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THE PRODUCTION OF INCOMPLETE ANTIBODIES IN HUMAN BEINGS

I. Reactivity of adolescents coming from different environments

By

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In our preceding communications (Wagner, Rejholec, 1955; Padovcová, Rejholec, Suda, Wagner, Malý, 1956) it was shown that subjects with a past history of rheumatic fever respond to single non-streptococcal stimuli such as *Brucella abortus* vaccine with substantially higher titers of incomplete antibody than are found in control subjects without such a history. This observation raised a number of issues which seemed worth exploring. It suggested that the immunological response might be related to environmental conditions as well as to nutritional factors. We have studied this particular problem on a group of healthy individuals, confining our scrutiny of immunological reactivity to the investigation of the production of incomplete antibody after a single inoculation with *Brucella abortus* vaccine.

MATERIALS AND METHODS

Immunization and serological testing: In October 1953 single subcutaneous injections of 0.5 ml of *Brucella abortus* vaccine were given to 146 subjects belonging to the same age group. The vaccine was of grade 3 density by McFarland's

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scale (McFarland, 1907) which corresponds to a content of about 200 million bacteria in 1 ml. On the 14th day following the inoculation in all subjects blood samples were taken and the titer of incomplete antibody in their sera assessed. For a detailed description of the method applied we refer to a previous paper (Wagner, Rejholec, 1955).

Selection of subjects to be tested and mode of investigation: In a school for apprentices in different crafts 5 of the primary forms, were chosen for study. Within 14 days of the school opening, all pupils underwent a general physical examination. Particular attention was devoted to the state of tonsils, teeth and regional lymph nodes; the respiratory tract and cardiovascular system were examined physically and x-rays; irregularities and defects of the locomotor system and signs of past-rickets were noted; boys with any traces of past rheumatic diseases were excluded from the tests so that only 146 healthy boys remained. A number of anthropometric data were also gathered; standing height, sitting height, weight, armspread, chest circumference at inspiration and expiration, pigmentation type, degree of sexual development, etc.

Anamnesis: Each of the boys was questioned individually, by an investigator who did not change in the course of the tests; no third person was admitted. The investigator had not been told to what immunological reactivity type he belonged. The talk was informal and suggestive question were strictly barred. The questionnaire bore upon basic personal and family data, descent (from a village, a provincial town or a city), domicile before entering the school, the parent's occupation and social standing, social conditions in general, sanitary conditions of living quarters and of previous school, crowding of lodgings (number of bedroom-mates), all past diseases since childhood and the morbidity of other members of the family, so far as remembered by the pupil, sports in which the pupil was engaged, his progress in school, especially in the last year, etc. Reasons which had desired the pupil to enter the school and to choose his present craft were inquired into in order to establish whether his decision had been free or had been forced

upon him by extraneous influences against his wishes. The nutritional conditions were fully investigated for as many years back as possible. Preference for particular dishes and inclination to certain habits at meals, especially to indiscriminate salt adding and seasoning, were ascertained as well as the consumption of eggs and liking or dislike for dishes containing eggs.

From the data gathered in this way only those are further elaborated here which seemed sufficiently objective and extensive to permit statistical evaluation.

Statistical methods: The 146 investigated subjects were divided into three categories according to the results of the serological test for incomplete antibody:

- I. Negative subjects, i.e. those who upon immunization did not produce antibody, at least not up to the titer of 1:20.
- II. Positive reactors with titers ranging from 1:20 to 1:80.
- III. Hyperreactors with titer from 1:160 upwards.

As the characteristics which had to be compared with the titer level were almost without exception qualitative, the χ^2 test appeared the best indicated for evaluating this relationship (Bradford Hill, 1949). For each of the observed frequencies we have computed the "expected" frequency, i.e. such frequency as could be expected on the assumption that the characteristic in question was *independent* of the titer level. On the basis of the expected and the observed frequencies the values of χ^2 were computed and their significance was determined with the aid of Fisher's statistical table (Fisher, 1950).

RESULTS

Comparison of the "expected" and the observed distribution among serological categories I, II and III of the groups formed on the basis of the explored characteristics (basic, somatic, social, nutritional etc.) has revealed associations which, for

some of these characteristics, appear very clearcut, for others not quite convincing, and for the majority none whatever. In this paper we do not concern ourselves further with the last mentioned characteristics, although we do not exclude the possibility that tests on other samples might bring to light associations which remained hidden from us.

Characteristics whose association with the titer of incomplete antibody has been demonstrated by our tests are as follows:

1. with significance at the 1 % level:
susceptibility to infections of upper respiratory tract following chilling, sweating, change of temperature, and frequent eating of tinned food (at least twice a week);
2. with significance at the 5 % level:
living in humid, insanitary defective lodgings, predilection for seasoned dishes, indiscriminate salt adding, and shortage of eggs in meals (less than 3 a week) or repulsion for eggs and for dishes containing eggs.

For the statistical evaluation of these six characteristics we refer to Table I.

Association of the following characteristics with immunological reactivity may be considered as tentatively suggested, but not convincingly proved by the evaluation of the collected statistical materials:

stronger pigmentation (the dark type),
descent from cities or towns,
higher age of the mother, and
exposure to colds, like bathing in cold water.

DISCUSSION

There is no doubt that, apart from impulse by a specific antigen, immunity, or the rate of production of antibody, is affected by many non-specific agents. From this point of view

TABLE I
Statistical Evaluation of the Characteristics whose Association with Immunologic Reactivity is significant at the 5 % or the 1 % level.

Titer	Num- ber of boys	E - 3 Dwelling in humid lodgings		C - 5 Propensity to infectious colds		F - 1 Frequent eating of tinned food		F - 2 Immoderate seasoning of food		F - 3 Indiscriminate salt adding		F - 4,5 Egg penury in food, aversion to eggs	
		o	e	o	e	o	e	o	e	o	e	o	e
Negative	75	17	27.7	12	28.8	8	21.1	14	23.6	26	37.0	42	34.4
1:20-60	40	19	14.8	25	15.3	14	11.2	17	12.6	26	19.7	13	17.7
1:160 & above ...	31	18	11.5	19	11.9	19	8.7	15	9.8	20	15.3	12	14.9
Total	146	54		56		41		46		72		67	
$\chi^2 =$		8.999 +		20.186 + +		21.027 + +		8.201 +		6.729 +		6.531 +	

o = observed frequency.

e = frequency expected on the assumption of independence of the two characteristics compared.

+ = value of χ^2 square is significant at the 1 % level.

+ + = value of χ^2 square is significant at the 5 % level.

the role of food has been a subject of intensive research, especially as regards vitamins, and the obnoxious consequences of a shortage of these have been demonstrated on experimental animals (Schneider, Webster, 1945; Axelrod, Carter, McCoy, Geisinger, 1947; Schneider, 1948; Carter, Axelrod, 1948; Lanza, 1949; Tripodo, 1950; Büsing, 1950; Wertman, Crisley, Sarandria, 1952; Wertman, Sarandria, 1952; Meyer, Malgras, Ponelle, 1955; Guinchi, Scuro, Sorice, Fidanza, 1953; Stoerk, Eisen, John, 1947; Wertman, Smith, O'Leary, 1954; Wertman, Groh, 1959; Pruzansky, Axelrod, 1955). The influence of metabolism of proteins upon immunity has been investigated by many authors (Cannon, 1942; Cannon, 1943; Cannon, 1945; Wissler, Woolridge, Steffee, 1946; Wissler, Woolridge, Steffee, Cannon, 1946; Veršilova, 1954; Guggenheim, Buechler, 1946; Guggenheim, Buechler, 1948; Klimentova, 1954; La Via, Barker, Wissler, 1956; Schneider, Lee, Olitzky, 1957; Schneider, 1948; Schneider, Webster, 1945; Steffee, 1950). Hereditary influences have also been studied, but mostly in experiments on animals (Sang, Sobey, 1954). The specific synergetic effect of salt with desoxycorticosterones upon the genesis of several pathologic syndromes has been demonstrated experimentally (Knowlton, Loeb, Stoerk, Seegal, 1947; Harrison, 1951; Mangakis, 1954). An exclusive literature has arisen likewise on endocrine and nervous factors; its quotation is omitted here as this facet of the issue is intended to form the subject of a special study.

Extact observations in man, bearing upon the relationship between external environment on the one side and immunizing processes and antibody production on the other are very scarce. We quote the study of Balch, 1950 who draws attention to a certain dependency of antibody production in man upon protein metabolism. He postulates that subjects with a lower protein concentration in the serum possess a somewhat increased faculty of antibody production. His conclusions have been to some extent corroborated by Havens, Bock, Siegel, 1954 who carried out immunizing tests on severely wounded men in the

Korean war. These men were producing antibody to diphtheria toxoid more abundantly than the control groups. The authors were, however, not able to verify dependency of the antibody production on the protein concentration at the time of immunization or on other aspects of the protein spectrum. Neither did they find any relationship with age or nutritional conditions. Larson, Tomlinson, 1952 arrived at similar conclusions.

The works dealing with immunological reactivity of patients with rheumatic fever are referred to in our preceding communications (Wagner, Rejholec, 1955; Rejholec, 1957). As far as the relationship between the state of nutrition and the pathogenesis of rheumatic fever is concerned it is important to point out the study of Coburn and Moore (1943); Wallis (1954) who ascertained a statistical association between the consumption of eggs and the incidence of rheumatic fever. A statistically significant proportion of patients with rheumatic fever confessed either to aversion for eggs or to protracted shortage of eggs and this significance increased with the gravity of the disease. These studies does not explicitly mention any association with the immunological response, but increased faculty of rheumatic subjects to produce incomplete antibody has already been established (Wagner and Rejholec, 1955; Padovcová, Rejholec, Suda, Wagner, Malý, 1956). Consequently, this immunological peculiarity of rheumatic subjects may also be put into relation with dietetic conditions. The effect of the egg factor upon allergy was experimentally demonstrated by Chang and French (1956) and upon anaphylactic arthritis by Coburn, Graham and Haninger (1954). The relationship of the scarcity of ascorbic acid and the genesis of rheumatic fever was pointed out by Long, (1954); Long (1955).

While planning the experimental research here, we did not have at our disposal any preparatory pioneer work from which to start. Thus, we were bound to range our investigations over a very wide front so as to embrace in our field of observation, as yet fairly unexplored, the largest possible number of associations of immunological reactivity with all sorts of environmental conditions. The intensity of this research would only

suffer from its extension. It was easily foreseeable that not a few of the characteristics we undertook to follow were bound to lead into blind alleys. We have succeeded in establishing true statistical significance of the association of immunological reactivity with no less than six different characteristics. Undoubtedly there may be many others. For four additional characteristics our results suggest the existence of such an association at least tentatively.

The greatest part of the investigated characteristics could be ascertained with all the precision which was called for, like age, weight, height, anthropometric features, descent, age of parents, number of brothers and sisters, crowding of the lodging, etc. The result of the serologic test was also very exact, owing to the centralised carryingout of investigations and elaboration of results. There were other characteristics in which the data gathered had to be taken with caution, for instance the family anamnesis of the boys: nearly 50 % of the boys had but the vaguest notion of the state of health of their parents. It may be pointed out that the six characteristics whose relationship with immunological reactivity was found to be statistically significant belong to the first category.

The characteristics which appeared to be the most appropriate for statistical evaluation were those by which the sample could be divided into two, or most three, group with a fairly regular distribution. This for instance was the case of indiscriminate salt adding, seasoning of meals, of the susceptibility to infectious colds, of shortage of eggs, etc. In respect of these characteristics we have arrived in fact at distinct conclusions. The other characteristics, namely those in which the distribution was very dispersed, did not show clear and convincing conclusions. For instance, the proportion of subjects coming from big cities was so small in our sample as to exclude statistical evaluation. Given a sample selected on other lines, belonging to different age groups, taken from yet other surroundings, further associations might very possibly be revealed which have remained hidden to us. Thus, it may be said that the observations reported here allow generalized conclusions

rather in the positive than the negative sense, that is rather in those characteristics whose association with the immune response could be demonstrated than in those whose association could not be proved.

The characteristics which, according to the results of our tests, can be considered as statistically associated with immunologic reactivity fall under two heads. The first is concerned with certain nutritional conditions and habits; here specially noteworthy is the habit of indiscriminate salt adding to meals, excessive seasoning of meals, excessive consumption of canned food and scarcity of eggs in food. Although our knowledge of these data was founded only on personal admissions, we felt that the simplicity of the matter in itself entitled us to evaluate the statistically. The same may be said for the second category of characteristics, protracted dwelling in lodgings with sanitary defects and the susceptibility to infections of the upper respiratory tract. As to the lastmentioned group, it may be pointed out that higher antibody titers were found as well in delicate boys prone to catching colds as in uncommonly hardened boys loving to bathe in the open in cold water. This apparent discrepancy may be partly explained by a too frequent exposure of the lastnamed subjects to chilling. Nevertheless, it seems that the separate factors whose relationship with the immunologic response was revealed or confirmed by our observations, may not be the sole agency responsible for the creation of a certain type of immunologic reactivity and that they may be only *contributing* factors. In fact, many of these characteristics were repeatedly observed to be present in hyper-reactive subjects *simultaneously*. Given this state of things, it is very difficult to decide which of these elements may be the causal factor, or whether only concomitance of several distinct elements is decisive for forming or changing types of immunological reactivity. Only observations carried out on substantially more material can give an answer to the question of complexity of external influences.

Several boys did not respond by elevated antibody titers although they had been exposed to the same agencies and, in

contrast, for several hyperreactors no previous exposure to these agencies could be established. This fact postulates existence of further factors which were not embraced by the scope of the present research; they may be either internal (genetic, hormonal, nervous) or external, either harmful or favourable (protective).

Reflections about the real nature of the ascertained association with increased production of incomplete antibody remain purely speculative. It is possible to offer an explanation of certain of them, for instance to try to explain the effect of exaggerated salt adding by the well-known theory of Selye. Similarly, the effect of frequent past infections might perhaps be looked upon as a misguided attempt of the system to adapt itself to agencies which are in mutual contradiction. The action of hygienically defective lodgings may be very complex too. To attempt to explain it exceeds the scope of the present study.

It would be undoubtedly premature to pronounce upon the nature of the relation of the findings reported here with the pathogenesis of rheumatic fever. Here we confine ourselves to pointing out that we were already able to demonstrate by the level of incomplete antibody that persons with a past history of rheumatic fever have an altered immunological reactivity (Wagner, Rejholec, 1955; Padovcová, Rejholec, Suda, Wagner, Malý, 1956). In a subsequent paper (Rejholec, 1957) it was shown that subjects in whom an increased disposition to produce incomplete antibody has been found, possess an increased propensity to become victims of rheumatic fever, and that the immunological reactivity of rheumatics is *not* a sequela of rheumatic fever. The need of further research in this field is self-evident.

SUMMARY

A group of 146 persons of average age 16 years was immunized by a single injection of the *Brucella abortus* vaccine, and the faculty of each of them to produce incomplete antibody was determined and graded. The whole sample was subjected to somatic, anamnestic, anthropometric and sociologically ex-

amination, and the results were compared with the grade of immunological reactivity in each individual.

The evaluation has shown that an increased faculty of producing incomplete antibody is encountered in subjects who for protracted periods had been lodged in unsanitary quarters, in those with a propensity for infections of the upper respiratory tract as a result of a cold, in those accustomed to indiscriminate adding of salt to their meals, in those frequently consuming tinned or strongly seasoned food, as well as in persons who during a longer period had suffered from scarcity of eggs in their food or who have an aversion to eggs. Several other characteristics were found whose association with immunological reactivity is at least suggested as possible by the statistics. The significance of these findings is discussed with reference to the pathogenesis or rheumatic fever.

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