentrations caused by the phenomenon of recrystallisation.
Therefore topical products with urea require stabilisation (either with triacetin, lactic acid or polysaccharides). Non stabilised urea containing preparations can only be used safely for periods of up to six weeks (the stabilised preparations can be stored for two or even three years).
In conclusion it can be said that urea containing formulations for cosmetic and/or dermatological purposes have to be developed with great care to provide perfect results.

Riassunto

L'urea é una sostanza cristallina e inodore, facilmente solubile in acqua e praticamente insolubile nei solventi apolari quali il cloroformio e l'etere. Una volta disciolta l'urea si decompone facilmente in anidride carbonica ed ammoniaca.
Data la sua poca stabilità in soluzione i preparati topici a base di urea debbono essere ben stabilizzati (sia con acido lattico che con polisaccaridi).
Si deve fare anche molta attenzione alla sua concentrazione di utilizzo per evitare il fenomeno di ricristallizzazione che provoca il cosidetto "effetto sabbia" ben noto agli utilizzatori abituali. In conclusione si può affermare che le preparazioni cosmetiche o dermatologiche a base di urea debbono essere formulate e controllate con grande cura.

Introduction

Jean Rouelle (1718-1778), a french apothecary, discovered urea as a natural constituent of human urine in 1773 ("Identification d'une substance savonneuse dans l'urine"). Friedrich Wöhler (1800-1882), M.D. and chemist, succeeded in synthesizing urea from ammonium cyanate. He therefore proved that no mystical "vis vitalis" is necessary to synthesise organic materials from inorganic precursors.

Manufacture and chemistry of Urea:

Urea (U) is the diamide of carbonic acid. It is a colourless, odourless (or nearly odourless), slightly hypogroscopic prismatic crystalline substance with a cooling saline taste (2).
The world production of urea is mainly used in fertilizers and for the synthesis of plastics (altogether 40 million tons in 1980).
These large amounts of U are manufactured from ammonia and carbon dioxide under high pressure (100-200 atm) and high temperatures (170-250°C). In the laboratory U is still synthesized by the method of Dr. Wöhler.
Apart from the many favourable effects of topical urea, this substance is cheap. 1 kg of Urea pura of the quality specified in the Austrian pharmacopoeia would cost less than 50 AS.
Due to its ability to form intramolecular dipoles, U resembles the water molecule. Therefore it readily dissolves in polar solvents such as water or alcohol but it is almost insoluble in nonpolar media such as chloroform or ether.
U is a weak acceptor of protons and would give in water a solution with a pH of 7,5, at least theoretically. Deviations occur due either to the carbon dioxide content of water or to impurities and decomposition of U itself.

Decomposition of urea (Fig. 1)

Once in solution, urea decomposes and, in simple terms, the following reactions occur. First U is converted into ammonium cyanate. The equilibrium lies completely on the side of the unchanged U. In the subsequent reaction ammonium cyanate is hydrolytically split. Other U molecules then form ammonium cyanate in order to maintain the equilibrium of the first reaction. Ammonium cyanate is split into two molecules of ammonia and one molecule of carbonic acid. Carbonic acid is a weak and instable acid ($H^+ + HCO_3 \Leftrightarrow H_2CO_3 \Leftrightarrow CO_2 + H_2O$), the two molecules of ammonia react as proton (H^+)- acceptors.

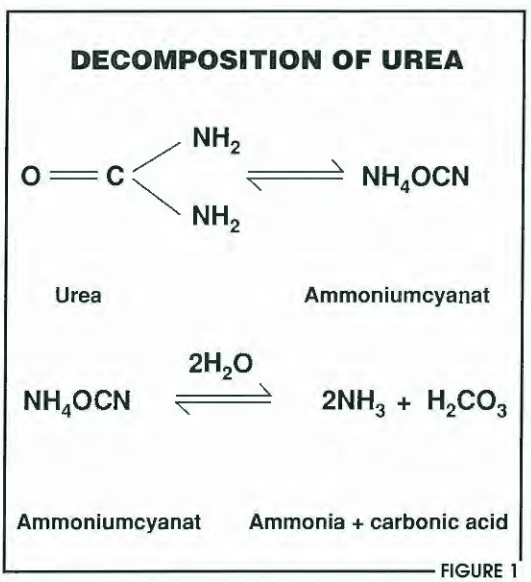

FIGURE 1

Therefore the pH constantly increases.
Some factors such as the steadily increasing pH, raising of the temperature and open storage, which permits the escape of the produced ammonia and carbon dioxide, enhance the decomposition. Open storage (and high temperature in addition) favours evaporation of water. The result could be a recrystallization of U. The risk is greater with the higher initial concentrations of U. The crystals act like sand on the skin and cause irritation.

Therefore topical preparations containing urea should be made airtight after each usage and stored at normal room temperature or below. Before application it should be made sure that no sandiness has developed (4).

Stabilization of Urea:

The above mentioned facts explain why industrially produced topical preparations containig urea must be stabilized.
Stabilization reduces and delays disintegration and keeps the pH constant over longer periods (2).
One possibility for stabilizing U is the addition of triacetin. Triacetin is an ester of glycerol with three molecules of acetic acid. As soon as pH increases, the ester bonds are hydrolytically split and the released acetic acid will keep pH constant. Another possibility is the addition of lactic acid, wich is as effective as acetic acid. Moreover, lactic acid is part of the NMF of the skin and will therefore increase one of the effects of U. However stabilization with lactic acid can lead to burning sensations.
At present the most sophisticated method of stabilization is the adsorption of U to polysaccharides (for instance corn or rice starch). There are no problems with local tolerance, and the pH in these formulations can be adjusted as desired.

Urea containing preparations for topical use upon special prescription:

Some problems arise if one prescribes an U containing topical preparation. Generally spoken this task is easier the lower the required U concentrations and tbe higher the required water content are. Before introducing U into the formulation the crystals have to be pulverized. The use of an ointment mill will cause disappearance of sandiness (4).
For cosmetic and dermatological purposes such as augmentation of the skin-moisture, general skin protection and therapy of scaly lesions, 3-5% U in an O/W emulsion are recommended (5,6). This will have an immediate effect on the upper horny layers (Fig. 2 and 3).

UREA IN O/W

Urea purae	5,0
NaCl	5,0
Tween 80	20,0
Aquae dest.	40,0
Vas. alb. ad	100,0

FIGURE 2

UREA IN O/W

Urea purae	3,0
Allantoin	0,2
Karion F liqu.	3,0
Vas. flav.	10,0
Lanette N	15,0
Guajazulen 25%	0,04
Aquae dest.	100,0

FIGURE 3

For the treatment of pronounced dermatological disturbances such as psoriasis vulgaris, different forms of ichthyosis, atopic dermatitis and extremely dry skin, 10% U in W/O should be applied (5,6). U in W/O has not such a distinct immediate effect but has a longer lasting beneficial action due to its deeper penetration into the

skin (Fig. 4). For painless onycholysis, 40% U concentrations are necessary. The surrounding skin should be protected with a paste.

UREA IN W/O

Urea purae	10,0
NaCl	10,0
Aquae dest.	20,0
Ungt. alc. lanae aqu. ad	100,0

FIGURE 4

After 5-10 days of occlusion the nail can be removed (7). As shown in Fig. 5, U in this case is incorporated into a vehicle, which consists only of various lipids. It is not dissolved but merely suspended. Therefore sandiness is inevitable. No improvement will be brought about by ointment mills as their use will lead to separation of the different parts of the vehicle (4).

ONYCHOLYSIS WITH UREA

Urea purae	40,0
NaCl	5,0
Aquae dest.	20,0
Ungt. alc. lanae aqu. ad	100,0

Occlusion (5-10 d)

FIGURE 5

Industrially produced urea containing preparations for topical use:

Industrially manufactured products have some distinct advantages over those upon special prescription. They have a guaranteed stability over 2-3 years on an average, whereas the prescribed products can only be used for 4-6 weeks. The quality of manufactured creams, ointments or lotions is good and constant.

Urea itself shows some antimicrobial action (5). Therefore little or no preservative need be added, and it is well known, that preservatives are rather disadvantageous from the allergological point of view.

In summary it can be said, that urea is a somewhat difficult substance to incorporate into good and stable topical formulations. Therefore urea containing preparations for cosmetological and dermatological purposes need to be developed with the utmost care to guarantee perfect results.

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BIOCHEMISTRY, PHARMACOLOGY AND THERAPEUTIC USE OF UREA

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Key words: *Urea; Safety; Preservatives; Atopic Eczema*

Synopsis

Modern dermatology looks more and more closely into "old" substances wich proved to be effective and safe. In addition, most of them are much cheaper than the new compounds. Urea is one of the old substances which were used more and more often in topical therapy of dermatoses, either alone or in combination with a steroid, anthralin, retinoic acid or salicylic acid. In this paper, biochemistry and pharmacology of urea with special reference to its topical application were outlined. In many dermatoses, urea containig preparations may be successfully applied. Lasty, the possibilities of urea in cosmetology are briefly discussed.

Riassunto

L'urea é una delle sostanze più vecchie di uso dermatologico, utilizzata in terapia da sola o in associazione con steroidi, atralina, acido retinoico e acido salicilico. Viene descritto l'aspetto biochimico e farmacologico dell'urea in relazione sopratutto al suo uso topico. In molte dermatosi le preparazioni a base di urea vengono utilizzate con grande successo. Infine ne viene discusso il suo uso cosmetologico.

Introduction

Urea (carbamide, the diamide of carbonic acid) may be found in all organs, tissues, and body fluids.
Physiologically, urea is present on the skin surface, too, as a component of the hydrolipid emulsion. Urea here stems from sweat (content 0.4% urea) and from keratinization (end product of arginine degradation).
In former times, urea mainly was used as a diuretic and an antiedema drug. Doses amounted to 15 g per day orally or 1.0 g/kg/d intravenously. Urea was well tolerated even in these high doses.
From the beginning of the forties, urea was used for dermatological therapy in the form of creams and ointments (1, 2, 4). Numerous experimental investigations proved its valuable therapeutic actions. In the last years, urea is also increasingly found in cosmetic preparations.
In December 1988, a symposium was held in Salzburg on "Urea in dermatology". The proceedings of this conference contain all the documentation on this topic (2).

Dermato-toxicology of urea

The topical use of urea never provokes systemic resorptive effects as urea by itself is an atoxic substance.
On healthy skin, urea may be applied in concentrations up to 20%. (Due to chemical factors, such concentrations are not easy to reach!). On inflamed skin, concentrations of urea should be limited to 2 or 10%, depending upon the state of the lesions. Urea in a 40% concentration may be used for chemical onycholysis, e.g. in onychomycoses.
Urea lacks sensitizing and pbotodynamic activities. Urea is color- and odorless and does not stain either the skin or the linen.

Pharmacological activities of urea upon topical use

Applied externally, urea exerts a variety of dermatologically and cosmetologically important actions:

Moisturizing action: Urea binds water by including it into its crystal structure. In a concentration of 70%, urea is an important component of the natural moisturizing factor of normal human skin. In contrast to the effects of humectants (glycerol, propylene glycol), urea acts a moisturizer even in xerotic skin conditions. As water is the most important plastifying agent in stratum corneum, humidity significantly improves smoothness of the skin. Atopic skin with its lack of water binding capacity needs urea for its care.

Keratolytic - keratinolytic action: By splitting hydrogen bonds, urea in high concentrations (40%) exerts a proteinolytic (keratinolytic) activity. This effect may be used for a chemical onycholysis.

Desquamating action: Urea loosens the intercellular connections between the corneocytes thus facilitating desquamation of superficial cells and, on the other hand, increasing penetration. This effect may activate of drugs which are applied concomitantly witb urea.

Antimicrobial action: By absorbing water, urea hinders the growth of microorganisms, without provoking an antimicrobial effect in the usual sense. Thus, preservation of urea-containing products needs less potential allergens in the form of the usual microbistatic substances.

Antiinflammatory action: The antiinflammatory action of urea consists of several components: antiproliferative (in states of increased cellular turnover, only), antiedematous (topical

"diuretic" effect, as could be demonstrated in cases of lymphostatic papillomatosis cutis verrucosa), and antipruritic (inhibitory action on enzymatic activities which promote itch).

Dermatological indications for urea

Topical preparations containing urea may successfully be used in a variety of dermatoses:
- Atopic eczema (therapeutic application, skin care in states of dryness and various forms of subacute and chronic, dry eczemas.
- Psoriasis vulgaris and other scaly diseases.
- Senile skin and other states of excessive dryness and itch.
- Ichthyosis
- Hyperkeratoses, keratoses.
- Chemical onycholysis, e.g. in onychomycoses.

Urea combined with other drugs

By its desquamating and hydrating actions, urea increases the bioavailability of other drugs. Furthermore, urea enhances the topical activity of some substances by influencing their solubility and crystal structure.
Urea can be successfully combined with the following substances:
- Glucocorticoids: The addition of urea increases the therapeutic activity of the glucocorticoids without changing the extent of undesirable actions. E. g., 1% hydrocortisone reaches the therapeutic effectiveness of 0.025% fluocinonide when 10% urea is incorporated. In combination with glucocorticoids, the antimicrobial action of urea is of special importance.
- Anthralin: The addition of 17% urea to anthralin 0.05 - 0.2% improves the antisporiatic action, in short contact therapy as well as in day-time care. Irritation and staining by anthralin is diminished, so compliance is increased.
- Tretinoin: In severe ichthyoses, with the exception of the inflammatory and erythrodermatic forms, a combination of 0.03% tretinoin with 10% urea may be used. Such a product may also prove to be successful in stubborn cases of chronic psoriasis.
- Salicylic acid: In stubborn cases of hyperkeratoses, a combination containing 10% urea and 10% salicylic acid was recommended.

Urea is cosmetology

In cosmetic products creams, ointments or - best - lotions, urea is incorporated for skin care purposes in concentrations between 2 and 5%. For cosmetic purposes, the moisturizing action of urea is of greatest importance. Skin care products for senescent people should contain urea. One may assume that the use of urea is cosmetic products will steadily increase (3).

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CHANGES IN STRATUM CORNEUM AFTER UREA APPLICATION TO HUMAN SKIN IN VIVO. ELECTRON MICROSCOPIC INVESTIGATIONS

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Key words: *Stratum Corneum Changes; Urea and Keratin; Electron Microscopic Investigation*

Synopsis

Urea, 10% in cream or ointment, applied in vivo for 24 and 48 hours with part occlusion changes the inner structure of the horny cells, depending on time and the excipients. Splitting of the keratin changes the matrix and the osmiophilic behaviour, especially in the upper regions. After 48 hours fine granulation within the horny cells and enhancement of cavities can be demonstrated. There is no evidence of any changes in the osmiophilic material in the intercellular spaces. Urea does not enhance permeability per se, it increases the surface of the keratinous material and its capacity to bind water and other substances with low molecular weight.

Riassunto

L'applicazione topica mediante bendaggio parzialmente occlusivo di una crema o di un unguento al 10% di urea provoca modificazioni della struttura dello strato corneo, dipendente dal tempo di contatto e dal tipo di veicolo. Si osserva del materiale cheratinico con variazioni a livello delle matrici. Dopo 48 ore si osserva una fine granulazione delle cellule cornee con comparsa di cavità. Non si evidenziano cambiamenti degli spazi intercellulari. L'urea non facilita di per se la permeabilità ma aumenta la superficie del materiale cheratinizzato e la sua capacità di legare acqua e altre sostanze a basso peso molecolare.

Introduction

The influence of urea on the horny layer and the ensueing changes in function have been researched very carefully (1, 2, 3, 5). The external use of urea, incorporated into different bases, in dermatology and cosmetology depends on such data (6).

The changes in the structure of the horny layer after topical application of urea to human beings have not however, until now been examined electron microscopically, either in vivo or in vitro.

Stratum corneum can be divided into 3 layers (Orfanos 1981).

1. Flat horny cells in the basal zone having electron dense membranes which enclose the homogeneous relatively light material.
2. The middle zone consists of horny cells with an electron - dense network of different structures which can be interrupted by small cavities.
3. Finally the superficial zone is characterised by broad intercellular spaces and lack of desmosomes, which are visible as electron dense threads only in - the lower horny layer .

Tonofilaments and the hyaline granules are the material of which the keratin, in the form of bigger tonofibril hyalin complexes is composed. The formation of horny layer is a quick process, more or less a jump, into keratinisation.

Horny cells with an osmiophobic filaments, embedded in an osmiophilic matrix are known as a A-cells. Horny cells with a pattern of osmiophilic filamens embedded in an osmiophilic matrix are classified as B-horny cells. The intercellular substance is formed by membrane coating granules (Odland-bodies) which are extruded into the intercellular space in the granular layer and form glycosphingolipids, ceramides, nonesterified sterols and fatty acids. This material forms the bilipid layers which as lamellar sheets surrounding the horny cells (4).

Methods

We took punch biopsies (2mm in diameter) after application of 10% urea in creams or ointment for 24 hours or 48 hours and examined them by elettron microscopy.

For the first 24 hours occlusive dressings were used, subsequently the applications were lettopen. As a control the effect of cream or ointment without urea, was also examined.

Excised skin (for the region around a skin tumour) was used for an in vivo experiment at 30°C with the same conditions as in vitro.

The region used was to the right and left of the umbilical line and an area of 25 cm2 was used for the applications.

The structure of the horny layer in the same area was examined prior to any applications. Basodexan cream and ointment with and without 10% urea were made available by the courtesy of Röhm Pharma. The experiment was performed on healthy probands, who gave their consent to the procedures.

The punch slices were cut with an ultratom DMU 3 (Reichardt) and examined by an electron microscope Dm 9 of Carl Zeiss. After fixation (2% glutaraldehyde, 2% O5SO4 in phosphate buffer 7.4) the slices were embedded in araldite.

Parameters of the effect of urea are: the amount of electron dense material in the horny cells, including the cell envelopes, and of the intercellular substance, the thickness of the cells and the width of the intercellular space.

Results

The composition of the horny layer structures of the skin treated with urea shows the following changes in comparison with the control skin:

The thickness of the horny cells has diminished, especially in the region towards the epidermis.

The number of horny layers, usually 11 to 12, is reduced to 8 to 10.
Additionally vacuolisation, development of cavities and changes to the inner structures towards the skin surface are obvious.
The density - the osmiophilic behaviour - changes and this is especially obvious in the horny layer, as is the smaller diameter of the transverse cross sections.
The intercellular substance and the intercellular space show no changes. The width of the intercellular space seems in general not to be changed. The desmosomes, separated from the tonofibrils are now part of the intercellular material and disappear into the upper region of the horny layer (Fig. 1,2)

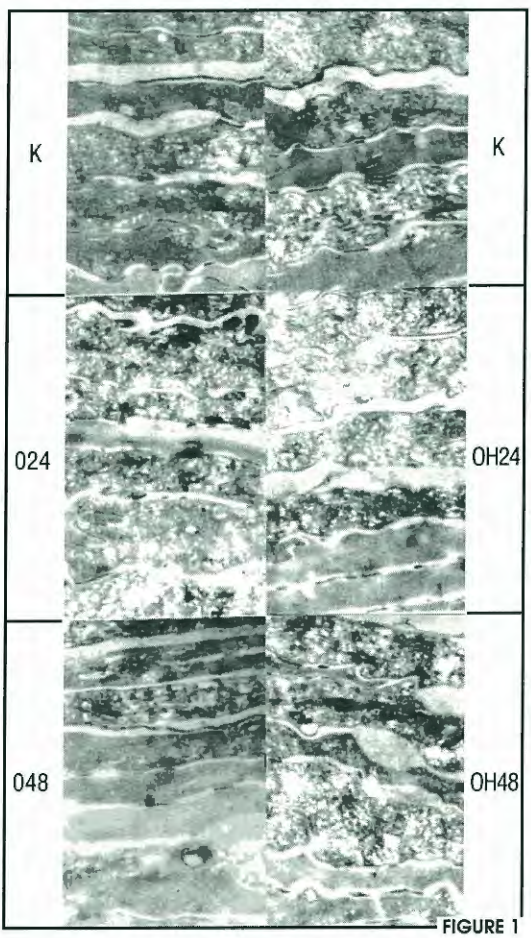

FIGURE 1

Urea ointment effect in vivo on human horny layers (x 23750)
K = Biopsy before treatment
O24 = 24 h after application of ointment without urea
OH24 = 24 h after application of 10% urea ointment
O48 = 48 h after application of ointment without urea
OH48 = 48 h after application of 10% urea ointment

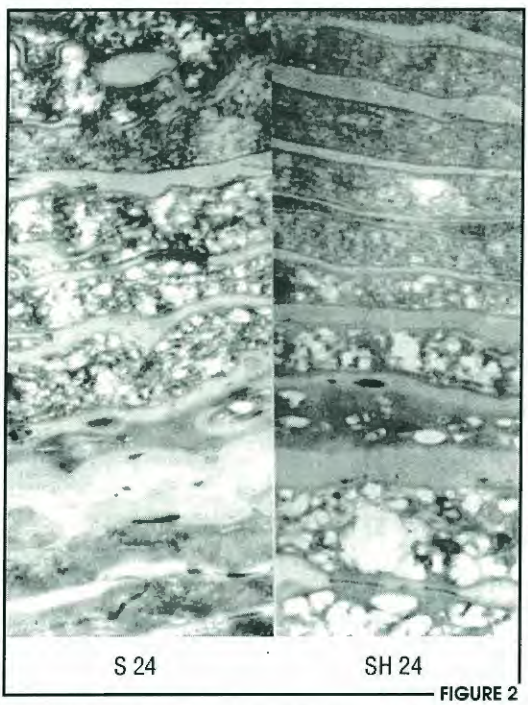

FIGURE 2

Urea ointment in vitro on human horny layer (x23750)

O24 = 24 h after application of ointment without urea
OH24 = 24 h after application of 10% urea ointment
O48 = 48 h after application of ointment without urea
OH48 = 48 h after application of 10% urea ointment

The swelling of the horny cells can be combined with bulging and narrowing of the intercellular space. It is obvious that the target of the urea is the horny cell, which show evidence of loosening of the hydrogen bonds of the keratin.
This phenomenon is obviously more expressed after 48 hours (occlusive dressings for 24 hours, followed by 24 hours open application). The envelopes remain intact, irrespective of cream, ointment or time. (Fig. 3)

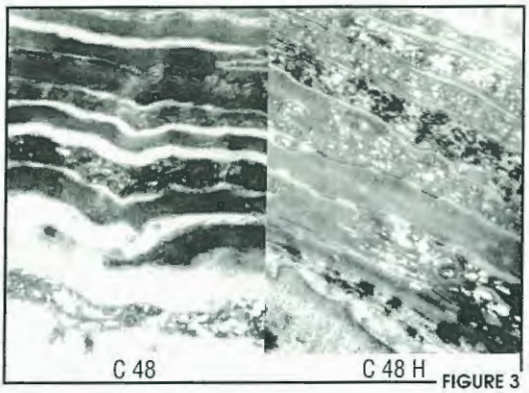

FIGURE 3

Urea cream effect in vivo on human horny layer (x 23750)
C48 = 48 h after application without urea
CH48 = 48 h after application of 10% urea cream

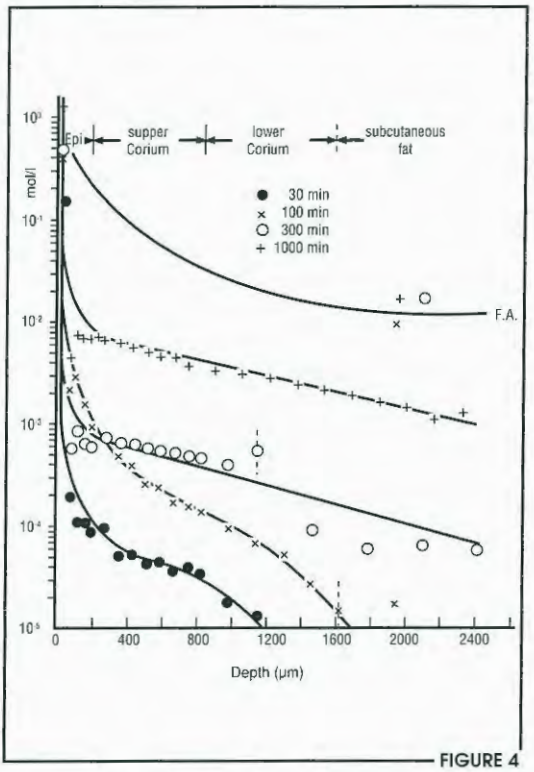

FIGURE 4

Permeating of urea 10% cream
Examinations with chamber technique in vitro using human skin (abdomen)
Application of 5 mg cream/2 cm² = 250 µ urea/cm²
TA = stripped skin (8 x with Tesafilm)

Discussion

Urea applied in vivo and in vitro shows binding to filaments of the keratin and the envelopes around the keratin filaments which are less tightly packed, and permits accumulation of water in its variable forms. The inner structure of the horny cells has changed and shows clear "splitting" of the horny filaments. These effects of urea, replacing water on the one hand and binding water on the other, and the action as a solvent on the different micro elements of the cell provide the key to a broad spectrum of effects both medical and cosmetic importance (11, 12).

From the toxicological and histological points of view there are no objections in regard to an impaired barrier function using 10% urea which permeates the skin (Fig. 4). The intercellular spaces with their lipid layers and proteoglycans are adequate to inhibit uncontrolled permeation. Steroids show an increased rate using urea. On the other hand smaller molecules such as Imidazoles (Antimycotics) show an increased accumulation in the horny layer and a smaller flux towards the corium (10).

The effects of urea do not greatly differ between living skin and excised skin in vitro . The water uptake from the subcorneal layers to the horny layer has also to be taken into consideration. The microbial material of the horny layer is also by urea.

The base in which urea is incorporated is responsible for the depth of its action which depends on the diffusion. Urea cannot be regarded as a general enhancer of permeability of the human stratum corneum in the same sense as dimethylsulfoxide (DMSO) or laurocapram (Azone). The intercellular space with its bilipid layers is only passively involved by swelling of the horny cells without any visible change of the envelope.

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2

Every day Problems in Dermatology: The Cosmetic Connection

2nd International Meeting on Cosmetic Dermatology, Rome, Italy: May 19-22, 1987

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Announcement

IV INTERNATIONAL MEETING ON COSMETIC DERMATOLOGY

PROGRESS IN COSMETIC DERMATOLOGY: SCIENCE AND SAFETY

October 30 - November 2 , 1991
Villa MIANI - ROME - ITALY

PRELIMINARY PROGRAM
PROGRAMMA PRELIMINARE

OCTOBER 31 th THURSDAY / GIOVEDI' 31 OTTOBRE

09.00 - *General considerations* / Considerazioni generali (C. Jacobson - U.S.A.)
09.30 - *Opening remarks* / Note introduttive (P. Morganti - I)
09.45 - *Cosmetic preparation: state of the art* / I prodotti cosmetici: stato dell'arte
10.00 - *Safety evaluation of cosmetic ingredients in the European Community and in other countries* / Valutazione della sicurezza degli ingredienti cosmetici nella CEE e negli altri paesi (N. Loprieno - I)
10.15 - *Role of lipids in biological membranes* / Ruolo dei lipidi nelle membrane biologiche (B. Berra - I)
10.30 - *Advances in percutaneous absorption* / L'assorbimento percutaneo secondo le più recenti acquisizioni (W. Shalla - D)
10.45 - *Liposomes: future prospects and alternative solutions* / I liposomi:prospettive future e soluzioni alternative (G.Gregoriades - U.K)
11.00 - *Break*
11.15 - *Pediatric cosmetology: current and future trends* / La cosmesi della prima età: oggi e domani (C. Jacobson - U.S.A.)
11.30 - *Social role of cosmetics in elderly people* / Ruolo sociale dei cosmetici nella terza età (A. Tosti - I)
11.45 - *Cosmetic dermatology and mucous membranes* / Cosmesi dermatologica e mucose (S. Mancuso - I)
12.00 - *EEC cosmetic ingredients and labeling* / L'etichettatura degli ingredienti cosmetici (De Giuli - I)
12.15 - *Quality control to protect EEC consumer* / Il controllo qualità a difesa del consumatore (L. Gagliardi - I)
13.00 - *Brunch*

SKIN SURFACE AND PERMEATION / CUTE E ASSORBIMENTO

14.00 - *Liposomes as natural-like membranes* / I liposomi quali membrane naturali simili
14.15 - *Liposomes as topic carriers: progress working* / I liposomi come carrier per uso topico: prospettive e realtà (G. Gregoriades - U.K.)
14.30 - *Function and stability of liposomes as cosmetic vehicles* / Funzione e stabilità dei liposomi come veicoli cosmetici (E. Menegatti - I)
14.45 - *New biodegradable and biocompatible capsules for the cosmetic industy: the collaspheres* / Le nuove capsule biodegradabili e biocompatibili per l'industria cosmetica: le collasphere (A.Huc - F)
15.00 - *Discussion* / Discussione
15.30 - *The choice of vehicles in cosmetic dermatology* / L'importanza dei veicoli nella dermatologia cosmetologica (B. James - U.S.A.)
15.45 - *Activity of vehicles and diffusion through the horny layer* / Attività dei veicoli e loro diffusione attraverso lo strato corneo (W. Shalla - D)
16.00 - *Skin permeability in infants and young children* / Permeabilità cutanea nella prima infanzia e nella pubertà (C. Jacobson - U.S.A.)
16.15 - *Skin permeability in elderly people* / La permeabilità cutanea nell'anziano (F. Kerdel Vegas - YV)
16.30 - *Permeability of buccal mucosa membranes* / La permeabilità della mucosa orale (A. Jarret - U.K.)
16.45 - *Permeability of vaginal mucosa surfaces* / Permeabilità ed assorbimento della membrana vaginale (S. Mancuso - I)
17.00 - *Discussion* / Discussione
17.15 - *Break*

IV INTERNATIONAL MEETING ON COSMETIC DERMATOLOGY

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The 18th World Congress of Dermatology will take place in New York City from June 12-18, 1992. In an effort to encourage the participation of young dermatologists, the Congress will award a limited number of scholarships, as follows:

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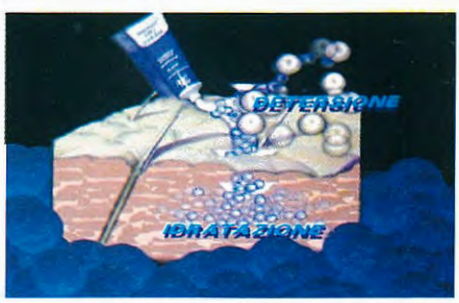

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