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THE PRODUCTION OF INCOMPLETE ANTIBODIES IN HUMAN BEINGS

II. *Changes in titres owing to the hygiene of working surroundings and to the contentment with the conditions of life*

By

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Our preceding papers (*Wagner, V., Rejholec, V., Malý, V.*, 1955; *Padoucová, M., Rejholec, V., Suda, F., Wagner, V., Malý, V.*, 1956) brought to light the fact that subjects with a past history of rheumatic fever respond to single stimuli of *Brucella abortus* vaccine with significantly higher titers of incomplete antibody than healthy controls. A further communication (*Rejholec, V.*, 1957) showed that this increased faculty of production of incomplete antibody is present before the onset of rheumatic fever and is not just a sequela of this disease. Finally, the first part of the present paper (*Rejholec, V., Hrubcová, M., Malý, V., Wagner, V.*) has demonstrated that immunological reactivity of apprentices, measured at their first arrival in the hostel from different surroundings, depends to a certain degree on conditions of those former surroundings, especially on lodging and food.

The results reported in the above-mentioned communications seem to justify the hypothesis that increased ability to produce incomplete antibody is in pathogenic association with rheumatism. In the light of this hypothesis it seemed indicated to investigate whether and in what degree the enhanced immuno-

logical reactivity can be modified by changes in environmental conditions.

MATERIALS AND METHODS

Adolescents subjected to the tests of this research were identical with those examined in the last-mentioned study (*Rejholec, V., Hrubcová, M., Malý, V., Wagner, V.*). Likewise the method of assessing the degree of reactivity was the same: immunization was performed by a single subcutaneous injection of *Brucella* vaccine, and blood samples were taken 14 days later. Titers of incomplete antibody in the serum were ascertained in the way previously described. The only difference consisted in that this time the antigenic impulse was a second one, following the first after an interval of 9 months.

During the 9 months' stay in the hostel all investigated adolescents were also subjected to a new examination as regards external influences. Most of the former differentiating factors which had been followed up in the foregoing paper (*Rejholec, V., Hrubcová, M., Malý, V., Wagner, V.*) having been equalized (lodging, food), attention focussed on differences in sanitary conditions in which the apprentices had to work, and on the individual attitude of the boys towards their occupation and their lot in life.

The observed sample could be divided into two groups: 84 boys were locksmith apprentices and 63 boys learned to be electricians or mine-engine maintenance-men. The locksmiths' workshops showed few hygienic defects, they had cold concrete floors; when the lessons were over, the boys did not wash, shower or change; often, wet with sweat, they raced to line up for the autobus to be taken to the hostel and had to wait for it in the open for 10 to 20 min. In comparison, conditions in the classes of electricians and of mine-engine maintenance-men were much more satisfying: their workshops had deal floors; the lessons over, the boys washed thoroughly under supervision, changed and were taken to the hostel in orderly manner, without being exposed to chilling. Lodgings and food were equal for both groups.

Attitudes toward occupation and toward lot in life in general were ascertained in individual, intimate and detailed talks between physician and pupil. The boys were accordingly classified as "satisfied with their lot" or "dissatisfied".

RESULTS

The titers of incomplete antibody, recorded after the second antigenic stimulus, were compared with those ascertained in the same subjects after the first stimulus, 9 months earlier. This comparison is illustrated in Fig. 1. The left-hand columns represent the distribution of titers (in percentages) at the entry in the hostel after the first inoculation in 1953, those on the right the distribution after the second inoculation in 1954. The figure shows that during the intervening 9 months the rate of

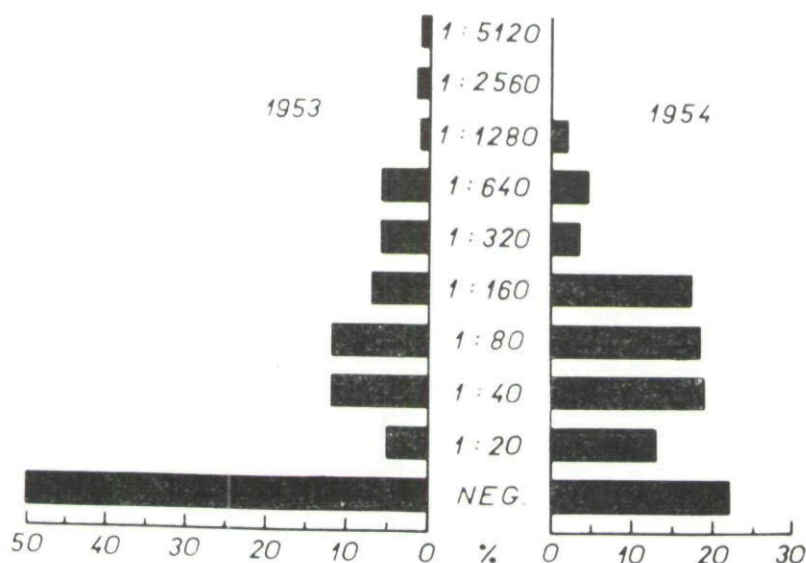


Fig. 1.

Distribution of incomplete antibody titers after the first and the second inoculations by Brucella vaccine. The left side shows the percentages on the admission to the hostel in September 1953, the right side the percentages at the end of 9 months in June 1954, after a second inoculation of the same type and potency as the first.

boys who responded by titers higher than 1:160 sank from 15.5 to 10 per cent. Inversely, the rate of those who did not respond even by the lowest assessed titer (1:20) sank from 50 to 22 per cent. Thus, the rate of the subjects who reacted by the medium titers of 1:20 to 1:160 rose from the initial 46 to 68 per cent.

Among the 13 boys with titers exceeding 1:160, ten belonged to the group which worked in inadequate sanitary conditions, though the remaining 3 were not of this group, they were in return among those dissatisfied with their occupation. In the past history of all these 13 hyperreactors before their admission to the hostel we encounter 8 cases of damp lodgings, 6 cases of susceptibility to illnesses after chilling, 7 cases of habitual salt adding and seasoning of dishes, and 7 cases of reduced egg consumption. These cases are, of course, overlapping.

With regard to the changes in titers of incomplete antibody since the initial immunization, the investigated subjects were divided into 3 groups as follows: Group A included boys whose titers had sunk by two degrees or more, group B comprised boys whose titers had risen by two degrees or more. Figure 2 shows this distribution, first in relation to conditions of the workshops (the left hand diagram) and, second, in relation to the boys attitude towards occupation and lot in life (the right hand diagram). In both diagrams black columns represent the actually observed frequencies and the hatched ones the statistically "expected" frequencies, i.e. frequencies which might be expected on the assumption that there is no causal link between the compared characteristics.

The comparison of adequate and deficient hygienic surroundings shows that the number of boys whose titers had sunk in the course of the year, does not sensibly diverge from the "expected" number. In return among the apprentices who had to work in unfavourable conditions, the rate of those whose titers had substantially risen was considerably higher, and the rate of those whose titers did not appreciably change was considerably lower than could be expected statistically. On

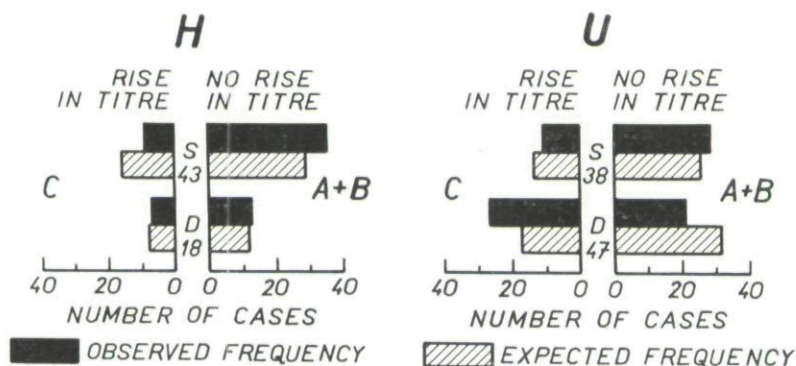


Fig. 2.

Distribution of the sample according to working conditions (U = unhygienic, H = hygienic) and to mental disposition (S = satisfied, D = dissatisfied) towards occupation, in relation to alterations in the titers.

A = decline of the titer by at least 2 degrees (reduced reactivity).

B = titer practically unchanged.

C = Rise in titer by at least 2 degrees (enhanced reactivity).

the other hand, among apprentices who had worked in favourable sanitary conditions, the opposite phenomenon took place. The rate of increased titers is lower and the rate of titers which had not changed is greater than expected. The recorded differences between the expected and the actual changes were found to be statistically significant at the 5 % level (value of $\chi^2 = 5.516$). The hyperreactors (with titers 1:160 or more) are to be found for the most part (10) in the inadequate-surroundings group, and only 3 in the other.

The results are very similar when one compares the degree of immunological reactivity with the attitude of the investigated subjects toward occupation and lot in life. The righthand diagram shows an unmistakable shifting of titers towards lower values for those who are satisfied with their lots and towards higher values for those dissatisfied. Here too the difference is statistically significant at the 5 % level (value of $\chi^2 = 2.220$).

In Figure 3 we tried to illustrate the combined interrelationship of all three characteristics under examination: conditions in the workshop (left hand diagram—favourable, right hand

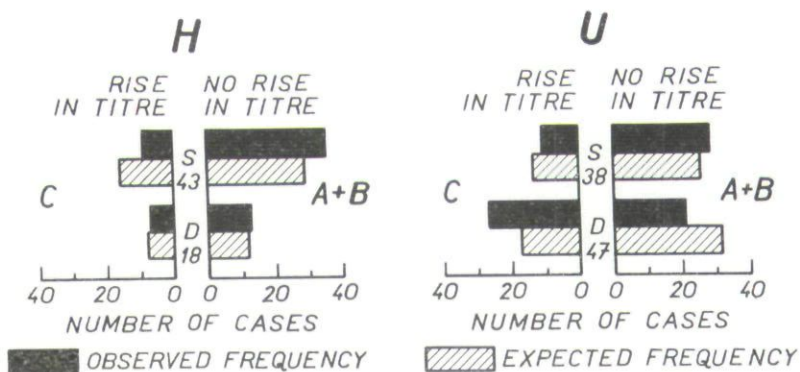


Fig. 3.

Changes in antibody titers in relationship to sanitary working surroundings and to mental disposition together. For description see fig. 2.

diagram—unfavourable), attitude toward occupation and lot in life (upper pairs of columns in each diagram—satisfied, lower columns—dissatisfied) and changes in titer (left side of each diagram—rise, right side—fall or no sensible change).

It appears that immunological reactivity of people working in favourable sanitary surroundings tends to decline as far as they are contented; otherwise the beneficial effect of this external factor seems to be neutralized by the adverse mental disposition (the observed frequency roughly equals the expected frequency. Similarly, hygienically unfavourable working conditions reduce the reactivity of those contented with their lots only in a very slight degree, though they substantially raise the rate those who react hyperergically in those who are dissatisfied. Statistical significance ($\chi^2 = 14.963$) is at the 1 % level. Not a single hyperreactor emerged in the group of satisfied subjects or in that working in favourable surroundings.

Figure 4 illustrates the association of reactivity with changes in bodily weight and also with former consumption of preserved food. It can be noted that the decline of the titer of incomplete antibody does not appear to be significantly linked with increase or decrease of bodily weight. On the other hand, increase in weight seems to step up the response to immuno-

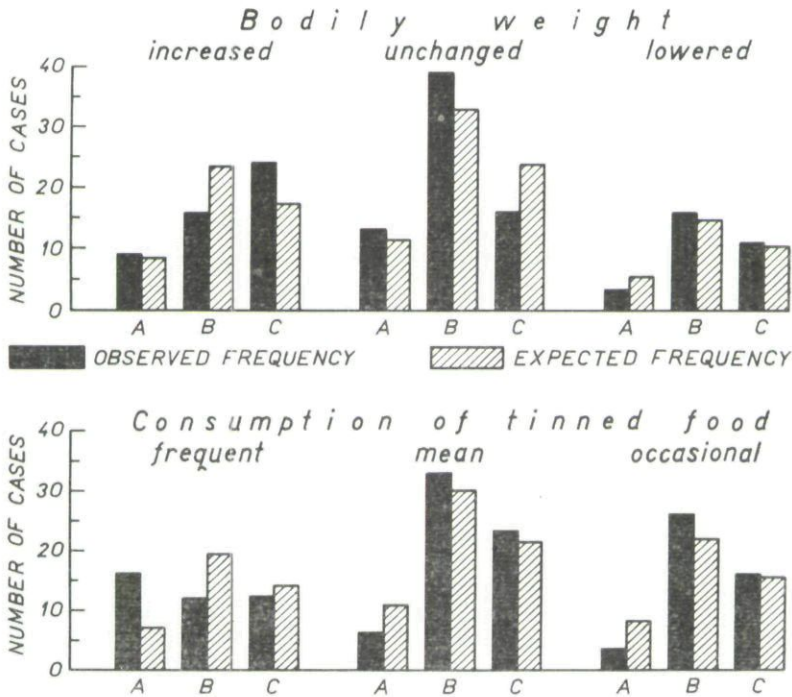


Fig. 4.

Distribution of changes in incomplete antibody titers in relation to changes in bodily weight and to former consumption of preserved food.

For description see fig. 2.

logical stimulus, whilst in cases in which the weight did not change (meaning, of course, did not change more than would correspond to normal bodily development in the given age) the rate of those whose titer remained constant was significantly higher than that of the others.

A reduction in titers was observed in those who, before admission to the hostel, had been consuming an inordinate proportion of preserved food; this did not appear on the bill of fare of the hostel. The majority of boys who had not eaten preserves at all or not too often, had retained their previous titers.

The value of χ^2 for the weight was 10,284, which corre-

sponds to the 5 % level of significance, for preserved food $\chi^2 = 21,533$, corresponding to the 1 % level.

DISCUSSION

The foregoing communications (*Wagner, V., Rejholec, V., Malý, V., 1955; Padovcová, H., Rejholec, V., Suda, F., Wagner, V., Malý, V., 1956; Rejholec, V., 1957*) have clearly established the relationship between the ability of producing incomplete antibody against *Brucella* vaccine and susceptibility to rheumatic fever. The findings contained in this paper offer statistical analysis of some of the factors which determine the changes in this aptitude in youthful subjects, i.e. in their individual immunological reactivity.

The sample under examination suited the purpose of this research very well. The boys had come to the hostel from very different surroundings, had very disparate habits and their former living conditions were dissimilar. This enables us to divide the sample manifoldly, from a variety of viewpoints, into distinct groups as shown by the figures. On the other side, the boys were approximately of the same age and had already been living 9 months under circumstances admitting easy comparisons, in the same hostel where lodging and food conditions were identical. The only material difference lay in the sanitary conditions of the workshops allotted to different crafts, and this difference also allowed us to divide the sample into large, well circumscribed groups and facilitated their comparison.

The reason for repeating the immunization of our sample was to see in what measure, if any, a regular, comparatively hygienic way of life affect immunological reactivity. We were fully alive to the fact that the same antigen being administered for the second time, the immunological nature of the material under examination was already altered. Thus we were prepared to encounter in this second immunization a significant anamnestic reaction in the production of antibody and we expected a substantial, uniform rise in titers of antibody practically in every boy. Surprisingly, such a phenomenon did not take place or only in a slight degree. It is true that after the

second inoculation (Fig. 1) the rate of subjects who did not produce antibody (up to the titer of 1:20) was observed to have fallen from the initial 50 % to 22 %. Thus, the number of those who reacted at least with low titers, rose, but, in return, the expected shift into really high titers did not show at all. From this experience it may be deduced that a regularization of living conditions on a certain hygienic level makes for some sort of standardization of immunological response of the population on a certain—one may perhaps say—optimum level. An analysis of the 13 hyperreactive cases has brought to light the fact that in each of them several detrimental factors, both in the past and in the present time, concurred to induce the state of high reactivity.

The elimination of preserved food from the bill of fare made for a reduction of immunological reactivity in a number of boys. We regret that other quantitative food components could not be followed up in this work. But it is not without interest to compare the changes in reactivity with changes in bodily weight. Even though a decrease of the latter did not affect the production of incomplete antibody, there were among those boys whose weight did not change (leaving, of course, out of account the normal growth) much few cases of increase in titer of incomplete antibody. In those boys whose (relative) weight was higher at the second immunization, shifts into higher titer values were clearly discernible.

The difference in working surroundings between the two groups of apprentices whose lodging conditions were otherwise equal has shown that cold working rooms, together with a few other defects, are clearly correlated with hyperreactivity. Contentment in the observed conditions is conducive to a certain regularization of immunological response, while in return hyperreactors are to be found more often among those dissatisfied with their lots. We encounter here a very interesting connexion between higher nerve-center activity and immunological response.

Incidentally, conjunction of two stimulating factors (unfavourable working surroundings and discontentment) pro-

duced a far greater effect than either of these factors by itself. Inversely, concurrence of a stimulating and a suppressing factor virtually balanced out the effects of both.

Generally speaking, such external or internal conditions which spur on the alertness of organism in man, are apt to step up the adaptation to immunological stimuli in a certain percentage of the population. Thus, the alterations of immunological reactivity which we have brought to light are but so many expressions of this altered alertness of the organism against unfavourable conditions of life. In this way we arrive at the role of any strain on the organism in those diseases whose pathogenetical background lies in immunological hyper-reactivity (allergy, autoimmunization, rheumatic fever). In this connection it may be observed that conditions of external environment as well as nerve factors are subjects of a lively discussion by a number of authors about allergy where otherwise immunological background of phenomena is unquestioned (*Spoujitch, V., Živković, M.*, 1960; *Wolf, S., Holmes, T. H., Trenting, T., Goodell, H., Wolff, H. G.*, 1950; *Burden, S. S.*, 1955; *Funkenstein, D. H.*, 1953; *Abramson, H. A.*, 1956; *Dornbusch, S.*, 1957; *Queiron, A. N. de, Strauss, A.*, 1958; *Weiss, E.*, 1959) and abundant literature quoted herein).

This communication leaves out effects of hormonal factors, refrains from trying to establish individual types of nerve activity and abstains from following up genetic influences. Consequently any discussion of internal mechanisms through which the suggested changes of immunological adaptivity may be brought about would perforce remain a mere speculation. This problem cannot be tackled without further research work.

SUMMARY

Titers of incomplete antibody after an antigenic impulse by *Brucella abortus* vaccine were assessed in 146 boys for the first time on their admission to the school for apprentices and anew after a stay of 9 months. The number of those who had at first reacted either by negative or by the highest titers of incomplete antibody having decreased, the dispersion of titers was found

to have become much compacter. It was demonstrated that working conditions defective in sanitary respect as well as dissatisfaction with one's lot in life lead to a rise in antibody titers and that, inversely, sanitary surroundings and mental contentedness contribute to the decline of titers.

Two concurring factors, operating in the same sense, have a stronger effect than one factor by itself.

Action of a few food factors came also to light.

The significance of the obtained results was checked up by statistical methods.

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