Two Types of Allergy (to Quinine) Occurring Simultaneously § in two Patients

By

Prof. Dr. L. H. JANSEN, Holland.

In general the dermatologist does not distinguish too sharply between different types of allergy.

In this article we will discuss two different types of allergy, viz. the "delayed type allergy", appearing 6-24 hours, sometimes even later, after administration of an allergen and the "immediate type allergy" which may already appear after some minutes.

We often noticed that patients who became hypersensitive to a certain drug (e.g. penicillin, streptomycin or quinine) and who showed eosinophilia, urticaria, erythema and shock-like symptoms (all belonging to the immediate type allergy) after administration of this drug, sometimes also developed a positive patchtest, read 24 hours after application of the causal agent.

The following two patients each showed both types of reaction; we believe that a double sensitization did occur in both cases.

Patient A, a man aged 20, visited the outpatient's department for skin diseases of the University of Utrecht, one day after the development of a quickly spreading contact dermatitis of the face, the throat, the hands, the forearms and the genitals.

He had been working for 3 weeks at a quinine factory. In this period he had daily contact with many quinine substances. He had never been suffering before from eczema, asthma, allergic rhinitis or urticaria; these diseases do not occur in his family.

Patchtests indicated that he was hypersensitive to sulfas-chinini, sulfas-chinidini and quinine bark. After 6 weeks of hospitalization he was discharged as competely recovered.

At home a relapse appeared, caused by clothes contaminated with quinine. One month later he suffered from another relapse, although he did not reappear at his work in the factory. These relapses were caused by incidental contact with material contaminated with quinine in his house and by the fact that he tried to wear clothes which we advised him not to wear which were contaminated with quinine as well. At last he was free from dermatitis during 3 years.

The next relapse, an itching erythemato-papular eruption, developed 24 hours after his drinking a bottle of Tonic.* This eruption disappeared within a few days.

---

§ From the Dermatological Department of State University of Utrecht, Holland.

* Such a bottle of Tonic contains about 5-8 mg. hydrochloras-chinini.

8 months afterwards he worked aboard a ship containing a cargo of quinine bark. *A few minutes* after entering the hold, contaminated with quinine, he was sick, perspired, had an accelerated pulse and collapsed. *Next day* a generalized dermatitis developed; again he had to be treated in a hospital, this time for one month.

Another relapse of the dermatitis appeared at home after wearing his scarf contaminated with quinine (this could be demonstrated chemically.

The same symptoms (collapse after about 10 minutes, followd by eczema 24 hours later) occurred once more after his taking a pill, containing sulfas-chinini, prescribed by his physician.

A scratchtest with 1 0/00 HCl-quinine produced an urticarial reaction after about 20 minutes; one hour later the patient became dizzy, itching appeared in the neck, on his back, the medial sides of the thighs and the genital region. Patchtests with an aqueous solution of HCl-quinine 1 0/00 and 1 0/00 in alcohol both showed a vesiculopapular reaction after 24 hours. The blood picture was normal. The passive transfer reaction (Prausnitz-Küstner), carried out with his serum on a normal person, proved to be negative.

Patient B, a man aged 34, visited the outpatient's department because of contact dermatitis of the forearms, the folds of the elbows, the face and scrotum.

The eruption appeared 3 weks after he started working at a quinine factory (the same as A). He had neever suffered from asthma, allergic rhinitis, urticaria or eczema before; these diseases do not occur in his family.

After hospitalization for 6 weeks he was discharged as recovered.

Some relapses appeared during the next months, although he did not go back to his work in the quinine factory.

6½ yeaers afterwards he developed an extensive perianal dermatitis, which appeared about one day after injection of hemorrhoids with quinine-urethane. This eruption disappeared completely within one month.

Three years afterwards, after drinking a bottle of fruitjuice (?) he developed a generalized dermatitis. Two years later, before going to sleep, he took a pill, prescribed by the neurologist for balance-disturbances. After approximately half an hour he woke up by paraesthesias of the fingers, followed after some minutes by cold shudders, oppression, sickness, heavy headache, and fever (39°C). He recovered after 3 hours.

During the next day a generalized redness and swelling of the skin and mucous membrane of the mouth appeared. The skin alterations developed into papulo-vesicular dermatitis. After treatment in the hospital during one month he was discharged as completely recovered.

During examination in the hospital sickness, heart-pulsations, oppression, swelling of the site of injection (forearm) and lips appeared

half an hour after an intraacutaneous injection of 0,1 ml 1 0/00 acqueous solution of HCl-quinine, followed 18 hours later by a generalized dermatitis of short duration, probably caused by resorption of a minimal quantity of quinine from the site of injection. The patch-test with 1 0/00 quinine in water produced a vesicula-papular reaction after 24 hours.

General examination showed no abnormalities, except eosinophilia of 17%.

The passive transfer (Prausnitz-Küstner), carried out with the patient's serum, did not yield a positive result.

DISCUSSION

At first both patients only developed a "delayed type allergy", manifested as contact dermatitis. It was apparent that this type of allergy had developed after a period of 3 weeks, during which they were intensely exposed to quinine substances.

Patient A developed a relapse of dermatitis after drinking a beverage containing quinine and after wearing clothes contaminated with quinine. Patient B showed the same symptoms after injections with quinine-urethane and after drinking a fruitjuice (?. Perhaps some relapses were caused by contacts with material in their houses contaminated with quinine.

8 months after the last relapse patient A also developed an immediate type allergy. This was apparent from the manifestation of shock-like symptoms some minutes after inhaling quinine dust and once again after taking a pill containing quinine. Both times these symptoms were followed 6-24 hours later by a more or less generalized dermatitis.

The development of an immediate type allergy in patient B became manifest 2 years after the last relapse of his dermatitis; it was observed half an hour after taking a pill containing quinine. These symptoms were also followed (after 18 hours) by a generalized dermatitis (which was a symptom of the still at the same time existing delayed type allergy). The scratchtests with quinine substances were positive in both patients (urticarial reaction after 10-20 minutes) and also the patchtests (papulo-vesicular reaction after 18-24 hours). The reaction of Prausnitz-Küstner, carried out with serum of these patients, was negative in both cases.

The reactions in our patients give us the opportunity to discuss the delayed type allergy (a reaction which will appear after 6-24 hours) and the immediate type allergy (a reaction appearing after a few minutes).

Delayed type allergy :

It has repeatedly been tried in the past to transfer this type of allergy which does exist in contact dermatitis from the patient to a control person or to an experimental animal.

It has been tried for example to obtain this result by injecting intracutaneously a small quantity of the patient's serum in a normal control, and 24 hours later the suspected agent at the same site. An urticarial reaction appearing after 10-20 minutes may be considered to indicate the presence of circulating antibodies in the patient; antibodies which remain fixed at the site of injection in the control person; this method was used by Prausnitz and Küstner. This test almost never yields positive results in patients suffering from contact dermatitis. Therefore, it has been suggested that positive results, obtained in the past, lay within the limits of normal variability of a biological test.

Furthermore, it is difficult to understand the relation between an urticarial reaction and the pathogenesis of contact dermatitis.

The contact dermatitis reaction is a delayed type allergy, a reaction developing approximately 24 hours after applicating the antigen on the skin of the sensitized patient. Thus a patient suffering from dermatitis caused by novocaine will show after about 24 hours a positive reaction to a patchtest with novocaine in low concentration.

Although appearing under somewhat different circumstances the sensitization which develops after chronic infectious diseases, for example tuberculosis, is also a delayed type allergy. After intracutaneous administration of a small quantity of tuberculin the development of an infiltration papule can be observed after approximately 24 hours.

A.O. Landsteiner and Chase (1942) and Skog (1955) succeeded to transfer passively the hypersensitivity to certain eczematogene agents and to tuberculin from one guinea pig to another, although not by injecting serum of the sensitized animal into a not sensitized animal, but by transmitting intravenously or intraperitoneally intact lymphocytes of the sensitized animal to the normal animal.

It appears that a hypersensitivity passively obtained in this manner usually does not last for more than one week and probably gets lost because the injected "sensitized" lymphocytes disappear from the circulating blood.

It has been assumed that, if the animal from which the lymphocytes are obtained, is sensitive to tuberculin, a number of these lymphocytes, injected in a healthy control animal will move to the site where the tuberculin has been injected, and cause an infiltration-papule to appear at this site.

Should a hypersensitization to an eczematogenic agent exist, the lymphocytes thus transmitted will move to the site where the patchtest has been carried out and cause an eczematous reaction there.

Thus the delayed type allergy is tied to the lymphocytes.

Epstein and Kligman definitedly proved that allergic contact type delayed sensitivity also can be transferred in man.

Immediate type allergy :

Two groups of immediate types of allergy can be distinguished :

I. Atopy (Coca);

II. Anaphylaxy.

To the atopic reactions belong allergic rhinitis, conjunctivitis vernails and some types of asthma; shock symptoms too may appear. Principally complex compounds, polypeptids and polysaccharids function as allergen. The most notorious allergens (atopens: mostly inhalation allergens) are derived from pollen, fungi and housedust.

The atopic constitution, Coca mentioned this already, is a typical heredital abnormality. It always appears that some members of the family suffer from atopy; some suffer from asthma, others from rhinitis or some other type.*

Usually in cases of this type of allergy, eosinophilia appears after exposition to the allergen; in less severe cases only in the shockorgan (e.g. the mucous membrane of the nose), in serious cases also in the blood.

This type of allergy is based on the presence of antibodies (the so-called reagins) partially circulating, partially bound to the cells. These antibodies can also be differentiated from the normal antibodies as they are not or much less clearly present in the Y-globulin-fraction and as they are thermolabile.

As a rule an (urticarial) reaction is visible 10 or 20 minutes after a scratchtest or intracutaneous test with the causal agent, because a.o. histamine is liberated during the reaction between the allergen and the reagain. The passive transfer is positive as the reagins from the serum of the patient also combine with the cells at the site after an intracutaneous injection in a healthy control person, so that they may cause an urticarial reaction after injection of the "atopen" at this site.

The second type of immediate allergy is anaphylaxy. The anaphylactic shock, which may appear after a second injection (for instance two eweeks after the first) with foreign protein (serum shock), is generally known. This reaction appears because the first, the preparatory injection with foreign protein (the antigen) induces specific anti-bodies. These antibodies which appear in the Y-globulinfraction of the blood, will combine with the antigen after a second injection. During this reaction a.o. histamine is liberated, causing shock. The difference with the atopic reagins is that it is possible to prove the presence of these antibodies in vitro (e.g. as praecipitins, agglutinins, or haemolysins). The anaphylactic shock in humans may be accompanied with

*Some members of these families also suffer from atopic dermatitis, but until now the exact nature of atopic dermatitis is not well known.

urticaria; Quincke's edema, asthma, sometimes with slight eosinophilia.

Landsteiner framed the following hypothesis to explain the appearance of shock symptoms caused by drugs: these substances combine in the body with a protein fraction and thus become a complete antigen. The antibodies developed by this compound combine with these drugs when administrated again, thus causing the anaphylactic reaction.

In some cases of drug allergy (as in our two patients), the scratch-tests or (and) intracutaneous tests yield positive immediate type (urticarial) reactions.

The above described patients first developed a delayed type allergy, appearing as a dermatitis reaction. Afterwards an immediate type allergy was observed appearing as shock-like symptoms. Some minutes after applicating quinine shocksymptoms appeared, followed by a dermatitis-eruption after 6-24 hours.

Other kinds of immediate type reactions may also occur in cases of drug allergy: thrombocytopenia ((usually accompanied by purpura), haemolytic anaemia, agranulocytosis etc. Some investigators suggest that in these cases the antigen combines with one of the bloodcorpuscles and that antibodies against this combination (drug+corpuscle) develop. Repeated administration of the drug causes the binding of the allergen (drug+corpuscle) with antibody (globulinfraction), resulting in damage to the cells. This type of allergy can not be proved by patchtests or scratchtest, but (not in all cases) by experiments in vitro. The most obvious way to prove this allergy is to administrate the drug again, but this experiment is not justified as very serious side-effects may develop.

Often antihistaminics can be used as therapeutics in cases of atopic or anaphylactic reactions. It has no sense, however, to treat contact dermatitis with an antihistaminic; the only effect produced by these drugs is based on their sedative capacity. Histamine plays no part in the development of contact dermatitis. This explains the failure (observed by every physician) of antihistaminics in treatment of contact dermatitis.

Should our patients have been in a critical condition when seen by us, then a trial with corticosteroids, prednison or ACTH had beeen justified, because these drugs have a favourable effect on allergic reactions.

In our opinion, however, the primary use of these drugs, when treating skin diseases generally should be restricted to vital indications, as serious and frequently appearing side-effects may develop, even when low doses are administrated. Only when the normally applied therapeutics fail the use of these drugs may be justified. Of course, exceptions to this rule ought to be permitted.

The above described patients show that some insight into allergic processes may be of great value when examining and treating our

patients. The importance of a good administration of the observed hypersensitizations is also apparent from these data.

Although hypersensitization sometimes (spontaneously?) may disappear, one should never rely on this phenomenon.

SUMMARY

Description of two cases of allergy to quinine substances; in both cases first a delayed type allergy developed, manifestating itself by contact dermatitis. After some years also an immediate type allergy (shocksymptoms) became apparent.

In both cases the immediate type urticarial skin tests (scratch, intracutaneous) and the delayed type (patchtests) were positive.

LITERATURE

Landsteiner, K. and M.W. Chase (1942), Proc. Soc. Biol. and Me. *49*, 688.

Skog, E. (1955), Acta Derm.—Ven. *35*, 93.

Chase, M.W. (1945), Proc. Soc. Exp. Biol. and Med. *59*, 134.