

5162

The First Manifestation of the Developing Hypersensitiveness.

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The response of tuberculous guinea pigs to the treatment with egg white, if introduced into tuberculous lesions, differs in 2 important points from the response of normal animals.¹ 1. In tuberculous animals all manifestations of the immunization process (the sensitization and antibody production) develop in a largely increased measure. 2. There develops often a strong tuberculin type of skin sensitiveness to egg white, which we never observe in normal animals. This usually precedes the other manifestations of the sensitiveness and for a few days it might persist in pure form. A little later it is followed by the development of acute anaphylaxis, the anaphylactic type of skin sensitiveness, the protracted anaphylactic shock and the appearance of antibodies in the serum.

These characteristics of the immunity response of tuberculous animals suggested the possibility that the immunization process of normal animals also passes through a phase corresponding to the tuberculin sensitiveness, which is only slightly developed and has so far escaped attention. The tuberculin type of skin sensitiveness is possibly the strong development of this early stage of the immunization process. Observations support this supposition, namely, that the slight skin reactions in normal guinea pigs soon (5 to 7 days) after treatment are in many respects different from the usual anaphylactic type of skin reactions and more like very slight tuberculin reactions. They often appear delayed and although very slight, persist for 48 hours, in marked contrast to the quickly developing and transient reactions in passively sensitized guinea pigs. The recognition of marked differences in the microscopical structure between the tuberculin and anaphylactic type of skin reactions, described in the foregoing note, offered us a method of determining to which type the slight reactions belong, and of testing the place of the tuberculin sensitiveness in the whole immunization process.

We performed the following experiment. Two groups of guinea pigs (each group 4 animals) were injected intraperitoneally with 0.4 and 2 mg. egg white respectively. On the 5th, 6th, 7th and 8th day after treatment we cut out the skin tests produced with 0.2 mg.

¹ Dienes, L., and Schoenheit, E. W., *Am. Rev. Tuberc.*, 1929, **20**, 92; *J. Immunol.*, 1927, **14**, 9; 1928, **15**, 141, 153.

egg white, from one guinea pig in each group, 6 and 24 hours after the test injection. As controls we examined the skin tests of 3 non-treated guinea pigs. The skin reactions were very slight, consisting in a trace of redness and of swelling which after 24 hours was more pronounced than after 3 to 6 hours. The controls gave no reactions.

The results obtained were uniform; in the microscopical structure, the skin reactions were similar to the tuberculin reaction. A more or less intense infiltration with mononuclear cells occurred, which 6 hours after the injection was in several cases very pronounced around the blood vessels and was considerably increased in intensity in the 24 hour test. Leucocytes appeared only in moderate number. In the anaphylactic type of skin reactions in passively sensitized animals or after a longer period following the treatment, we find mainly an infiltration with polymorphonuclear leucocytes.

The experiments substantiated our supposition that in the immunization process the appearance of antibodies in the serum and the development of the usual type of hypersensitiveness is preceded by a stage similar in many respects to the tuberculin type of hypersensitiveness. The specific sensitiveness of the tissues in this first stage manifests itself in the accumulation of mononuclear cells at the site of injection with a relatively slight influence on the circulatory system. We do not want to express, at present, an opinion concerning the origin and nature of the cells taking part in the cellular reaction. It is very probable that the tuberculin type of skin sensitiveness is an exaggerated development of this first phase of the immunization process, under the increasing influence of the infection and it is hardly necessary to mention that the study of this first phase of the immunization process, which has so far escaped attention presents great interest in connection with the development of immunity in infectious diseases.