Delayed Hypersensitivity and Antibody Response in Rheumatoid Arthritis

The possibility that immunological mechanisms might play an important part in the pathogenesis of rheumatoid arthritis is admitted by many authors[1-6].

This communication presents data showing some abnormalities of delayed hypersensitivity and the specific antibody response to minimal doses of antigen in patients with rheumatoid arthritis. Accepting the premise that streptococci are in some way related to rheumatoid arthritis[2], streptococcal antigens (streptokinase-streptodornase) were used in this study.

Material and methods. Two groups of patients were studied: (1) 107 patients with rheumatoid arthritis, who satisfied the diagnostic criteria proposed by the A.R.A. 67 patients were treated with corticosteroids or resochin, 20 persons with another therapy and 20 subjects were not taking antirheumatic drugs. (2) 33 patients with degenerative joint diseases served as control group. We excluded patients with other concurrent diseases.

Throat cultures of all patients examined at weekly intervals were negative for haemolytic streptococci. None of the patients had historical or clinical evidence of an upper respiratory infection within one month previous to or during the period of observation.

All patients were injected intradermally with 0.1 ml of Dornokinase corresponding to 25 units of streptokinase. Skin reactions were read at intervals of 24, 48 and 72 h. The maximum reactions developed 48 h after injection and, therefore, the 48-h readings were used for calculating our results. Since the majority of the skin reactions were elliptical, the skin index was obtained by measuring the longest and the shortest diameters and multiplying their product by $^1/_4\,\pi$.

Blood was taken for estimation of antibodies at the time of skin testing with Dornokinase and again three weeks later. No other antigenic impulse was used. Each serum specimen was heat inactivated and tested for antistreptokinase (using the fibrinolytic method of CHRISTENSEN[7]) and for antistreptolysine O (using the modification of Todd's technique[8]). All serological tests were done in duplicate.

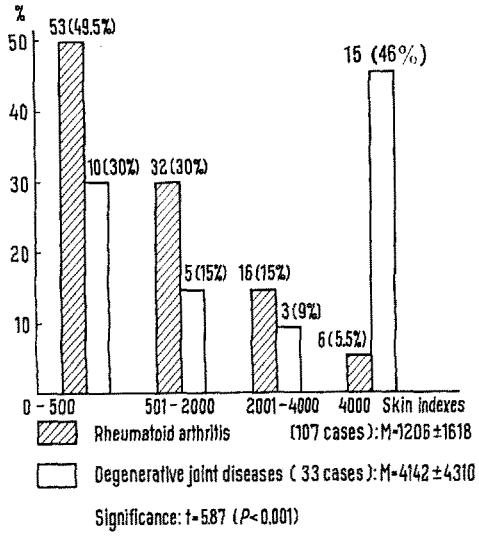

Fig. 1. Skin indexes in both groups of patients.

Results. The results of skin testing with Dornokinase in both groups of patients are outlined in Figure 1. The comparatively high incidence of negative or low indexes in patients with rheumatoid arthritis is notable. The average of skin indices of the rheumatoid group is distinctly lower than that of the control group, being 1206 and 4142 for the two groups, respectively. This difference is statistically significant ($P < 0.001$). The values of skin indices of the rheumatoid group without therapy in comparison to those of the control group were also significantly decreased ($P < 0.001$).

The initial geometric mean of antistreptokinase levels for the rheumatoid patients was 38 units and for the control subjects it was 33 units. Three weeks after the skin testing with Dornokinase the antistreptokinase levels of rheumatoid patients had risen to a geometric mean of 91 units. This increase is statistically significant (Figure 2). Such a marked rise was not observed in control subjects (geometric mean 51 units, Figure 3).

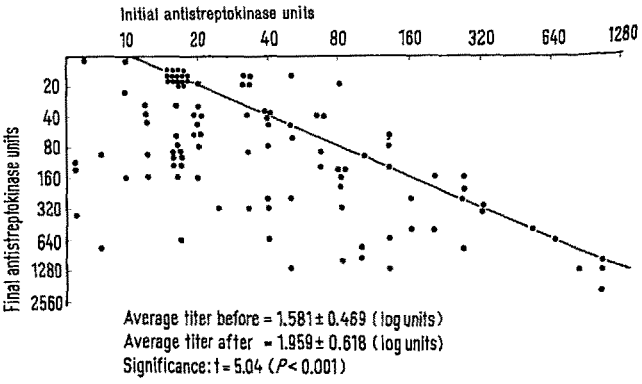

Fig. 2. Antistreptokinase titres before and after skin-testing (107 patients with rheumatoid arthritis).

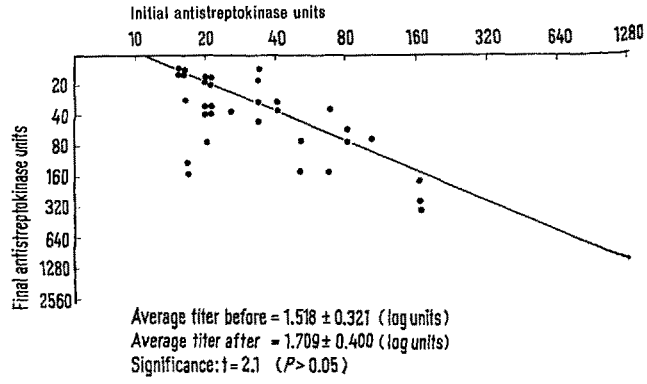

Fig. 3. Antistreptokinase titres before and after skin-testing (33 patients with degenerative joint diseases).

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The therapy (corticosteroids, resochin) did not influence either of the immunological reactions ($P > 0.05$) mentioned. There was no significant relation between either of the immunological reactions and the duration of the rheumatoid arthritis.

At an interval of three weeks after the skin testing a significant rise of antistreptolysine O titre occurred simultaneously with antistreptokinase in only one of all our patients with rheumatoid arthritis.

Discussion. In order to explain the inhibition of skin reaction in patients with rheumatoid arthritis, two postulates may be considered: the desensitization of delayed hypersensitivity and immunological hyporeactivity. There is no evidence favouring the first possibility. The mechanism of desensitization is immunologically specific and as yet we have no basis for a special disposition to desensitization in rheumatoid patients. More acceptable is the second possibility, that the inhibition of delayed hypersensitivity is a general reaction of rheumatoid subjects. EPSTEIN and JESSAR[9] demonstrated the decrease of reactions to conjugated antigens of chemical compounds. Although different antigens were used, our results are in agreement with this report.

The increase of antistreptokinase titres might be caused by recent streptococcal infection. With respect to the lack of clinical symptoms, to the negative throat cultures and to the negative responses in antistreptolysine O titre, the above-mentioned possibility may be rejected. The failure to demonstrate antistreptolysine O rise consistent with antistreptokinase is evidence that no kind of non-specific antibody response occurred.

The increased specific antistreptokinase antibody responses in rheumatoid patients could be interpreted as indicating that a considerable proportion of rheumatoid subjects have had contact with this antigen either fairly recently or on numerous occasions – or that these patients had for some other reason been able to respond immunologically to the minimal dose of the skin testing antigen better than the other patients.

Our results are in agreement with generally accepted immunological hyper-reaction in rheumatoid subjects. MEISELAS et al.[5] showed in patients with rheumatoid arthritis an increased antibody response to Brucella vaccine, and GREENWOOD and BARR[4] to tetanus toxoid.

In conclusion, it should be emphasized that immunological reaction in rheumatoid patients undergoes a change: symptoms of delayed hypersensitivity are inhibited but the specific antibody response is, however, increased. Whether this discrepancy of immunological reaction has some relation to the pathogenesis of rheumatoid arthritis remains for further work to elucidate.

Zusammenfassung: Es wird über die immunologische Reaktivität von Patienten mit progressiver Polyarthritis berichtet. Nach Injektion von 25 E Streptokinase (Präparat Dornokinase) zeigten die Patienten eine gewisse Dissoziation der immunologischen Vorgänge: Herabsetzung der Hautreaktionen und erhöhte spezifische Antikörperreaktion.

V. HOUBA, M. ADAM,
J. MALEČEK, and B. TESÁREK

Research Institute for Rheumatic Diseases, Prague (Czechoslovakia), May 15, 1964.

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Light Sensitivity in the Amphipode, *Niphargus aquilex schellenbergi* Karaman

Amphipodes of the genus Niphargus are colourless, transparent arthropodes without lateral or medial eyes. They live in subsoil water in rock crevices (new red sandstone), coming to the surface in springs. Observations on the diurnal periodicity of Niphargus showed that light acts as a time giver[1]. In order to study the photic response of the amphipodes more specifically, 14 medium sized specimens (6–9 mm) were put into a flat test chamber of 3 cm diameter filled with spring water. One half of the chamber was in the dark, the other half was lit from above by a 1000 Watt xenon arc passed through a set of double interference filters and neutral density filters. Threshold determinations were made by counting the relative numbers of animals at the end of a 5 min stay in the dark and after 2 min in the light. During exposure to intense illumination, the organisms showed strong negative photokinetic reactions. In order to measure the absolute threshold, the light intensity was reduced in steps of 0.15 log unit until the organisms ceased to show any movement in response to light. With illumination by white light, the absolute threshold was at 3.5 lm/m^2 (about 10^6 times the absolute threshold of the human eye). No change of sensitivity was seen after the animals had been kept for several hours in darkness. However, the organisms showed slight signs of fatigue at the end of a 4 h experiment. Further, after several days, the sensitivity was found to be slightly increased, being constant during the later stages of the investigation.

Dividing the test chamber into two parts differentially illuminated by two beams of light, the organisms preferred the darker half of the chamber if the difference of illumination between the two parts was more than 17%. This ratio was fairly constant throughout the range of illumination, 3.5 to 2240 lm/m^2.

The results of measurements of the spectral sensitivity of Niphargus are shown in the Figure (circles, mean values of two days). Sensitivity is highest at 515 mμ and declines towards either side. Compared with the absorption spectra of known photopigments, the sensitivity data between blue and green are close to the absorption of lobster rhodopsin[2] (drawn-out line in the Figure). However, in the region of shorter and longer wavelengths, the sensitivity of Niphargus is definitely lower than the absorption spectrum of both lobster rhodopsin and visual pigment 515 mμ[3]. Since the spectral variation of the amount of

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