ALLERGIC SENSITIZATION AND PHOTOSENSITIZATION TO PHENERGAN CREAM*, †

E. SIDI, M.D., M. HINCKY, M.D. AND MRS. A. GERVAIS

A number of years ago, when the antihistamines became available it was thought by many that substances had been found which, even if not panaceas, at least would be effective against many allergic diseases.

At this time it must be stated that, even though these drugs have proven helpful in some ways, they have also frequently caused eczematizations. Particularly their topical use, such as in a cream or ointment, has led to many difficulties. While in other countries eczemas caused by Pyribenzamine, Antistine and other drugs have been reported since 1947 (1–6), Phenergan cream has been the main cause in France. As a matter of fact the first sensitizations to Phenergan were seen so soon after its appearance on the market as a cream that we have avoided prescribing this remedy from the start.

In France many physicians and pharmacists appear to consider Phenergan cream a suitable treatment for minor skin irritations and a specific treatment for urticarias, eczemas and sunburn. It is obviously necessary that the side-effects of this form of treatment should be known to all those who prescribe it. On various occasions one of us has already called attention to some of these undesirable side-effects (7–10). The present paper gives us an opportunity to review these and to present our more complete data.

In the course of the last three years we have had reason to suspect Phenergan as a causal or contributory factor in 262 cases of eczema. In 128 patients this hypothesis has been confirmed and the skin tests were positive.

The importance of this number becomes evident from the fact that, according to our statistics, it represents 50% of our cases of eruptions due to topical medicaments and 15% of all our cases of eczema produced by external causes.

Often Phenergan cream brings about transformation of a mild eruption into an acute dermatitis which is especially difficult to cure because the patient himself, temporarily relieved by the local anesthetic effects, often is difficult to convince of the harmful action of the Phenergan cream and does not want to stop it.

During the first days after sensitization to Phenergan cream, the eruption manifests itself as acute eczema. The appearance and evolution depend on the subject and on the type of lesion to which it has been applied: acute oozing and vesicular eczemas, severe edematous and erythematous dermatitis, wet and bright red scaly plaques, with outlying patches, and papulo-vesicular patches of eczema are seen. As the eruption continues, all these different clinical types tend to take on a more uniform appearance characterized by involvement of the

* From the Department of Dermatology and Allergy of the Fondation Ophthalmologique Adolphe de Rothschild, Paris (France).

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exposed areas, i.e. the neck, face and forearms. These localizations are a sign that photosensitization has occurred. They are reminiscent of what others as well as we saw some years ago after the application of sulfonamides. Later on in this report we shall discuss the stubborn character of photosensitization dermatitis due to Phenergan.

CUTANEOUS ALLERGIC SENSITIZATION TO PHENERGAN—REACTIONS TO ORALLY ADMINISTERED PHENERGAN

The antipruritic and hypnotic properties of orally administered Phenergan are at present utilized by many practitioners in the treatment of acute eczemas. As far as we are concerned we are unwilling to run the risks involved in this treatment. The majority of patients whom we see have eczemas in which a great number of topical medicaments, more or less well tolerated, have already been tried. Among them are many patients who are not conscious of having been treated with Phenergan cream, and who will develop a reaction after internal administration of this compound. It is impossible to predict beforehand the extent and severity of these reactions. Usually there is a single rise in temperature 4–5 hours after ingestion of the tablet followed by reactivation of the eruption the next day. Moreover, there may be extension of the eczema with development of an erythroderma as well as systemic manifestations such as fever, chills, intestinal upsets and sometimes even syncope.

The severity of these reactions is not necessarily dependent on the dose of Phenergan and the length of time during which it is taken. In some subjects we have seen local reactivations after absorption of Phenergan in homeopathic dilution (11).

On the other hand a nurse, who had become sensitized by contact with injectable Phenergan and who had taken 2 tablets of Phenergan every evening against her itching and insomnia, developed during the first few days an intense, edematous dermatitis of the face and arms. During the subsequent days the eruption first remained stationary and then regressed to some extent despite continued ingestion of the same dose of Phenergan. In other patients such treatment might well have provoked a progressive generalization and an erythroderma.

It is obvious that it is important that one knows to which products these patients have become sensitized in order to institute proper management and to avoid the risks of reactions and recurrences entailed in exposing them to Phenergan cream, tablets, syrup or injections.

SKIN TESTS—THE ROLE OF THE VEHICLE IN SENSITIZATIONS TO PHENERGAN CREAM

The skin tests were carried out by the standard patch test technic and were read after 48 hours. The systematic performance of these tests was helpful in establishing in our patients the respective role which Phenergan and the cream vehicle played in the genesis of their sensitizations.

In 83 of our patients in whom the clinical data suggested intolerance to Phen-

TABLE 1

Tests in 83 subjects for sensitizing capacity of phenergan cream and phenergan solution

Number of Patients	Reactions to Phenergan Cream	Reactions to Phenergan	Reactions to the Cream Vehicle
27	+	0	+
11	+	0	0
5	0	0	+
5	+	+	+
1	0	+	+
2	±	0	±
2	+	+	0
1	0	+	0

ergan, tests were carried out with the commercially available Phenergan cream, aqueous Phenergan solution and with the cream vehicle alone (Table 1). A surprising number of reactions were produced by the vehicle alone. These almost always sharply defined reactions varied from a simple erythema with slight edema to a sharply defined intense erythema with a peculiar dryness and irritation of the skin. In the severe cases of dermatitis the reactions showed edema and vesiculation accompanied by pruritus. The vehicle itself was irritating to the skin and at times eczematogenic. In the 27 patients who reacted to Phenergan cream and to the vehicle alone (but not to Phenergan solution) one could ask oneself whether the reaction was caused by irritation or sensitization due to the vehicle rather than by sensitization to Phenergan. In these cases the ingestion test has helped us to solve the problem. The reactions which we have observed after giving one tablet of Phenergan by mouth have shown us clearly that there was *in addition*, or perhaps as a basic cause, a sensitization to Phenergan itself.

In the 11 subjects who reacted to the Phenergan cream but not to Phenergan solution and to the cream vehicle alone one can think that the reaction was due to a combination of the irritant or penetrating properties of the vehicle and the sensitizing capacity of the drug itself. It is logical that the Phenergan solution without the penetrating power of the cream vehicle would be tolerated by a healthy skin whose defenses are unimpaired.

To restate the important points:

1) The vehicle of the commercial Phenergan cream has drying and irritating properties which have produced slight to strongly positive reaction in 40 of 83 patients.

2) It is obvious that the association of that cream with a compound with strong sensitizing properties such as Phenergan might bring about a particularly dangerous synergism.

3) The relatively small number of reactions to Phenergan solution points up the importance of the vehicle as a preparative factor. It explains why, at a time when we used Phenergan in solution with Subtosan,* as suggested by Bensaude

* Subtosan is a 3.5% solution of polyvinylpyrrolidine isotonic and isoviscous to blood.

for the treatment of anal pruritus, we observed an insignificant number of sensitizations.

PHOTOSENSITIZATIONS TO PHENERGAN

Sensitizations to Phenergan cream are important because of their frequency, the extent of the eruptions and the recurrences which occur after ingestion of Phenergan syrup or tablets. They are negligible, however, in comparison to the photosensitizations caused by this drug. The frequency and persistence and the great difficulties which the photosensitizations cause in these patients have already been described by one of us (20).

In the usual cases of sensitizations to a medicament, a cosmetic product, a chemical agent, the patient can, if he knows the causal agent, remove or avoid it and can carry on a normal life. The patient who is allergic to Phenergan becomes, in the large majority of cases intolerant to sunlight as well as to *regular daylight!* It is obvious that there are few reaction-causing agents which are more difficult to avoid and in order to cure these patients we are forced to hospitalize them in a dark room at times for as long as several weeks. We take great precautions before we let them return to a normal life and even then only after having ascertained which is the best tolerated topical sunfiltering preparation for their particular case. Moreover, we warn them that the photosensitization can persist for several years.

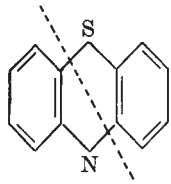
In most cases the photosensitization presents a very suggestive appearance. After the first few days the vesicular eczema disappears and is replaced by a chronic, erythematous, dusky or carmine-colored dermatitis which is accompanied by dryness, fissuring and slight scaling. The existence of a photosensitization can be recognized by the selective involvement of the face and hands with borders at the neck, decolleté and sleeves. In some instances the reactions produced by light consisted not only of simple eczema of the exposed regions but also other peculiar features which merit further study. Eruptions which had been caused by topical and oral administration of Phenergan changed under the influence of light into eruptions which resembled more light hypersensitivity lesions than eczema. Here we have seen conditions resembling pellagra where the skin was dusky red, thinned, atrophic, and tight with an ectropion of the eyelids so much so that the face looked mummified. In two cases this was so striking that we did porphyrin studies which, however, revealed normal values. The cure of these eruptions presents much difficulty. One of our cases took three weeks in total darkness to clear. Similarly we had the opportunity to treat and follow patients in whom the Phenergan dermatitis disappeared only to make room for a typical lupus erythematosus.

It is absolutely essential that physicians be aware of the frequency with which Phenergan cream leads to light hypersensitivity, especially because of its serious clinical features and its protracted course.

PHENERGAN INTOLERANCE AND CROSS-SENSITIZATION

Experiences with sensitizations to the group of compounds containing an amino group in the para position have shown how the intolerance to a simple

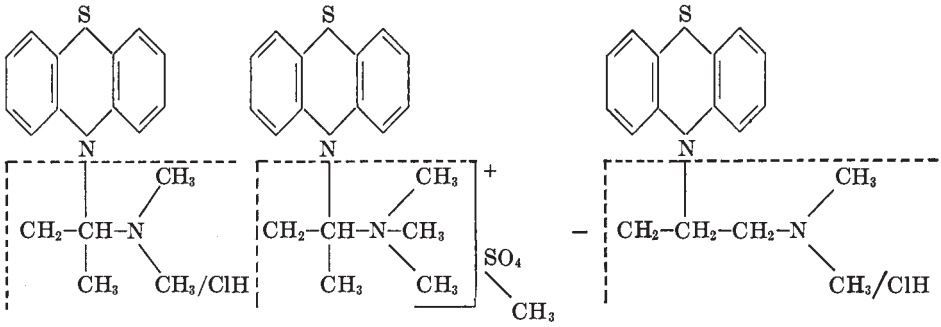
TABLE 2



PHENOTHIAZINE

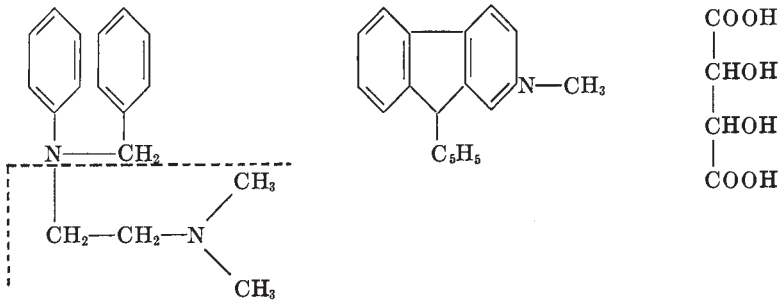
The broken line shows where reduction could produce a primary amine

Antihistamines with a thiazine nucleus (1)



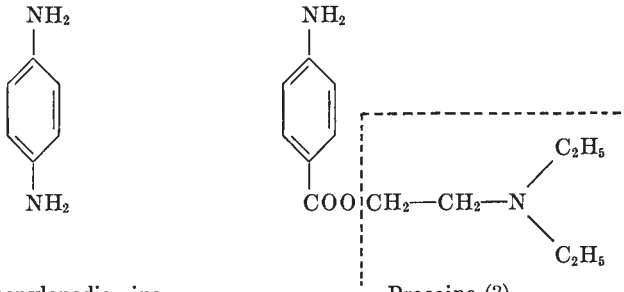
Phenergan Multergan Largactil

Other antihistamines (2)



Pyribenzamine Thephorin

Para amino compounds



Paraphenylenediamine Procaine (3)

(1.) All these compounds contain a tertiary amine (broken line). Multergan is a quaternary ammonium salt, closely related to the tertiary amines.

(2.) Only Pyribenzamine contains a tertiary amine in its molecule.

(3.) Procaine, like other local anesthetics, contains a tertiary amine.

chemical can have far reaching consequences and can lead to reactions caused by chemically related substances. It was logical to ask whether Phenergan would also produce cross-sensitizations, a problem which has already been studied by one of us (10).

A. Phenergan and the other antihistamines

Clinical experience has proven that allergic sensitization to Phenergan was often associated with sensitization to Multergan but only rarely to Thephorin and Pyribenzamine. The similarity of the structure of Phenergan and Multergan is evident (Table 2). In effect these two are related because they are both derivatives of the group of thiazines. Thephorin and Pyribenzamine, two compounds which appear to be usually well tolerated by patients who are allergic to Phenergan, belong to different groups of compounds. This does not mean that Thephorin and Pyribenzamine are not themselves capable of engendering allergic sensitization. We have seen such cases and in Switzerland and in the USA these two compounds appear to be frequent causes of dermatitis.

B. Phenergan and compounds containing a para-amino group

Of 128 Phenergan-intolerant patients 39, i.e. 30.7% reacted also to p-phenylenediamine. Some of them also had a sensitivity to the local anesthetics of the novocaine series and to sulfonamides. This proportion is much too great to be explainable by a simple coincidence.

One of us has already reported in 1952 that the reverse phenomenon was not seen: subjects sensitized to p-phenylenediamine as a rule do not react to Phenergan. Why then do Phenergan-sensitive patients often become intolerant to p-phenylenediamine? The cross-sensitizations studied to date involved always series of products of which the chemical parent substance was evident from the examination of their breakdown products. *A priori* there is no chemical relationship which would explain a cross-sensitization between Phenergan and compounds containing a p-amino group. In order to do this one would have to admit that Phenergan is converted into a compound related to p-phenylenediamine or into one of its breakdown products. From a chemical viewpoint one can think of oxidative or reductive splitting mechanisms leading to primary amines. One must recognize, however, that despite the uncertainty which still surrounds many phenomena of chemical degradation in the organism or at the skin surface, that there is little likelihood of their occurrence *in vivo*.

Even if one could admit that Phenergan could be transformed into substances close to p-phenylenediamine and related compounds, it is absolutely certain that p-phenylenediamine cannot be transformed into substances even distantly related to Phenergan.

*C. Phenergan and Largactil**

Largactil, a new ganglioplegic agent which is much used in psychiatry and dermatology, has shown itself to be sometimes harmful in subjects sensitized

* In the United States of America Largactil is called Chlorpromazine hydrochloride; in Germany: Megaphen; in Argentina: Ampliactil; in Brazil: Amplictil; in Sweden: Hibernal.

to Phenergan. This phenomenon is easily understandable because of the great chemical similarity of the two compounds (Table 2). In the beginning we used this compound in all our eczema patients. We noted then that in some of them the eruptions were aggravated, especially when they had had an eczema due to Phenergan or to a member of the p-phenylenediamine group of compounds.

Among 11 Phenergan-sensitive patients, whom we tested with Largactil, positive reactions were seen in three. In two, a reactivation of the eruption occurred after taking one Largactil tablet. One of these reactions was frightening because of its intensity and the general phenomena with which it was associated. This was a nurse whose case we have reported with our teacher, Dr. Tzanck, before the Société Francaise de Dermatologie. This subject had become sensitized to Phenergan and Largactil which she had handled daily in the form of the injectable solution. Her eruption was practically entirely cleared when 12 hours after taking a Largactil tablet she developed severe edema of the hands, arms and face as well as vertigo and tendency to fainting. This reaction subsided slowly over a 15 day period.

Largactil itself apparently has a considerable sensitizing capacity. We have seen such sensitizations repeatedly in workers engaged in its manufacture and, as stated above, in nurses handling it in injectable form. Pellerat (12) in Lyon has already called attention to the frequent occurrence of eczemas among the nurses handling this compound in a psychiatric center.

Even if Largactil renders great services, it should under no circumstances ever be used topically. Recently such use has been suggested but it can be expected that it would cause even much stronger sensitizations than those which have already been caused by Phenergan (12, 13).

One should be aware of the fact that study of the chemistry of Phenergan, Largactil, Pyribenzamine and certain local anesthetics reveals that they have in common a tertiary aliphatic amine which certain authors (14) have considered a determining factor in sensitization to Novocaine. Finally we want to recall the fact that certain cosmetologists wanted to incorporate antihistamines in cosmetic preparations in order to avoid intolerance reactions. One can imagine how many sensitization and photo sensitization reactions this type of product could produce.

SUMMARY AND CONCLUSIONS

One-half of all eczemas of therapeutic origin seen by us in 1953 were due to Phenergan cream. This leads us to no longer prescribe Phenergan internally because we are always afraid that at some previous time the patient may have applied this medicament locally against a dermatitis or itching. The stubborn photosensitizations which follow Phenergan intolerance represent a severe handicap to the patients. The incorporation of Phenergan in a cream actually produces the maximum chances for sensitization. It would have been preferable to use it in solution like in a calamine lotion. In our hands this type of Phenergan preparation has shown itself to be much less reaction-producing.

It is of equally great importance for the physician and his patients to know

the relationships between the different synthetic drugs and the consequences which may occur because of these relationships. We advise our patients who have become sensitized in this way to avoid the application of antihistamine ointments (especially of Phenergan cream), the oral or parenteral administration of certain antihistamine drugs (Phenergan, Largactil, Multergan); and we also call attention to the possibility of sensitization to other substances (local anesthetics of the novocaine series, hair dyes, sulfonamides).

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