STUDIES OF SKIN-HYPERSENSITIVITY TO LANOLIN*†‡

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Many dermatologists have in the past studied the phenomenon of eczematous hypersensitivity of the human skin to lanolin (wool fat) (1–6). The reasons for this continuing interest are clear. Lanolin hypersensitivity is of practical importance because of the very wide-spread modern use of this valuable substance in topical medicaments like ointments, pastes and emulsions, in cosmetics of many kinds (creams, lipsticks, shampoos, soaps, shaving creams, scalp lotions etc.), and in a very great variety of other consumer products (shoe polishes, floor waxes, clothing, etc.).

Moreover, lanolin, a product of the sheep's skin, has many features resembling human sebum; and indeed these two fatty mixtures have numerous chemical constituents in common. The possibility therefore arose that lanolin hypersensitivity might actually prove to be an example of allergic sensitization to autogenous body substances—i.e. an instance of "auto-sensitization" of the human skin (5–7).

The more recent studies of lanolin hypersensitivity attempted to discover the fractions or constituents responsible for the allergenic action of the mixture. These attempts had the twin objective first, of finding the allergenic substances and eliminating or reducing their sensitizing potential; and second, of studying the possible chemical or immunologic relationship of these allergenic ingredients to autochthonous substances found in, or on, the human skin.

Our present report deals with further investigations in these directions, and particularly with expansion of the earlier findings of Sulzberger and Lazar (5) that the eczematogenous allergenic constituents of lanolin are found mainly in the fraction designated as "mixed lanolin alcohols" (1–18).

METHODS

From March 1951 through March 1952, patch tests with anhydrous lanolin (USP) were applied in standard fashion to the grossly intact skin of 1048 patients who were attending the Section of Allergy of the New York Skin and Cancer Unit because of various dermatologic ailments. In addition, 120 apparently healthy volunteers were tested in the same manner.

Every individual who showed a positive reaction, as well as seven additional patients who had been found hypersensitive to lanolin prior to the above-de-

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‡ With the technical assistance of Dorothy Furman and David Kirman.

scribed screening examinations, were subjected to several series of further patch tests. While not all the selected individuals were tested with each and every material listed below, each was tested with lanolin from two different manufacturers, with various lanolin derivatives, and a considerable number of its constituent fractions.[1]

The following list specifies the substances used in these tests:

	Concentration
I. Lanolin A (USP anhydrous, Botany Mills)	As is 5% in olive oil 1% in olive oil
II. Lanolin B (USP anhydrous, Merck & Co.)	As is
III. Lanolin modified by introduction of the acetyl radical (proprietary product*)	As is
IV. Lanolin A, modified by introduction of the acetyl radical	5% in olive oil 1% in olive oil
V. Lanolin modified by introduction of the propionyl radical (proprietary product†)	As is
VI. Cholesterol A (Botany), derived from lanolin	5% in olive oil 1% in olive oil
VII. Cholesterol B (Armour & Co.), derived from spinal cord of cattle	5% in olive oil 1% in olive oil
VIII. Lanosterol (Botany)	5% in olive oil 1% in olive oil
IX. "Mixed lanolin alcohols" (containing free aliphatic alcohols and sterols from lanolin A)	5% in olive oil 1% in olive oil
X. "Mixed lanolin alcohols" (from lanolin A) modified by introduction of the acetyl radical	5% in olive oil 1% in olive oil
XI. "Aliphatic alcohol fraction" (from lanolin A)	5% in olive oil 1% in olive oil
XII. Cetyl alcohol (from spermacet.)	5% in olive oil 1% in olive oil
XIII. "Aliphatic alcohol fraction" (from lanolin A) modified by reacting with the acetyl radical	5% in olive oil 1% in olive oil
XIV. "Mixed lanolin fatty acids" (from lanolin A)	5% in olive oil 1% in olive oil
XV. "Combined lanolin fatty acids and lanolin alcohols" (equal parts of each, from lanolin A)	5% in olive oil 1% in olive oil
XVI. Olive Oil (USP)	As is

* Modulan, American Cholesterol Products, Inc. (U.S. Pat. appl.)
† Elfanol, Lehn and Fink Products, Corporation (U.S. Pat. appl.)

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[1] We are deeply indebted to Drs. H. Ehrhardt of Botany Mills, Inc., E. G. Klarmann of Lehn and Fink Products, Corporation, and L. I. Conrad, American Cholesterol Products, Inc., for their cooperation in this work.Our present investigations would not have been possible without their interest and help.

The complex of aliphatic alcohols listed under XI was found to represent about 30% to 50% of the unsaponifiable material (lanolin-alcohols) of lanolin A. Thus far, the following alcohols have been isolated from this fraction: Cetyl, ceryl, lanyl, lano-octadecyl, and carnaubyl alcohol. Of these, cetyl alcohol was the only one available to us for testing.

The chemical modifications listed under III, IV, V, X, and XIII, were obtained by processing the products with either acetic or propionic anhydride. This resulted chiefly in esterification of the alcohols and hydroxy fatty acids, but also in formation of a small amount of ethers (1% to 2%).

In addition to the applications as orthodox patch tests, anhydrous lanolin (from two different lots), as well as hydrous lanolin (USP, Merck & Co.) were applied by simple inunction to the uncovered skin of subjects who had shown a positive patch test-response. This was done in order to investigate the skin responses of these hypersensitive individuals to the most usual form of the human skin's exposure to lanolin. Each inunction was carried out for 20 seconds, by means of the rounded end of a glass rod. The test sites were examined immediately, as well as after 48 hours.

For the purpose of clinical trials, several subjects who had been proved hypersensitive by skin tests received treatment with the propionic modification of lanolin.

RESULTS

A. Incidence and degree of positive reactions to lanolin and modified lanolin

Twelve of the 1048 dermatologic patients attending the N. Y. Skin and Cancer Unit's Section of Allergy showed consistently positive skin reactions to patch tests with lanolin. Thus, the incidence of hypersensitivity to lanolin was more than one per cent (1.14%) in this selected population. In contrast, no positive reaction was encountered in any of the 120 apparently healthy subjects investigated.

The positive responses observed in the group of patients varied in intensity among the individual reactors, and ranged from erythema ("+") to erythema, infiltration, and extensive blistering ("++++"). The two samples of lanolin from different manufacturers produced essentially equal intensity of the response in a given hypersensitive individual (see table I).

Eighteen subjects with positive patch tests to lanolin received inunctions (i.e. uncovered tests) with three different samples of lanolin (two anhydrous, one hydrous). Only two of the eighteen showed any reaction whatsoever to the inunctions. These two developed a mildly erythematous response to all three samples employed—48 hours after the application.

Tables I, II, and III analyze our results in 19 lanolin hypersensitive subjects—15 to 63 years of age—patch tested with a series of different brands and chemical derivatives of lanolin.

Only three of 18 individuals with positive reactions to undiluted lanolin reacted to the five per cent dilution in olive oil, and no positive responses were obtained with the one per cent solution.

TABLE I

Skin-reactions to lanolin and lanolin modifications (in subjects with eczematous responses to lanolin)

	SUBJECT, SEX									
	(1) M.C. ♀	(2) J.W. ♀	(3) M.G. ♀	(4) I.G. ♀	(5) F.B. ♀	(6) R.T. ♀	(7) B.H. ♀	(8) F.F. ♀	(9) R.S. ♀	(10) L.S. ♀
	Diagnosis									
	Derm. ven.	Derm. ven.	Derm. ven.	Numm. ecz.	Derm. ven.	Derm. ven.	Derm. ven.	At. derm.	Derm. ven.	At. derm.
Inunction on Uncovered skin:										
I. Lanolin A (anhydrous)	0	0	0	0	0	0	0	0	0	0
II. Lanolin B (anhydrous)	0	0	0	0	0	0	0	0	0	0
Hydrous lanolin	0	0	0	0	0	0	0	0	0	0
Patch tests:										
I. Lanolin A (anhydrous)	++	(+)	+++	+++	+++	(+)	++	+	++++	+
II. Lanolin B (anhydrous)	++	(+)	++	+	+++	+++	++	++	++++	+
III. Lanolin modified with acetyl radical	0		+	+++					++	(+)
V. Lanolin modified with propionyl radical	0		(+)	(+)					0	0
XVI. Olive oil (control)	0	0	0	0	0	0	0	0	0	0

	(11) N.J. ♀	(12) N.C. ♀	(13) R.G. ♀	(14) B.A. ♀	(15) M.C. ♀	(16) B.G. ♀	(17) J.R. ♂	(18) H.P. ♂	(19) A.S. ♂
	Diagnosis								
	Derm. ven.	At. derm.	Derm. ven.	Derm. ven.	Derma-toph.	Derm. ven.	At. derm.	Seb. derm.	Cont. derm.
	0	0	0	0	0	(+)	0	(+)	0
	0	0	0	0	0	(+)	0	(+)	0
	0	0	0	0	0	(+)	0	(+)	0
	++	+++	(+)	+	+	++	+++	+	(+)
	+	+++	++	+	++	++	+++	+	++
	+	0	0	0	(+)	0		0	0
	+	0	0	0	0	0			0
	0	0	0	0	0	0	0	0	0

0 = no reaction
(+) = mild erythema
\+ = erythema
++ = erythema and infiltration
+++ = erythema, infiltration and vesiculation
++++ = erythema, infiltration and extensive blistering (bullae)

Derm. Ven. = Dermatitis Venenata
Numm. Ecz. = Nummular Eczema
At. Derm. = Atopic Dermatitis
Dermatoph. = Dermatophytosis
Seb. Derm. = Seborrheic Dermatitis
Cont. Derm. = Contact Dermatitis

TABLE II

Patch test reactions to components and modified fractions of lanolin, 5% in olive oil (in subjects with eczematous responses to lanolin)

5% SOLUTIONS IN OLIVE OIL OF	SUBJECTS (COMPARE TABLE I)																		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)
III. Lanolin A	0	0	(+)	0	+	+	0		0	0	0	0	0	0	0	0	0	0	0
IV. Lanolin A modified with acetyl radical			0	++							0	0	0	0	0	0			0
VI. Cholesterol (from lanolin A)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
VII. Cholesterol (from spinal cord of cattle)	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0
VIII. Lanosterol	0	0	0	0	0	0	0	?	0	0	0	+	0	0	0	0	0	0	0
IX. "Mixed lanolin alcohols" (from lanolin A)	+++	+	+++	+++	+++	+	+	++	++++	+	0	+++	++	(+)	++	+++	0	++	0
X. "Mixed lanolin alcohols" (from lanolin A), modified with acetyl radical	0		0	++					0	++	0	0	0	0	0	0			0
XI. Aliphatic alcohol fraction (from lanolin A)	++	0	+	++	++	++	0		+++	++	0	+++	+++	(+)	(+)	++	0	++	(+)
XIII. Aliphatic alcohol fraction (from lanolin A), modified with acetyl radical	0		0	++					0	0	0	0	0	0	0	0			0
XII. Cetyl alcohol	(+)	0	0	0	0	0	0		0	0	++	0	0	0	0	0	0	0	0
XIV. "Mixed lanolin fatty acids" (from lanolin A)	0	0	+++	0	0	0	0	+++	0	0	(+)	0	0	0	0	0	0	0	0
XV. "Lanolin fatty acids and alcohols" (from lanolin A)	+++	(+)	++	+++	++	+++	++	+++	++++	++	++	++	+	0	++	++	(+)	+	+
XVI. Olive oil (control)	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0

TABLE III

Patch test reactions to components and modified fractions of lanolin, 1% in olive oil (in subjects with eczematous responses to lanolin)

1% SOLUTIONS IN OLIVE OIL OF	SUBJECTS (COMPARE TABLE I)																		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)
III. Lanolin A	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0
IV. Lanolin A modified with acetyl radical			0	++						0	0	0	0	0	0	0			0
VI. Cholesterol (from lanolin A)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
VII. Cholesterol (from spinal cord of cattle)	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0
VIII. Lanosterol	0	0	0	0	0	0	0	?	0	0	0	0	0	0	0	0	0	0	0
IX. "Mixed lanolin alcohols" (from lanolin A)	++	0	+	++	+	+	0	++	++++	+	+	++	+	0	+	++	0	+	0
X. "Mixed lanolin alcohols" (from lanolin A), modified with acetyl radical	0		0	+					0	++	0	0	0	0	0	0			0
XI. Aliphatic alcohol fraction (from lanolin A)	++	0	0	++	++	+	0		+++	0	0	++	+++	0	0	++	0	++	0
XIII. Aliphatic alcohol fraction (from lanolin A), modified with acetyl radical	0		0	+					0	0	0	0	0	0	0	0			0
XII. Cetyl alcohol	0	0	0	0	0	0	0		0	0	+	0	0	0	0	0	0	0	0
XIV. "Mixed lanolin fatty acids" (from lanolin A)	0	0	+	0	0	0	0	++	0	0	0	0	0	0	0	0	0	0	0
XV. "Lanolin fatty acids and alcohols" (from lanolin A)	++	0	+	+++	+	+++	0	++	++++	+	0	+	0	+	+	++	+	+	0
XVI. Olive oil (control)	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0

There was a distinct difference in the incidence of hypersensitivity to lanolin and to the chemical modifications of lanolin tested.

The acetylated product (No. III-lanolin modified by introduction of the acetyl radical) evoked a positive skin response in six (50%) of 12 subjects hypersensitive to lanolin; and the "propionylated" product (No. V-lanolin modified by introduction of the propionyl radical) elicited a positive response in only three (25%) of the subjects. The reaction to the propionyl modification (No. V) was also weaker in intensity than the response to the other modification in two of the three individuals who showed a reaction to both modifications.

On the other hand, the difference in the incidence of positive patch test responses to lanolin and to either of the two acyl radical treated modifications was much less distinct when the respective materials were applied in dilution rather than in full concentration.

B. Results obtained with various chemical components, with untreated fractions, and with modified fractions of lanolin

As the tables (II and III) show, neither of the two cholesterols in solution produced any positive patch test response. A positive reaction to lanosterol (five per cent) was observed in one person, and a doubtful response to the same sterol (one and five per cent) in another.

It is evident from the tabulation that *of all the lanolin-components tested, the fractions defined as "lanolin-alcohols" and as "aliphatic alcohol fraction" possessed the strongest allergenic activity.* The incidence and intensity of positive reactions to these fractions, especially to the more concentrated (five per cent) solutions, closely approached the effect of the samples of (undiluted) wool fat. This holds true also for the activity of the fraction containing the "lanolin alcohols" in combination with lanolin fatty acids (No. XV); in fact, the effect of this combination even exceeded that of the fractions consisting mainly of the alcohols alone. Thus, the five per cent solution of the combination of "lanolin alcohols and lanolin fatty acids" elicited positive test results in 18 of the 19 individuals.

The fraction designated as "lanolin fatty acids" produced a positive skin response in three of the subjects, when applied in five per cent concentration, while the solution of one per cent evoked a reaction in two of these three individuals.

Cetyl alcohol (No. XII)—the only identified member of the aliphatic alcohol fraction available to us for testing—elicited a positive reaction in two of the subjects.

There was a striking difference between the effect of the "lanolin alcohols" (No. IX), as well as of the "aliphatic alcohol fraction" (No. XI), and the effect of the corresponding acetylated fractions. Thus, the five per cent solution of modified "lanolin alcohols" (No. X) produced positive patch tests in two (16.6%) of the subjects examined; whereas the original product (No. IX) evoked positive reactions in ten (83.3%). Similarly, the modified "aliphatic alcohol fraction" (No. XIII)—five per cent in olive oil—elicited a positive result in one (8.3%) of the 12 lanolin hypersensitive patients tested; while 11 subjects (91.7%) of the same group showed a positive response to the unmodified fraction (No. XI).

C. Clinical effects of modified lanolin

Thus far, only six patients with contact dermatitis and positive patch test-reactions to lanolin were subjected to a clinical trial with lanolin processed with propionic anhydride. Depending on the nature and extent of their skin disease, the subjects were asked to spread the preparation several times daily over the affected areas, either without any dressing, or with a protective cover of smooth cotton material (especially over night). Four of these patients tolerated the applications well and showed alleviations of the dermatitis within periods of one to several weeks. In the two remaining individuals, however, the eruptions under treatment flared up, and use of the cream had to be discontinued.

DISCUSSION

Several points must be borne in mind in interpreting the relatively and somewhat surprisingly high incidence of hypersensitivity to lanolin, found in 12 (1.14%) of 1048 patients attending the Section of Allergy at the N. Y. Skin and Cancer Unit. It is noteworthy that this group is distinguished by the fact that all the included subjects were suffering from proved or presumptive allergic dermatoses (see diagnoses as listed on Table I). As is well known, dermatoses of this kind are prone to occur in individuals who are predisposed to acquire *multiple* specific sensitizations of the skin to eczematogenous allergens. It may, therefore, be presumed that the incidence of hypersensitivity to lanolin in the general population will fall far below that observed in our group of patients. The fact that we did not obtain a single reaction to lanolin in our group of 120 "normal" persons, certainly does not contradict this assumption, although it is obvious that this control series was too small to allow statistical conclusions.

Furthermore, the apparently relatively rare occurrence of hypersensitivity to dilutions of wool fat may be of practical significance, since many cosmetic and consumer articles contain only small proportions of lanolin. The relatively low incidence of reactions to the five per cent (and one per cent) dilution also shows that the intensity of lanolin hypersensitivity is weak when compared with other eczematous hypersensitivity, e.g. with common forms such as hypersensitivity to poison ivy, local anesthetics, dyes, etc.

Moreover, the low percentage and mild character of positive reactions noted by us after the inunction of lanolin on the uncovered skin are important since this manner of testing simulates closely the commonest forms of exposure of the human skin to lanolin.

In spite of these "mitigating" features, the observed incidence of hypersensitivity to lanolin appears to be of considerable theoretical and practical interest. Even though lanolin hypersensitivity might preponderantly affect persons who are predisposed by eczematous contact-type hypersensitivity to other allergens, and those whose skin is exposed to intimate and relatively long lasting contacts with lanolin, the number of persons suffering from the effects of lanolin hypersensitivity may not be negligible. For among the countless individuals who suffer from different forms of eczematous skin allergy, a great propor-

tion is continually exposed to articles containing lanolin—daily exposures which often include the adjuvant factor of simultaneous friction of the skin, (e.g. during usage of massage creams, hair lotions, floor waxes, etc.).

The results of our attempt to identify the component(s) responsible for the allergenic properties of lanolin agree in general with the findings of Sulzberger and Lazar (5). In our present studies it was again the fraction consisting of "lanolin-alcohols" which proved to contain most, if not all, of the allergenic material. The present results also confirm the previous findings of Sulzberger and Lazar, that cholesterol did not produce any positive response—(in contrast to the results of Ellis (4)). Lanosterol, also, was inert in most instances. One of our additional findings of interest was the marked allergenic activity of the "aliphatic alcohol fraction" (No. XI), i.e. of the fraction containing the lanolin alcohols freed from sterols (cholesterol and lanosterol). It therefore appears almost certain that the allergenic properties of lanolin reside in the fraction containing the aliphatic alcohols. The occasional reactions obtained by us with fractions which one would theoretically assume to be free of aliphatic alcohols (i.e. "lanolin fatty acids", lanosterol) may actually have been caused by admixtures of such alcohols in these fractions. This possibility exists 1) because perfect separation and absolutely pure preparation of such fractions by the chemist are practically impossible; and 2) because secondary decompositions are likewise hardly avoidable, either before or during the materials' application and sojourn on the skin.

Regarding the hypersensitivity to the "lanolin fatty acids" observed in three of the subjects, there is also a possibility that the active principle was inherent in certain *hydroxy* fatty acids.[2] This possibility gains weight if one assumes that the *demonstrated hypersensitivity was in general directed against hydroxyl groups* of some components of the aliphatic fraction, and that certain individuals are more hypersensitive to these hydroxyl groups than are others.

Indeed, it is evident from the results we obtained with the products modified by acetylation or "propionylation", *that certain aliphatic alcohols* and their *hydroxyl groups* were in all probability largely responsible for the positive reactions. The considerably lower incidence of positive patch test responses obtained with the "esterified" modifications of lanolin and of the "aliphatic alcohol fraction", as compared with the incidence of reactions to the corresponding

[2] In view of the proportions in which the different components are actually present in lanolin, our test-concentrations of the "fatty acid" fraction may be regarded as relatively low. After submission of this manuscript, however, we tested three of our lanolin-sensitive patients with a 50% solution of this fraction in olive oil; and repeated at the same time the other tests of the series, together with the necessary controls. The latter included the application of a 17% solution of lanolin (A) in olive oil, since our "fatty acid" fraction had been found to contain 34% of unreacted lanolin. As a result of these tests, identical skin responses were obtained with both the 50% solution of the "fatty acid" fraction and the solution of 17% lanolin alone. In consideration of these results, as well as of the rare incidence of positive reactions obtained with the "lanolin fatty acids" (in lower concentration) in general, we do not believe that the hydroxy fatty acids play a *major*—if any—role in the precipitation of the reactions to lanolin.

unmodified products, may well be due to the extensive esterification (and etherification) of alcoholic hydroxyl groups, and the transformations associated Therewith. It would appear plausible that among the aliphatic alcohols also the responsible members were affected by this process, and thus significantly inactivated.

The positive skin tests to cetyl alcohol obtained in two subjects suggest that this alcohol may contribute to the allergenic effects of lanolin. On the other hand, the absence of a reaction in most of the lanolin sensitive individuals indicates that cetyl alcohol[3] is not the most important or essential offender. As soon as the other straight chain alcohols identified as components of the apparently responsible fraction of lanolin become available, they will be applied in patch tests. It appears to us that tests with these alcohols will be essential in future attempts to clarify the problems of eczematous allergy to lanolin.

SUMMARY

1. Twelve of 1048 (1.14%) subjects with a variety of established or suspected allergic skin diseases showed positive reactions to patch tests with pure lanolin from two different manufacturers.

2. No positive patch tests were obtained with lanolin in 120 healthy subjects.

3. Inunction of lanolin on the uncovered skin produced a positive reaction in only two of 18 individuals hypersensitive to patch tests with lanolin.

4. In confirmation of previous studies, patch tests with different fractions of lanolin showed that the allergenic material was present in the mixed alcohols.

5. In addition, our tests afforded direct evidence that the active allergenic material resided in the fraction containing the aliphatic alcohols of lanolin.

6. Of the aliphatic alcohols identified in this fraction, thus far only cetyl alcohol has been available to us for skin testing. It produced a positive patch test response in two of the 18 reactors to lanolin.

7. Acetylated or "propionylated" lanolin evoked a significantly lower incidence of positive skin reactions than did the unaltered product.

8. Of 12 subjects with positive patch tests to lanolin, 11 showed a positive patch test to the aliphatic alcohol fraction; but only one of these reacted to this same alcohol fraction after its acetylation.

9. It appears probable that one or more of the aliphatic alcohols of lanolin are largely responsible for the observed hypersensitivity; for their denaturation through esterification resulted in reduction or abolition of the allergenic capacity.

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[3] While it is certain that cetyl alcohol and the other identified aliphatic alcohols exist in esterified form in lanolin (A), their presence as free alcohols is more or less presumptive.

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DISCUSSION

DR. STEPHEN ROTHMAN, *Chicago, Ill.:* I would like to ask Dr. Sulzberger whether acetylation was complete. It is known that long chain alcohols are difficult to acetylate. Maybe incomplete acetylation was the reason for the few positive tests he obtained.

DR. MARION B. SULZBERGER, *New York* (closing): In reply to Dr. Rothman, according to the chemical titrations the hydroxyl groups were completely acetylated. We cannot explain the few reactions which these acetylated materials still produced except on the possible basis that hydrolysis may have occurred again—for example after the compounds were applied to the skin. That seems theoretically possible.