Rhinology, XVII, 185–191, 1979

Cellular allergy - one way to ozena? Rhinomanometry and histology in animal experiments compared with clinical aspects

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SUMMARY

Based on rhinorheomanometric examinations supplemented by rhinoscopic and histological findings, evidence could be provided that an allergy of type IV in the Coombs and Gell classification can be challenged in the nasal mucous membrane as well. The tuberculin reaction in guinea pigs was used as test model.

A critical evaluation of test results, immunological literature and some related challenge tests as to delayed reactions in human medicine are the reason for assuming the clinical symptoms of hypertrophy preceding ozena to be the clinical correlation to a type IV reaction.

This correlation to clinical symptoms is not only borne out by animal experiments but also by years of experience in intranasal challenge tests, in rhinorheomanometry including the preparation of allergens for intranasal challenge.

Allergologic investigations into rhinitis by intracutaneous testing often show delayed reactions to fungal spores and bacteria. These immuno-pathogenetic mechanisms must be assigned to the tuberculin or eczema reaction, to type IV according to the classifications by Coombs and Gell.

The allergic delayed reaction, the infectious allergy or bacterial allergy show a similarity in clinical symptoms without being identical. Their morphological substrate in the nose can be assumed to be the hyperplastic rhinitis as described by Naumann and Naumann (1977). The big question mark is referred too by Mygind and Prahl (1976): "Ob Mikroorganismen bei der sogenannten bakteriellen Allergie als Allergene wirken können, muß noch bewiesen werden."

Paper presented at the 7th Congress of the European Rhinologic Society. Davos (Switzerland), September, 1978.

Consequently the book by Mygind (1978) excludes the allergic rhinitis of type IV.

The term allergy and its definition were coined by C. von Pirquet, here already bacterial allergy receives mention. The reference to tuberculin makes clear that the delayed allergic reaction even to bacteria is to be interpreted as an allergy. Limiting the term allergy to well-known anaphylactic reactions (type I after Coombs and Gell) as done by some rhinologists – unconsciously or not – clearly contradicts the definition by its creator.

In the literature, differences appear in describing delayed reaction symptoms after challenge testing, on the hand as serous, seasonal rhinitis sensitive to pollen (Wüthrich et al., 1974) and on the other as purulent, perennial rhinitis sensitive to house dust (Callerame et al., 1972).

Since intracutaneous testing is often followed by delayed reactions a mere 2 tests are unsatisfactory particularly as different symptoms appeared. Therefore animal experiments were conducted to show if an adequate allergen quantity might challenge an intranasal and epimucous delayed allergic response and what clinical symptoms occurred.

Immediate reaction experiences from intranasal challenges in man allowed the determination of adequate allergen quantities for challenging delayed reactions equivalent to a spontaneous exposure. Thus it became possible in contract to Slavin et al. (1964) to correlate experimental findings to clinical ones. That is

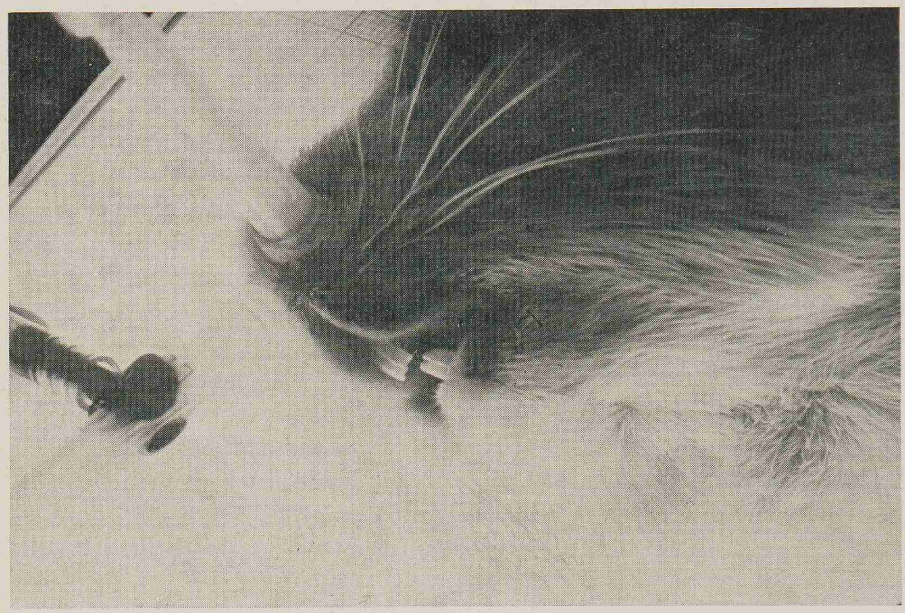
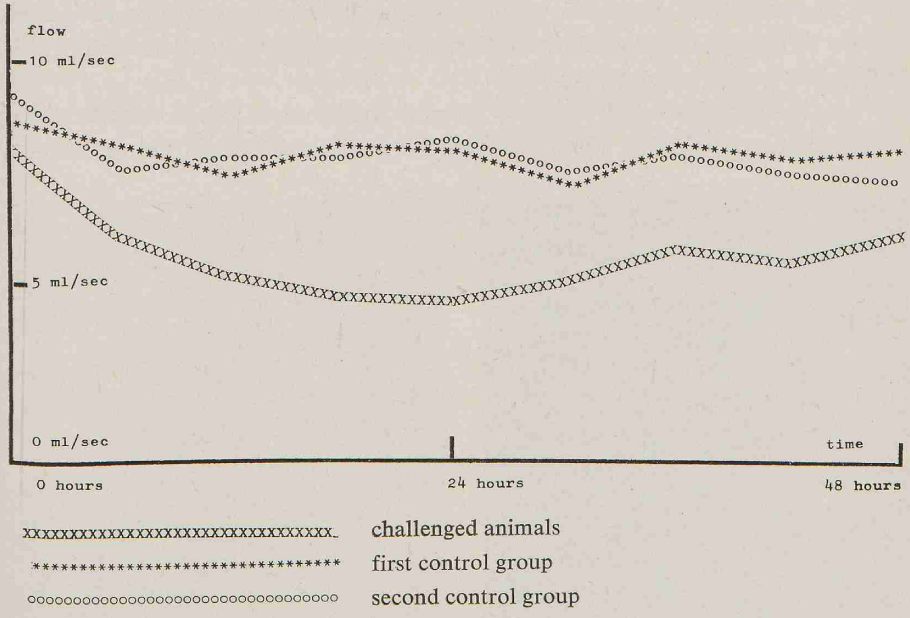


Figure 1. Site of the anterior rhinorheomanometry in the guinea pig: pressure and volume flow tube put on the nostrils adapted by vaseline. Measurement of the right nostril.

why our interpretation of reaction intensity differs essentially from preceding investigations.

Guinea pigs tuberculin-sensitized with complete Freund's adjuvant were used as test subjects. Pretests proved the repeated allergen application at several hours' interval to be the most effective one. A 6-hour interval was chosen at which 1 or 2 drops of the allergen were instilled into one nostril. The small dosage reduced the possibility of allergic alveolitis after allergen aspiration to a minimum.

An anterior rhinorheomanometry including an appropriate anaesthesia (Ketamin) for small animals was developed to evaluate any mucous membrane reactions (Figure 1). This was added by means of rhinoscopy with a 40-fold magnifying microscope and connected camera. Thus the anterior turbinal end and the anterior septum could be observed. 48 Hours after challenge, the animals were killed, a cross section of the nose was studied macroscopically and the septal mucous membrane histologically after straining in a hematoxilin-eosin and Giemsa solution.



The chart is based on values measured in 66 animals.

Figure 2. Cart showing the increase in nasal airway resistance after challenge. At the top two control animal groups, at the bottom the challenged animal groups. The abscissa shows time, the ordinate the value of nasal airway conductance expressed by the flow (1 mb $\cong$ 1 cm H_2O in the nasopharynx) of the right side. There is a clear peak between 18 and 24 hours. The control animals only show a continual, gradual increase in nasal airway resistance by the non-specific irritation due intranasal application of water-like drops.

The rhinorheomanometric values measured 18 hours after challenge were analyzed according to statistical tests by Kruskal-Wallis and Wilcoxon. 2 Control groups were used to exclude any non-specific irritation caused by the foreign protein tuberculin and also any changed reactivity of the nasal mucosa produced by test conditions. One control group consisted of sensitized animals, however, only "challenged" by saline, the second one of non-tuberculin sensitized animals (only treated with incomplete Freund's adjuvant) that had tuberculin inserted into one nostril. The test parameters' error probability was below 1% in the critical range.

The rhinorheomanometric follow-up was in line with prognosis. The maximum of nasal obstruction was between 18 and 24 hours. Neither animal control groups showed any similar reaction (Figure 2).

A pathognomic reaction of the mucous membrane did not result. Any morphological changes appearing were typical in their temporal progress. The changes were polymorphic.

A macroscopic thickening of the mucosa could be observed in only few nasal cross sections of highly sensitized animals. The left mucous membrane can be compared with that of the right nasal cavity because animals were challenged in the right nostril alone (Figure 3).

Yet low-sensitized animals and also animals with a slight skin test and rhinorheomanometric reaction partly revealed large subepithelial infiltrations com-

Figure 3. Cross section of the nose. The septal mucous membrane is thickened on the right side compared with the left.

posed of lymphoid cells. But other animals did not show a histologically detectable reaction (Figure 4, 5).

The symptom of a type IV reaction in man considering the differences in human and animal nose size (and mononuclear cells of nearly the same size leading to the obstruction of nasal airways by infiltration) is: only a slight obstruction of airways in the nose, hardly rhinorrhea or sneezing. Corresponding challenge tests using chromate, nickel, iron, propylenglycol, chloramphenicol but also tuberculin in sensitized men confirm this hypotheses.

Rhinoscopy revealed the same polymorphic mucous membrane in man as in animal. No pathognomic mucosa changes could be observed. In search of clinical symptoms in line with this reaction we came across a hypertrophy preceding ozena described by rhinologists working in histology. 48 Hours after challenge man as well shows histological changes in the mucous membrane of the anterior turbinal end corresponding to the histological drawing in the Beck and Bauer atlas (Figure 6).

Atrophic changes observed when testing the pinnal skin in our animals and the cytotoxic effect of type IV reaction well-known to immunologists support the assumption that suffering from a hyperplastic – even discrete – rhinitis for a long time and present delayed reaction in the nose will later cause trouble because of initially unnoticeable, destroying, immunological processes of a type IV reaction eventually leading to atrophy.

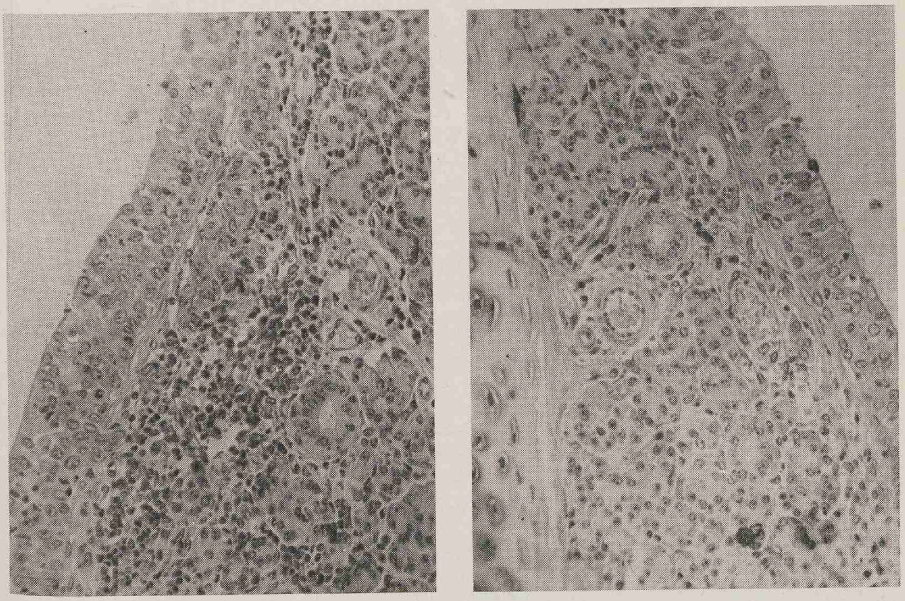
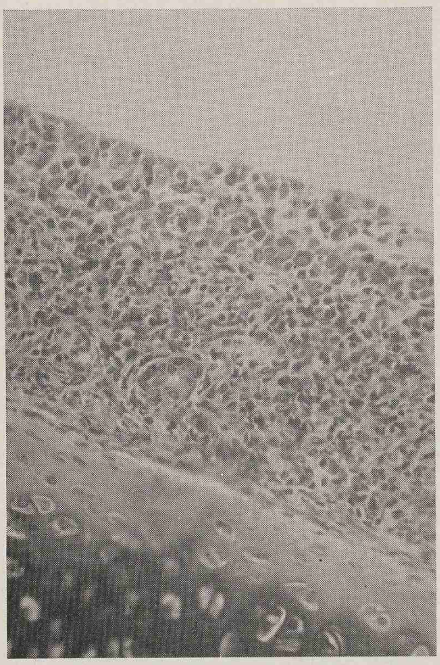


Figure 4 a, b. The positive reaction on the right (4a) can be recognized compared with the left side (4b).



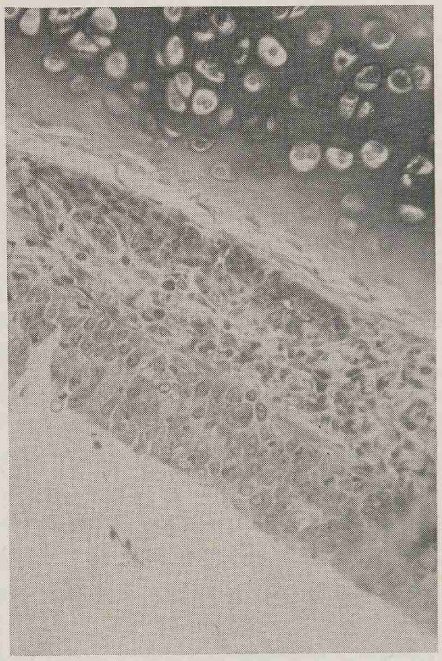


Figure 5 a, b. Clear positive reaction on the right part of the septum, (5a) concomitant reaction on the left (5b). Giemsa stain.

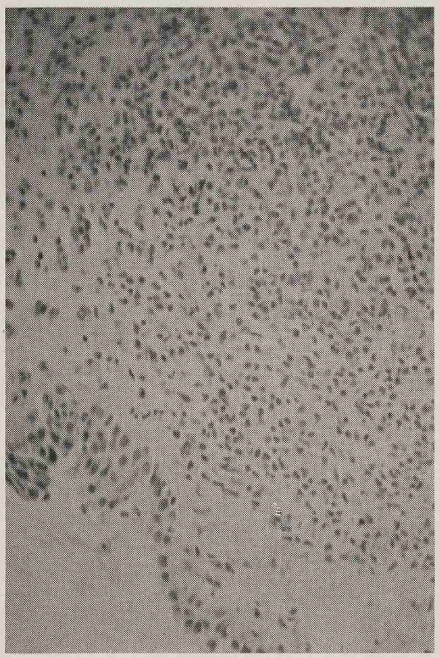


Figure 6. Reaction of the human mucosa, 48 hours after provocation (inferior turbinate).

ZUSAMMENFASSUNG

Aufgrund rhinorheomanometrischer Untersuchungen, ergänzt durch rhinoskopische und histologische Befunde, konnte nachgewiesen werden, daß auch an der Nasenschleimhaut eine Allergie vom Type IV in der Einteilung nach Coombs und Gell ausgelöst werden kann. Als tierexperimentelles Modell diente die Tuberkulinreaktion des Meerschweinchens.

Die kritischer Beurteilung der Versuchsergebnisse, der immunologischen Literatur und einiger orientierender Provokationstests auf Spätreaktionen in der Humanmedizin lassen als klinisches Korrelat der Typ-IV-Reaktion ein Krankheitsbild annehmen, das bei der hypertrophen Vorform der Ozaena einzuordnen ist.

Die Aussage zum klinischen Korrelat stützt sich nicht nur auf die Tierversuche, sondern sie wird auch aufgrund langjähriger Erfahrung mit dem intranasalen Provokationstest, mit der Rhinorheomanometrie einschließlich der Zubereitung der Allergene für den intranasalen Provokationstest gemacht.

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