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Chemical Analogue Theory of Antibody Formation

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The Ehrlich-Jerne theory of antibody formation assumes that all the antibodies that a rabbit can form in response to the injection of an antigen are formed in small amounts by the rabbit prior to the first injection of the antigen, and that the antigen somehow enhances the rate of formation of the specific antibody with which it is able chemically to combine. There is, however, within the framework of this theory no acceptable model that would indicate how this enhancement might be accomplished by the antigen, nor are the ~~questions~~ phenomena of the nmamestic response satisfactorily explained on the basis of this theory. The nmamestic response is obtained subsequent to the first injection of an antigen if one allows several weeks to pass and then injects the same antigen a second time. Antibody then appears after a latent period which is one-third to one-half of the latent period that follows the first injection, and the rate of antibody formation following the second injection may be ten times higher than after the first injection.

The Ehrlich-Jerne theory seems to have some elements of truth in it but it contains - so I believe - only half of the truth. The purpose of this paper is to supply what I believe to be the missing half of the Ehrlich-Jerne theory. It should, therefore - if I am correct - enable us to understand the basic phenomena of antibody formation mentioned before, and permit us to predict the outcome of certain, hitherto not performed experiments.

Our theory assume, in principle, like the Ehrlich-Jerne theory does, that the cells of the lymphatic tissues of the rabbit that are at all capable of making an antibody contain a template which is specific for that antibody. The apparent absence of appreciable quantities of that antibody prior to the injection of the specific antigen is explained on the ground that the formation of the specific protein by the template is not elicited as Ehrlich and Jerne would say, or is repressed as I shall say. Upon the injection of an antigen that has a hapten which can specifically combine with the antibody, according to Ehrlich and Jerne, the formation of an antibody is elicited or, according to our theory, the suppression of the formation of the antibody is temporarily lifted. But here the similarity between the two theories ends. I do not assume that the antigen reaches the specific antibody-template complex - at least not in the adult rabbit - which can form antibodies. On the contrary, we assume that if the antigen can reach the antibody-template complex, as may be the case in the newborn rabbit (which cannot form antibody), the antigen combines irreversibly with a specific antibody-template complex, and this results in tolerance against that particular antigen.

The theory here presented is based on the assumption that some cells of the lymphatic system produce a great variety of enzymes, E_N, each of which catalyzes a step in biosynthesis leading to a compound, H_N. All of these compounds are of small molecular weight, and they resemble each other by having one part in common - the carrier, R - so that they are characterized by the remainder of the compound which is designated by H_N. The compound can thus be described by the symbol $H_N - R$. The enzyme, E_N catalyzes the reaction

The compound acts as a repressor for the formation of the antibody that can combine with a hapten, H, which is a chemical analogue of H_N.

For the sake of simplification of argument, we are assuming here that the antigen is composed of a non-antigenic protein coupled with a hapten H. Antigen = . If the hapten H is a chemical analogue of some group H_N contained in the repressor that is present, and if there is present a template which is capable of making the antibody that is specific for the hapten H, then the repressor will irreversibly combine with the antibody-template complex. This is indicated by the symbol

While the antibody-template complex is covered by the repressor in the manner indicated in the figure, the template forms no antibody, but when the antibody-template complex is free from the repressor, antibody is formed by the template at the maximum rate. If the concentration of the repressor is low enough, the antibody-template complex will be free most of the time.

In contradistinction to the antibody-template complex which - in the adult rabbit - can be reached by the antigen, a certain fraction of the enzyme-template complex can be reached by the antigen. When an antigen comprising a hapten H reaches an enzyme-template complex where the enzyme is specific for H_N, but which H is a chemical analogue, the antigen forms an irreversible combination with the enzyme-template complex. This is indicated by the symbol

We further assume that the antigen can reach all the enzyme, E_N, that is present in the cytoplasm at a time when the antigen is injected, and the antigen combines irreversibly with the enzyme, E_N, to form a complex

We assume that the repressor molecules are metabolized in the rabbit with the order of magnitude of about a day, and that the enzymes, E_N, have a half-life of several weeks.