A Modification of Jerne's Theory of Antibody Production using the Concept of Clonal Selection

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There are three current theoretical interpretations of antibody production which, following Talmage (1957), may be referred to as the direct template theory in which the antigen serves as a template against which the specific pattern of the antibody is synthesized, the indirect template theory which postulates a secondary template incorporated into the genetic-synthetic processes of the antibody producing cells (Burnet, 1956), and the natural selection theory in which the antigen acts essentially by selection for excess production of natural antibody molecules of corresponding type (Jerne, 1955).

The two latter theories were devised primarily to account for two sets of phenomena for which the direct template theory seems quite irrelevant. The first is the absence of immunological response to "self" constituents and the related phenomena of immunological tolerance; the second is the evidence that antibody production can continue in the absence of antigen. Some means for the recognition and differentiation of potentially antigenic components of the body from foreign organic material must be provided in any acceptable formulation. In Burnet and Fenner's (1949) account, a positive recognition of "self" material was ascribed to the presence of "self-markers" in all potentially antigenic macromolecules, and corresponding recognition units in the scavenger cells of the body. At the time it was regarded as inconceivable that a mechanism could exist which would recognise in positive fashion all foreign material and no attempt was made to devise one, despite the fact that we have always recognised the clumsy character of the self-marker, self-recognition scheme.

It is the great virtue of Jerne's hypothesis that it provides an approach to this alternative method of recognising self from not self. There is no doubt about the presence in all mammalian or avian sera of a wide range of reactive globulins which can legitimately be called "natural antibodies." Jerne assumed that amongst these globulin molecules were all the possible patterns needed for specific immunological type reaction with any antigen, except for those patterns corresponding to body antigens which would be eliminated by in vivo absorption. When a foreign antigen enters the blood it unites, according to Jerne's scheme, with one of the corresponding natural antibody molecules. The complex is taken up by a phagocytic cell in which the antigen plays no further part, but the antibody globulin provokes the

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production by the cell of a fresh crop of similar molecules which are liberated as antibody. If this basis is accepted, most immunological phenomena can be well described in terms of the theory. Its major objection is the absence of any precedent for, and the intrinsic unlikelihood of, the suggestion that a molecule of partially denatured antibody could stimulate a cell, into which it had been taken, to produce a series of replicas of the molecule.

Talmage (1957) has suggested that Jerne's view is basically an extension of Ehrlich's sidechain theory of antitoxin production and that it would be more satisfactory if the replicating elements essential to any such theory were cellular in character *ab initio* rather than extracellular protein which can replicate only when taken into an appropriate cell. Talmage does not elaborate this point of view but clearly accepts it as the best basis for the future development of antibody theory. He stresses the multiplicity of the globulin types that can be present in the blood and is profoundly sceptical of any approach which attempts to "unitarian" an interpretation of antibody. In his view properdin has as much right to be called an antibody as any other globulin.

Before receiving Talmage's review we had adopted virtually the same approach but had developed it from what might be called a "clonal" point of view. This is simply a recognition that the expendable cells of the body can be regarded as belonging to clones which have arisen as a result of somatic mutation or conceivably other inheritable changes. Each such clone will have some individual characteristic and in a special sense will be subject to an evolutionary process of selective survival within the internal environment of the body.

It is believed that the advantages of Jerne's theory can be retained and its difficulties overcome if the recognition of foreign pattern is ascribed to clones of lymphocytic cells and not to circulating natural antibody. The resulting formulation may be stated as follows:

The plasma-globulins comprise a wide variety of individually patterned molecules and probably several types of physically distinct structure. Amongst them are molecules with reactive sites which can correspond probably with varying degrees of precision to all, or virtually all, the antigenic determinants that occur in biological material other than that characteristic of the body itself. Each type of pattern is a specific product of a clone of mesenchymal cells and it is the essence of the hypothesis that each cell automatically has available on its surface representative reactive sites equivalent to those of the globulin they produce. For the sake of ease of exposition these cells will be referred to as lymphocytes, it being understood that other mesenchymal types may also be involved. Under appropriate conditions, cells of most clones can either liberate soluble antibody or give rise to descendant cells which can.

It is assumed that when an antigen enters the blood or tissue fluids it will attach to the surface of any lymphocyte carrying reactive sites which correspond to one of its antigenic determinants. The capacity of a circulating lymphocyte to pass to tissue sites and there to initiate proliferation is now relatively well established (cf. Gowens, 1957; Simonsen, 1957). It is postulated that when antigen-natural antibody contact takes place on the surface of a lymphocyte the cell is activated to settle in an appropriate tissue, spleen, lymph node or local inflammatory accumulation, and there undergo proliferation to produce a variety of descendants. In this way preferential proliferation will be initiated of all those clones whose reactive sites correspond to the antigenic determinants on the antigen used. The descendants will include plasmacytoid forms capable of active liberation of soluble antibody and lymphocytes which can fulfill the same func-

tions as the parental forms. The net result will be a change in the composition of the globulin molecule population to give an excess of molecules capable of reacting with the antigen, in other words the serum will now take on the qualities of specific antibody. The increase in the number of circulating lymphocytes of the clones concerned will also ensure that the response to a subsequent entry of the same antigen will be extensive and rapid, i.e. a secondary type immunological response will occur.

Such a point of view is basically an attempt to apply the concept of population genetics to the clones of mesenchymal cells within the body. It is clear that the internal environment involved is an exceedingly complex one and in all probability many factors will impinge on clones of antibody-producing cells from that environment. It is equally certain that inheritable changes (at the clonal level) will occur as a result of somatic mutation or of the still obscure processes responsible for differentiation during development of regeneration and repair.

It would be inappropriate to elaborate this view much further in a preliminary communication, but it should be immediately evident that it has highly relevant implications for the general function of the lymphocyte, for the fact that sensitization and homograft immunity reactions seem to be mediated by lymphocytes or other mesenchymal cells without liberation of classical antibody, and for recent findings of extremely rapid liberation of antibody from normal cells. A preliminary survey of a variety of pathological conditions which involve anomalous immune reactions also suggests that this cellular approach has greater relevance to the problems than any of the other hypotheses. These aspects will be elaborated in a more extensive contribution now in preparation.

One aspect, however, should be mentioned. The theory requires at some stage in early embryonic development a genetic process for which there is no available precedent. In some way we have to picture a "randomization" of the coding responsible for part of the specification of gamma globulin molecules, so that after several cell generations in early mesenchymal cells there are specifications in the genomes for virtually every variant that can exist as a gamma globulin molecule. This must then be followed by a phase in which the randomly developed specification is stabilized and transferred as such to descendant cells. At this stage, again following Jerne, any clones of cells which carry reactive sites corresponding to body determinants will be eliminated. The necrotic effect of the tuberculin on sensitived fibroblasts might be taken as a crude analogue of the process by which clones with unwanted reactivity can be eliminated in the late embryonic period with the concomitant development of immune tolerance.

The hypothesis has many of the same implications as the Burnet-Fenner and the Jerne theories. Its chief advantage over the former is its relevance to the nature of normal antibodies including the red cell isoagglutinins and the simpler interpretation of tolerance to potential antigens experienced in embryonic life. Its advantages over Jerne's theory are its capacity to cover homograft and related types of immunity as well as the production of classical antibody, and to eliminate the very unlikely assumption that entry of a globulin molecule into a cell will stimulate the cell to produce exact replicas of that globulin.

Despite the speculative character of much of the detail of this modification of Jerne's theory—which might be referred to as the "clonal selection hypothesis"—it has so many implications calling for experimental inquiry that it has been thought justifiable to submit this preliminary account for publication.