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The Generative Grammar of the Immune System

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Grammar is a science that is more than 2000 years old, whereas immunology has become a respectable part of biology only during the past hundred years. Though both sciences still face exasperating problems, this lecture attempts to establish an analogy between linguistics and immunology, between the descriptions of language and of the immune system. Let me first recall some of the essential elements of the immune system, with which I shall be concerned. In 1890, von Behring and Kitasato (*1*) were the first to discover antibody molecules in the blood serum of immunized animals and to demonstrate that these antibodies could neutralize diphtheria toxin and tetanus toxin. They also demonstrated the specificity (*2*) of antibodies: tetanus antitoxin cannot neutralize diphtheria toxin, and vice versa. During the first 30 years or more after these discoveries, most immunologists believed that all cells of our body are capable of producing antibodies, and it took until the 1950's before it became clear, and until 1960 before it was demonstrated (*3*), that only white blood cells, named lymphocytes, can produce antibodies. The total number of lymphocytes represents a little more than 1 percent of the body weight of an animal. Thus, it would not be wrong to say that our immune system is an organ consisting of about 10^{12} lymphocytes, and a mouse, which is 3000 times smaller than we are, has an immune system consisting of about 3×10^8 lymphocytes. This brief description of the immune system disregards the fact that lymphocytes interact with most other cells in the body, which in my definition do not belong to the immune system in a strict sense.

Let me draw attention to the fact that this number of lymphocytes in the immune system is at least one order of magnitude larger than the number of neurons in the nervous system. Also, we should note that lymphocytes travel among most other cells of our body, that they circulate in blood and lymph, and that they occur in large concentrations in spleen, lymph nodes, appendix, thymus, and bone marrow. Strangely enough, however, they seem to be excluded from the brain. The 1960's was a very fruitful decade of immunological discoveries, of which I shall name a few. In the beginning of the decade, the primary structure of antibody molecules was clarified (*4*); then followed the demonstration that the dictum of Burnet (*5*) was correct, namely that all antibody molecules synthesized by one given lymphocyte are identical;

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and finally, toward the end of that decade, lymphocytes were shown to fall into two classes, called T cells and B cells, existing in the body in almost equal numbers (*6*). Only B lymphocytes, or B cells, however, can produce and secrete antibody molecules (*7*), but they are subordinate to the T cells that can either enhance or suppress this capacity (*8*).

It turned out that antibody molecules of different specificity have different amino acid sequences in the amino-terminal regions of their polypeptide chains (*9*). It became obvious immediately that the great diversity of antibody molecules, the great number of different antigens that antibodies can recognize, or in other words the great repertoire of antibody specificities, must result from an enormous number of sequence varieties in these regions. This insight does not solve our problems, however. It is like saying that the great variety of words or sentences in a language results from the enormous number of varieties with respect to the sequences of letters or of phonemes.

I shall now turn to some remarkable discoveries, made during the past 25 years, showing that the variable regions of antibody molecules are themselves antigenic and invoke the production of anti-antibodies. Kunkel (*10*) showed that monoclonal myeloma antibodies, when injected into another animal, induce specific antibodies that recognize the particular myeloma antibodies used but do not recognize any other myeloma antibodies isolated from other myeloma patients. This work was extended by others, but mainly by Oudin and his colleagues in Paris, who showed that ordinary antibody molecules that arise in an immunized animal are antigenic and invoke the formation of specific anti-antibodies (*11*). In other words, the variable region of an antibody molecule constitutes not only its "combining site," but it also presents an antigenic profile (named its idiotype) against which anti-idiotypic antibodies can be induced in other animals. Moreover, it turned out that this antigenic, idiotopic profile of the variable region of a given antibody molecule is not a single site, but consists of several distinct sites against which a variety of different anti-idiotypic antibody molecules can be made (*12*). These individual sites are now named idiotopes, implying that the idiotype of one antibody molecule is a set of different immunogenic idiotopes. And finally, it has been shown that the immune system of a single animal, after producing specific antibodies to an antigen, continues to produce antibodies to the idiotopes of the antibodies that it has itself made. The latter anti-idiotopic antibodies likewise display new idiotypic profiles, and the immune system turns out to represent a network of idiotypic interactions (*13, 14*).

Now imagine an "immunizing" antibody molecule that acts as an antigen, displaying its combining site as well as its antigenic idiotopes. We can then envisage the stimulation of B cells of two different types. In the α case, the combining site of the receptor on a B cell recognizes an idiotope of the immunizing antibody, and the cell may be stimulated to produce the corresponding anti-idiotopic antibodies. In the β case, however, it is the combining site of the immunizing antibody which recognizes an idiotope of the receptor on a B cell that may thus be stimulated to produce antibodies with idiotopes having shapes similar to the epitopes displayed by the original antigen. Experiments have shown that both these situations actually do occur. For example, if the original antigen is insulin, and the immunizing antibody is an anti-insulin antibody, then some of the anti-idiotypic antibodies of the β types show a similarity to insulin and can even be shown to function like insulin (*15*). Similar results in other systems have been obtained by Cazenave and Roland (*16*), by Strosberg (*17*) and Urbain (*14*) and their colleagues, and by others.

The point I wish to make, however, is to consider whether the two situations α and β are fundamentally different or not. Is there a difference between saying that the anti-idiotypic antibody recognizes the immunizing antibody, or that the latter recognizes the first? Can we, at this three-dimensional molecular level, distinguish between "recognizing" and "being recognized"? If not, it becomes meaningless to distinguish between idiotopes and combining sites, and we could merely say that the variable region of an antibody molecule displays several equivalent combining sites, a set of idiotopes, and that every antibody molecule is multispecific. I do not have to belabor this point, which has been made repeatedly (*18, 19*). Instead, I should now like to introduce some numerology into this discussion. How large is the number of different antibodies that the immune system of one single animal (be it a human or a mouse) can make? This number, during the past few decades, has been estimated, on more or less slender evidence, to exceed 10 million, and this enormous diversity has been designated as the "repertoire" of the B lymphocytes. Such a "repertoire" has been characterized by Coutinho as "complete" (*19, 20*). "Completeness" means that the immune system can respond, by the formation of specific antibodies, to any molecule existing in the world, including molecules that the system has never before encountered.

Immunologists sometimes use words they have borrowed from linguistics, such as "immune response." Looking at languages, we find that all of them make do with a vocabulary of roughly a hundred thousand words, or less. These vocabulary sizes are a hundred times smaller than the estimates of the size of the antibody repertoire available to our immune system. But if we consider that the variable region that characterizes an antibody molecule is made up of two polypeptides, each about 100 amino acid residues long, and that its three-dimensional structure displays a set of several combining sites, we may find a more reasonable analogy between language and the immune system by regarding the variable region of a given antibody molecule not as a word but as a sentence or a phrase. The immense repertoire of the immune system then becomes a vocabulary comprised not of words but of sentences that is capable of responding to any sentence expressed by the multitude of antigens which the immune system may encounter.

At this point, I shall quote Noam Chomsky (*21*) concerning linguistics.

> The central fact to which any significant linguistic theory must address itself is this: a mature speaker can produce a new sentence of his language on the appropriate occasion, and other speakers can understand it immediately, though it is equally new to them . . . . Grammar is a device that specifies the infinite set of well-formed sentences and assigns to each of these one or more structural descriptions. Perhaps we should call such a device a *generative grammar* . . . which should, ideally, contain a central syntactic component . . . , a phonological component and a semantic component.

For the size of the set of possible sentences in a language, Chomsky uses the term "open-endedness," and I now think that "open-ended" is the best description also of the "completeness" of the antibody repertoire. As for the components of a generative grammar that Chomsky mentions, we could with some imagination equate these with various features of protein structures. Every amino acid sequence is a polypeptide chain, but not every sequence will produce a well-folded stable protein molecule with acceptable shapes, hydrophobicity, electrostatics, and so forth. Some grammatical rules would seem to be re-

quired. It is harder, however, to find an analogy to semantics: does the immune system distinguish between meaningful and meaningless antigens? It would seem, at first sight, that the immune response to a sentence presented by an invading protein molecule is merely to select, from among its enormous preformed antibody repertoire, a suitable mirror image of part of this antigenic sentence.

I should perhaps explain that the sentences representing antibodies possess partial mirror images of an antigenic sentence. These antibodies are not echoes of the invading antigen but were already available to the animal in its repertoire of B cells before the antigen arrived. This is the important insight that followed the introduction into immunology of the selective theories in the 1950's. Also, I must emphasize another important quantitative aspect of the situation facing the immune system. It has been estimated that one human individual produces about 10,000 different proteins, such as enzymes, hormones, cell surface proteins, and the like. At the same time, we estimate that the immune system maintains a repertoire exceeding ten million different proteins, namely antibody molecules. This is a thousand times more than all other body proteins taken together.

I should therefore like to conclude that, in its dynamic state, our immune system is mainly self-centered, generating anti-idiotypic antibodies to its own antibodies, which constitute the overwhelming majority of antigens present in the body. The system also somehow maintains a precarious equilibrium with the other normal self-constituents of our body, while reacting vigorously to invasions into our body of foreign particles, proteins, viruses, or bacteria, which incidentally disturb the dynamic harmony of the system.

The inheritable "deep structure" of the immune system is now known: certain chromosomes of all vertebrate animals contain DNA segments that encode the variable regions of antibody polypeptides. Furthermore, experiments in recent years have demonstrated the generative capacities of this innate system. In proliferating B lymphocytes, these DNA segments are the targets for somatic mutations, which result in the formation of antibody-variable regions that differ in amino acid sequences, from those encoded by the stem cell from which these B cells have arisen (*22*). The experiments showed that it was still possible, however, to identify the original stem-cell genes that must have undergone these mutations. Expressed in linguistic terms, such investigations belong to the etymology of the immune system.

As immunologists, we should like to know the semantics of the inheritable gene structures. What is the meaning of the basic lexicon, or what are the specificities of the antibodies, B-cell receptors, and T-cell receptors as encoded in the genes of our germ cells? It is known that B cells recognize the language of the T-cell receptors. I have said nothing about the latter because T-cell receptorology is still in too early a stage of development. An immune system of enormous complexity is present in all vertebrate animals. When we place a population of lymphocytes from such an animal in appropriate tissue culture fluid, and when we add an antigen, the lymphocytes will produce specific antibody molecules in the absence of any nerve cells (*23*). I find it astonishing that the immune system embodies a degree of complexity that suggests some more or less superficial, though striking, analogies with human language and that this cognitive system has evolved and functions without the assistance of the brain.

It seems a miracle that young children easily learn the language of any environment into which they are born. The generative approach to grammar, pioneered by Chomsky (*24*), argues that this is only explicable if certain deep, universal features of this competence are innate characteristics of the human brain. Biologically speaking, this hypothesis of an inheritable capability to learn any language means that it must somehow be encoded in the DNA of our chromosomes. Should this hypothesis one day be verified, then linguistics would become a branch of biology.

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