Young, E. and *Weiffenbach, N.*: Dermatologica *118:* 74–86 (1959)

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About the Conversion of Salicylic Acid into Zinc Salicylate in Ointments and Pastes Containing Both Zinc Oxide and Salicylic Acid

By E. YOUNG and N. WEIFFENBACH

In 1946 *Siemens* and *Schreiber* [1] found that after application to the skin of an ointment containing a mixture of ammoniated mercury and salicylic acid, sublimate is formed. Originally, the intention of our investigation was to prove this once again with the help of a great number of patch tests.

At first it was observed that nearly all our patients showed a severe reaction to application of patch tests with 10% ammoniated mercury and 2% salicylic acid in petrolatum*, as was to be expected from the above mentioned research by *Siemens* and *Schreiber*.

On the other hand, it was surprising that ammoniated mercury, frequently used by us in pasta Lassar (containing 2% salicylic acid**) hardly ever evoked any unwanted reaction.

This may be explained by the fact that water is essential for such a chemical reaction as described above. This water must be supplied by the body itself, if a water-free ointment is used. With a patch test, however, water cannot evaporate, while under therapeutic conditions water might evaporate easily. Yet this explanation was not entirely satisfactory. Therefore patch tests were performed with 10% ammoniated mercury in pasta Lassar in 15 patients. Ammoniated mercury and salicylic acid were also tested individually to exclude hypersensitivity to one of these substances.

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* This is a toxic reaction, caused by the sublimate.

** Pasta Lassar Ph. Ned. Ed. V contains: 2% salicylic acid, 25% zinc oxide, 25% amylum in petrolatum.

Only two patients reacted to the patch test with ammoniated mercury in pasta Lassar, but these patients reacted also to the patch test with ammoniated mercury in petrolatum, which means that they were hypersensitive to ammoniated mercury.

Therefore it appears that pasta Lassar can prevent the formation of sublimate, while petrolatum cannot. Essentially this can be explained in three ways:

(a) amylum or zinc oxide (present in pasta Lassar) absorbs the water, indispensable for this chemical reaction;

(b) zinc oxide itself combines with the salicylic acid;

(c) the paste base is unsuitable for this patch test.

To eliminate (a) and (c), patch tests were performed with 10% ammoniated mercury and 2% salicylic acid in equal parts of amylum and petrolatum, and also with 10% ammoniated mercury and 10% salicylic acid in petrolatum separately.

The results were as follows:

Reaction after patch test with:

Patient No.	A 10% ammoniated mercury and 2% salicylic acid in equal parts of amylum and petrolatum	B 10% ammoniated mercury in petrolatum	C 10% salicylic acid in petrolatum
1	3	0	0
2	3	0	0
3	3	2	1
4	2	2	0
5	5	4	1
6	3	0	0
7	2	0	1
8	3	0	0
9	2	0	0
10	3	1	1
11	3	±	0
12	3	1	0
13	2	0	0
14	4	2	0

The patch tests are graded in accordance with the severity of skin reactions from 1 (redness) to 5 (necrosis).

Conclusion. The paste base does not prevent positive reactions; the amylum cannot absorb a sufficient quantity of water to prevent the reaction of ammoniated mercury with salicylic acid. The reactions in column A may be strongly positive, even in combination with a negative reaction in column B or C.

Thus the possibilities (a) and (c) being eliminated, there remains the binding of salicylic acid by zinc oxide (b).

To investigate this, patch tests were performed with 10% ammoniated mercury and 2% salicylic acid in equal amounts of zinc oxide and petrolatum, and moreover with 10% ammoniated mercury and 10% salicylic acid in petrolatum separately. The results were as follows:

Reaction after patch test with:

Patient No.	A 10% ammoniated mercury and 2% salicylic acid in equal parts of zinc oxide and petrolatum	B 10% ammoniated mercury in petrolatum	C 10% salicylic acid in petrolatum
1	0	0	0
2	0	0	0
3	2	2	1
4	1	2	0
5	4	4	1
6	0	0	0
7	0	0	1
8	0	0	0
9	1	0	0
10	2	1	1
11	0	±	0
12	1	1	0
13	0	0	0
14	1	2	0

Conclusion. The reactions in group A are only distinctly positive when combined with positive reactions in group B or C. So it is obvious that no sublimate is formed, and therefore it appears that the zinc oxide has combined with the salicylic acid.

To prove this, patch tests with 10% salicylic acid in equal amounts of zinc oxide and petrolatum were performed on patients who were known to be hypersensitive to salicylic acid. The results were as follows:

10% salicylic acid in petrolatum	10% salicylic acid in equal parts of zinc oxide and petrolatum
3	0
3	0
2	0
3	0

From this it appears once more that zinc oxide prevents the action of salicylic acid.

The chemical reaction: salicylic acid + zinc oxide → zinc salicylate + water, is most likely:

$$ZnO + 2\ C_6H_4OHCOOH \rightarrow Zn(C_6H_4OHCOO)_2 + H_2O$$

If this is correct 1 g. of zinc oxide must be able (on account of the molecular weight) to combine with about 3 g. of salicylic acid. However, in an ointment base it is to be expected that for a complete conversion of the salicylic acid, a somewhat greater amount of zinc oxide will be needed.

Next this hypothesis was verified by means of patch tests containing varying amounts of zinc oxide added to the combination of 10% ammoniated mercury and 2% salicylic acid in petrolatum.

All these patch tests were performed on patients who were known not to be hypersensitive to salicylic acid or to ammoniated mercury alone.

See results on page 78.

Conclusion. In many cases addition of 1% zinc oxide is sufficient to prevent a reaction; 2% zinc oxide (the same percentage as salicylic acid) nearly always prevents reactions.

This result strongly points to a chemical reaction between zinc oxide and salicylic acid.

Yet the question still remained how fast such a reaction could take place in an ointment.

So far all patch tests had been performed with ointments which had been prepared some weeks before application. Therefore patch tests were performed with 10% ammoniated mercury, 2% salicylic acid, 1% zinc oxide in petrolatum, both freshly prepared and 2 months old.

Reaction to patch test with:

Patient No.	10% ammoniated mercury +2% salicylic acid +50% zinc oxide in petrolatum	10% ammoniated mercury +2% salicylic acid +10% zinc oxide in petrolatum	10% ammoniated mercury +2% salicylic acid +5% zinc oxide in petrolatum	10% ammoniated mercury +2% salicylic acid +2% zinc oxide in petrolatum	10% ammoniated mercury +2% salicylic acid +1% zinc oxide in petrolatum	10% ammoniated mercury +2% salicylic acid in petrolatum
1	0	0	0	0	1	2
2	0	0	0	0	0	2
3	0	0	±	±	±	2
4	0	0	1	1	2	5
5	0	0	0	0	0	2
6	0	0	0	0	0	2
7	0	0	0	0	0	1
8	0	0	0	0	0	1
9	0	0	0	1	2	3
10	0	0	0	0	0	0
11	0	0	0	0	0	1
12	0	0	0	0	0	2
13	0	0	0	0	0	4

The reactions were as follows:

Patient No.	10% ammoniated mercury +2% salicylic acid +1% zinc oxide in petrolatum freshly prepared	10% ammoniated mercury +2% salicylic acid +1% zinc oxide in petrolatum 2 months old
1	2	0
2	3	0
3	1	0
4	1	±
5	1	0

There appears to be an obvious difference concerning the amount of free salicylic acid, present in a freshly prepared ointment and in an old one. Now the speed of the conversion of the salicylic acid into zinc saliycylate had to be established more precisely. Therefore patch tests were performed with the above mentioned ointment on several days successive in the same patient. These patients were also tested with 10% ammoniated mercury and 1 or 2% salicylic acid in petrolatum (not containing zinc oxide, and freshly prepared).

The results were als follows:

Reaction to patch test with:

Pat. No.	A 10% ammoniated mercury +2% salicylic acid +1% zinc oxide in petrolatum					B 10% ammoniated mercury +2% salicylic acid in petrolatum	C 10% ammoniated mercury +1% salicylic acid in petrolatum
	freshly prepared	after 1 day	3 days	5 days	3 months		
1	3	2	0	0	0	5	2
2	2	±	±	±	±	4	3
3	2	±	0	0	0	4	2
4	0	0	0	0	0	2	±

Conclusion. In a freshly prepared ointment, a part of the salicylic acid has already been converted into zinc salicylate. The reactions in the first column correspond for the greater part with those in the

last column, which means that in the fresh ointment about half of the salicylic acid must have been converted already.

In general no positive reaction can be obtained to this patch test after some days. From this follows that after a few days not enough free salicylic acid remains to evoke a positive reaction.

Our series of patch tests (A) was performed with 1 % zinc oxide, which does not correspond with any therapeutic prescription. By using a therapeutic prescription, for instance 10 % ammoniated mercury in pasta Lassar, no difference could be demonstrated between a fresh and an old ointment, all patch tests being always negative.

From this it may be concluded that all salicylic acid has already been converted into zinc salicylate if a freshly prepared ointment contains an excess of zinc oxide.

The same problem was also examined chemically. The aim of these chemical experiments was to show that:

(1) under the conditions existing on the skin, no free salicylic acid is present in pasta Lassar;

(2) the salicylic acid reacts with zinc oxide in the paste itself, without the addition of water;

(3) in case of an excess of zinc oxide, the reaction takes place instantaneously, therefore no difference exists between a pasta Lassar which is some weeks old and fresh one.

Different samples of pasta Lassar were analysed and also petrolatum containing various amounts of salicylic acid and salicylic acid with zinc oxide. The following experiments were carried out:

Ad 1. One gram of pasta Lassar was extracted with 5 ml of water. Next the pH of this extract was determined. The same was done with petrolatum containing 2 % of salicylic acid. There appeared to be no difference between the pH in the extract from a fresh or an old sample of the paste. The pH of the extract from petrolatum containing 2 % of salicylic acid, was lower than that from pasta Lassar *, which points to the fact that in the presence of water no free salicylic acid is present in pasta Lassar.

The ratio pasta Lassar/water = 1:5 was chosen, as the skin excretes in general between 500 and 700 g. of water in 24 hours [2, 3]. This amount decreases by about 20 per cent when covering the skin with zinc paste [4]. The amount of paste needed to cover the

* 1 g. of pasta Lassar contains 20 mg. of salicylic acid. The solubility of salicylic acid in water is 1:450.

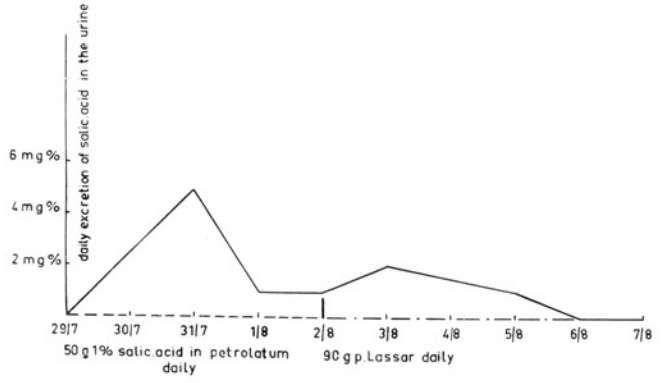
whole skin is about 100 g. Therefore we assumed that the ratio 1:5 is the normal ratio of paste to water existing on the skin.

From this we may conclude that under the conditions existing on the skin, the reaction between salicylic acid and zinc oxide takes place.

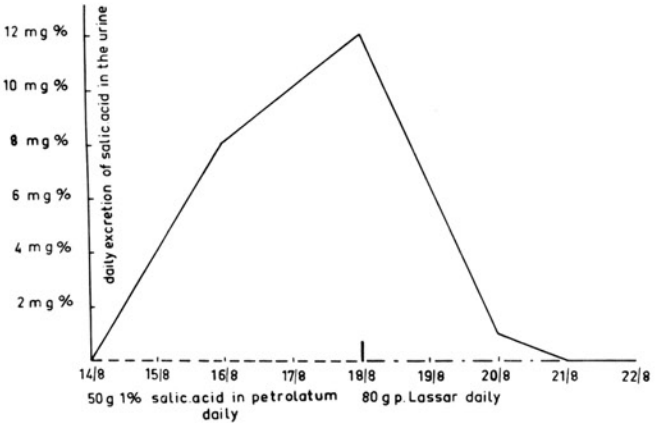
Ad 2 and 3. A freshly prepared, as well as one a few weeks old sample of pasta Lassar were extracted with alcohol, petroleum-ether and ether successively. In the residue zinc salicylate was present. As no water was added, we may conclude that zinc salicylate is present in pasta Lassar, in fresh as well as in old paste.

These chemical results therefore cover entirely the dermatological results; they will be published more in detail elsewhere.

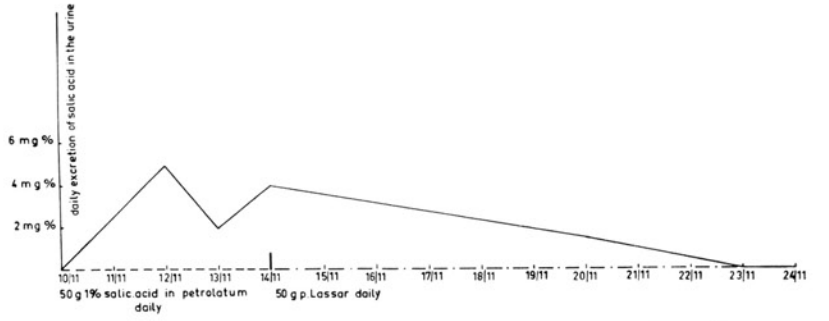
To verify the above mentioned results by still another way, the excretion of salicylic acid was determined in the urine of four patients, who were first treated with 1 % salicylic acid in petrolatum and next with pasta Lassar (see figs. 1, 2, 3 and 4). Notwithstanding the fact, that in general more of the latter ointment was used than of the former, and in spite of the fact that the latter ointment contains 2 % salicylic acid and the former only 1 %, it was shown that in the period during which the patients were treated with 1 % salicylic acid in petrolatum fairly high excretions of salicylic acid were determined. When starting the treatment with pasta Lassar, the salicylic acid excretion became invariably negative in a short time. From this it appears, that salicylic acid is absorbed through the intact skin (which has been known for a long time, see *Rothman* [5]), but not zinc salicylate which is present in pasta Lassar. This is also in accord-



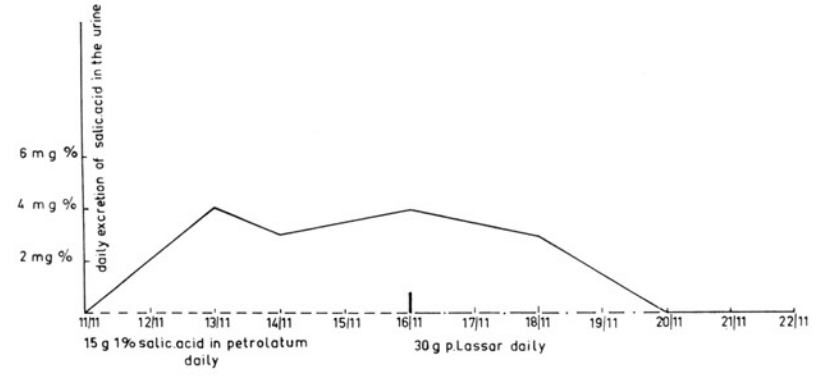
Patient 1. Was treated daily with 50 g. 1 % salicylic acid in petrolatum from 29/7 to 2/8. From 2/8 to 7/8 he was treated daily with 90 g. pasta Lassar.



Patient 2. Was treated daily with 50 g. 1% salicylic acid in petrolatum from 14/8 to 18/8. From 18/8 to 22/8 he was treated daily with 80 g. pasta Lassar.



Patient 3. Was treated daily with 50 g. 1% salicylic acid in petrolatum from 10/11 to 14/11. From 14/11 to 24/11 he was treated daily with 50 g. pasta Lassar.



Patient 4. Was treated daily with 15 g. 1% salicylic acid in petrolatum from 11/11 to 16/11. From 16/11 to 22/11 he was treated daily with 30 g. pasta Lassar.

ance with a publication of *W. Grothe* [6] who found that no zinc was absorbed from an application of zinc salicylate to the intact skin.

From all these facts, the following can be established: zinc salicylate is formed, if zinc oxide is added to an ointment or a paste which also contains salicylic acid. Zinc salicylate has not the same properties as salicylic acid. The reaction mentioned above is a chemical reaction, the rapidity of which is augmented if one of the substances concerned is present in excess.

Since there is a great number of prescriptions containing salicylic acid as well as zinc oxide, it must be realised that these prescriptions are unsuitable to obtain a keratolytic effect. In the first place, this refers to Lassar's paste.

Studying the literature about this subject, it appears that only very few authors have realised this problem and if they did so, they did insufficiently.

H. Kunz-Krause [7] was the only one to demonstrate a certain amount of zinc salicylate in Lassar's paste, but he supposed freshly prepared pasta Lassar to contain still a good deal of free salicylic acid. Very little attention has been paid, however, to this publication.

The only work citing this publication is "Salben, Puder, Externa" by *H. von Czetsch-Lindenwald* and *F. Schmidt-La Baume* [8].

"Skin therapeutics" by *M. K. Polano* [9] is the only purely dermatological work in which attention has been paid to this problem. *Polano* states (p. 58): "When standing for some time, the salicylic acid of the original pasta Lassar reacts with the zinci oxidum forming zinc salicylate."

The author therefore recommends to have this paste always prepared freshly.

Our investigations, however, have shown clearly that already in a freshly prepared pasta Lassar practically no free salicylic acid is present. Therefore there is no advantage in using pasta Lassar freshly prepared.

Generally salicylic acid is used in dermatology for three purposes:

(1) for keratolytic or macerating action;

(2) as an antiseptic;

(3) to promote the absorption of the other constituents of an ointment by the action mentioned sub 1.

Nothing is mentioned in dermatologic literature about the properties of zinc salicylate as it is not used in dermatology; the "Merck Index" [10] and the "United States Dispensatory" by *A. Osol* and

G. E. Farrar [11], however, report a slightly antiseptic and astringent action as its properties. As zinci oxidum has these same properties, this cannot justify the use of zinc salicylate.

As to a keratolytic action of the zinc salicylate, nothing was to be found anywhere, but according to *Fürst* [12] salicylates have in general no keratolytic effect.

Moncorps [13] and *Strakosch* [14] investigated the keratolytic properties of various percentages of salicylic acid in different ointment bases on the skin.

They noted no clinically or histologically perceptible keratolytic effect on the skin by adding salicylic acid to pasta zinci in percentages which are in use for ointments.

Without realising it, these authors have experimented with zinc salicylate; therefore they did not obtain any keratolytic activity.

We have tried to treat some localized hyperkeratoses of the skin with 60 % zinc salicylate in petrolatum, but without any results.

Therefore it can be concluded that there is no advantage in adding zinc salicylate to ointments, as this substance has about the same properties as zinci oxidum.

Therefore it appears to be useless to combine salicylic acid and zinc oxide in an ointment or paste.

Summary

From extensive investigations, consisting of patch tests, determinations of the salicylic acid excretion in the urine and chemical analysis of the related ointments, it may be concluded that by combining zinc oxide and salicylic acid in an ointment or paste, zinc salicylate is formed.

This substance has the same properties as zinc oxide. Therefore this combination is useless.

The rapidity of this conversion depends on certain circumstances described in detail; it appears that even in a freshly prepared pasta Lassar no free salicylic acid is demonstrable.

Zusammenfassung

Auf Grund zahlreicher vergleichender Studien mit Läppchenproben, Bestimmungen der Salicylsäureausscheidung im Urin und chemischen Untersuchungen der in Betracht kommenden Salben

konnten die Autoren nachweisen, daß in einer gleichzeitig Zinkoxyd und Salicylsäure enthaltenden Paste Zinksalicylat entsteht. Da diese Verbindung etwa dieselben Eigenschaften aufweist wie reines Zinkoxyd, kann die Kombination beider Stoffe als zwecklos angesehen werden. Bei einer näheren Analyse der Verhältnisse, die die Geschwindigkeit dieser chemischen Umsetzung bestimmen, ergab sich, daß selbst in einer frisch zubereiteten Pasta Lassar keine freie Salicylsäure mehr nachweisbar ist.

Résumé

Les auteurs ont démontré en se basant sur le résultat de tests épicutanés, de dosages d'acides salicyliques dans les urines et de l'analyse chimique des pommades étudiées, que du salicylate de zinc apparaît dans les pâtes contenant de l'acide salicylique et de l'oxyde de zinc. Comme le salicylate de zinc a sensiblement les mêmes propriétés que l'oxyde de zinc, il semble que cette combinaison n'est pas rationnelle. D'autre part, même dans une pâte de Lassar fraîchement préparée on ne trouve plus d'acide salicylique libre, comme l'ont montré des examens portant sur la rapidité de la formation du salicylate de zinc.

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Jabłońska, S. und *Formas, I.:* Dermatologica *118:* 86–93 (1959)

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Weitere positive Ergebnisse mit Auto- und Heteroinokulation bei Epidermodysplasia verruciformis Lewandowsky-Lutz

Von S. JABŁOŃSKA und I. FORMAS

In unserer früheren Arbeit (*Jabłońska* und *Milewski* 1957) berichteten wir über das positive Ergebnis von Auto- und Heteroinokultationen in einem typischen Fall von Epidermodysplasia verruciformis (E. v.) bei zwei Schwestern.

1946 hatte auch *Lutz* eine gelungene Autoinokulation bei der einen von zwei erkrankten Schwestern veröffentlicht. 1957 publizierte er eine weitere Beobachtung, deren Effloreszenzen er trotz des klinisch nicht ganz typischen Bildes glaubte als generalisierte Verrucae planae ansehen zu dürfen, wobei diese histologisch eine wie bei E. v. auftretende Vakuolisierung der Retezellen aufwiesen. Aus diesen Beobachtungen glaubte er den Schluß ziehen zu müssen, daß die E. v. als eine besondere Art der disseminierten Verrucosis anzusehen sein dürfte. Die Besonderheit dieser Form sei durch eine spezifische Eigenschaft der Haut bedingt, d. h. sie hänge von der Eigenheit des Terrains ab, auf dem sich der Krankheitsprozeß abspielt; möglicher-