

PROCEEDINGS

COMMUNICATIONS

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PENICILLIN ALLERGY

by JENS PEDERSEN-BJERGAARD, Copenhagen.

As early as in 1942, immediately upon the introduction of Penicillin, attention was directed to the various secondary effects of the drug, all of which were mainly of an allergic nature. In one of the first studies of the problem KEEFER et al. (1943) (1) reported findings from an examination of 500 patients who were treated by penicillin. Secondary effects were seen in 55 of the cases, viz.: fever, urticaria, arthralgia, anaphylactic shock, etc. In all essentials these reactions were found to be ascribable to impurities of the preparations.

Up to the present time 300 fatal cases of penicillin allergy have been published. From Denmark the first three fatal cases of penicillin allergy accompanied by anaphylactic shock were reported by Harrestrup Andersen (2) in 1955. According to American statistics based on large numbers the rate of mortality of penicillin allergy to be expected in Denmark should be: 1-2 fatal cases per year. Severe allergic conditions are particularly frequent after administrations of procaine penicillin. An examination of a large number of patients showed hypersensitivity to penicillin in 1-2 per cent of the cases.

The allergic conditions most commonly encountered include: urticaria, Quincke's edema, erythema, and reactions mimicking serumdisorders; anaphylactic shock occurs occasionally. Allergic patients, particularly patients who are allergic to hyphomycetes (mould fungi) are found especially susceptible. Considering the wide application of penicillin not merely within human but also within veterinary pathology, hazards are severe for sensitization and subsequent allergic reactions. Thus, Danish dairy products (e.g. cheese, milk, and chicken) contain presumably some penicillin. Even small quantities of penicillin suffice to release

severe allergic reactions; Lorenzen (3) e.g. has reported one case of allergic shock excited by polio vaccination (with a view to sterility small quantities of penicillin have been added to the Danish polio vaccine).

To substantiate or to repudiate a diagnosis of penicillin allergy is equally difficult; allergological examinations should include: patch tests (even pressure patch tests), scratch tests, conjunctival and intracutaneous reactions, provocative reactions, and demonstration, if possible, of circulating antibodies as suggested by Prausnitz-Küstner. These reactions are positive only in 70 per cent of the cases of penicillin allergy.

Own examinations.

41 patients were examined who at an earlier stage had presented symptoms of hypersensitivity after contact with penicillin. A careful study of the previous history of the patients was followed by intracutaneous tests using 0.1 ml of Natrium-G-penicillin, the highest intracutaneous tolerance dose being 1/100. If reliable allergic symptoms occurred after these tests the case would be classified as one of „manifest penicillin allergy”; if not it would be classified as a case of “non-manifest penicillin allergy”. Among the 41 examined patients were 13 cases of manifest, and 28 cases of non-manifest penicillin allergy.

Out of the 13 cases of manifest penicillin allergy 6 were found to react positively to the intracutaneous test within 20 minutes; a positive although retarded reaction was seen in 1 case after an interval of 24 hours (most probably an unspecific reaction); in the remaining 6 cases no local reaction were noted after the intracutaneous test. However, in 4 of the latter cases anaphylactic reactions of varying strength occurred; in 2 cases reactions were positive solely after provocative tests.

Treatment of Penicillin Allergy.

Some authors have reported satisfactory response to injections of penicillinase preparations during the acute stages of urticaria and of cases mimicking serum disorders. But animal experiments should be borne in mind in which the antigenous effects of penicillinase were demonstrated.

Prophylactic desensitization should be considered. Such treatment may last for a long time, the object being to develop in the patient a tolerance to contact with penicillin. It may be a matter of great occupational interest if e.g. physicians, nurses, etc. acquire a hyper-

sensitivity to penicillin. Generally in patients such desensitization *can hardly be expected* to develop a tolerance which will suffice if they are to be *treated by* penicillin.

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PRESENT CLINICAL EXPERIENCE WITH ANTI-SEROTONINE TREATMENTS

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For a long time it has been generally admitted that histamine is not the sole component in the allergic reaction mechanism.

In recent years attention has been focussed on Serotonine (5-hydroxytryptamine) which mainly is developed in the enterochromaphilic tissue of the intestinal canal, biliary ducts, and nerve tissues. In the blood it is noted mostly in the thrombocytes but also—to a smaller degree—in the leucocytes. In the connective tissue it is found in the mast-cells. Serotonine influences inter alia intestinal function and blood coagulation. An acceleration of the Serotonine production is seen in case of enterocarcinoids, thus involving intermittent flushing, profuse perspiration, bronchiostenosis and, at a later stage, pulmonary stenosis and tricuspid incompetence.

A few years ago histamine as well as serotonine were found to be liberated during allergic reactions in rabbits. Studies by *MacHaffie et al.* (1960) suggested that blood of allergics contained larger amounts of serotonine than blood of non-allergic patients. Intracutaneous serotonine injections have been found to give rise to a marked vasodilatation in human subjects but only insignificant exudation.

A synthetic anti-serotonine preparation is now available. The authors have used Cyproheptadine (Merck, Sharp, & Dohme). *Klaus Jensen* (2) has demonstrated that the development of papules would diminish if this drug were given to allergic patients and also that the rash following intracutaneous reactions would be less pronounced. A marked anti-histamine effect of the drug has been demonstrated in animal experiments: the broncho-stenotic effect of histamine is greatly inhibited.

Differences between the effects of serotonin and of histamine seem to be of a fundamental nature. Oedema is known to develop in experimental animals after intraperitoneal Dextran injections. Such development may be prevented by administrations of anti-serotonine but not by anti-histamine.

Any secondary effects of Cyproheptadine have not been noted apart from a certain sedation seen in a few cases (mostly during the initial therapeutic stages). But this secondary effect is less than secondary effects caused by e.g. Phenergan.

Own examinations.

In the allergological out-patients' department of the University Clinic (Rigshospitalet) Cyproheptadine has been used for the last 6 months and a certain clinical experience has been gained. A total of 50 patients have been treated by the drug, even patients with hay-fever who, because they applied too late, could not be desensitized by pollen-extracts before the beginning of the season; the drug was used also in cases of severe bronchial asthma, urticaria, and Quincke's oedema which previously had failed to respond to other therapies.

Results from these treatments were as follows: effects were found to be satisfactory in cases of urticaria; they were relatively satisfactory in cases of hay-fever and vasomotor rhinitis; but, generally there would be no response in cases of asthma and Quincke's oedema. The study is to be continued and further details will be reported.

DISCUSSION

In patients applying to an out-patients' unit P.-H. Nexmand had been studying the anti-urticarial and anti-pruriginous effects of Cyproheptadine (prurigo (Besnier) patients). The anti-urticarial effect was found to be marked but, the itching accompanying Besnier's prurigo remained unaffected. Hence, anti-serotonine preparations should be used exclusively in cases of urticaria and not in cases of prurigo.

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