MEDICAL PRACTICE

Clinical Problems

Myeloma Workshop

Under the auspices of the Leukaemia Research Fund a "Myeloma Workshop" was held at the Royal Postgraduate Medical School in London on 24 and 25 March 1971. The Chairmen for the two sessions were respectively Professor Jan Waldenström and Professor J. V. Dacie, F.R.S. Below we print versions of most of the papers presented at the workshop. These have been prepared from the speakers' original scripts or abstracts of their papers supplied by them.

A Model for the Development of Immunocyte Monoclones**J. F. HEREMANS**

I want to start this contribution by considering the probability of antibody activity occurring in randomly chosen immunoglobulins. If we make a number of assumptions about the antigen-binding sites of immunoglobulin molecules we can construct a probability curve which allows two predictions. Firstly, that any Ig molecule—for example, myeloma globulin—has a chance of slightly less than 1 in 2 of engaging in a reversible antibody-like association with any given test substance chosen as the "antigen." Secondly, that any affinity of the antibody for the substance is likely to be moderate. Furthermore, antigens of simple structure ("easy antigens," such as phosphorylcholine, dinitrophenol) are more likely to fit randomly chosen Ig molecules than are stereochemically highly differentiated structures ("difficult antigens").

In considering the initiation of the immune response we may make a further three assumptions. Firstly, that each type of immunoglobulin is the product of a separate clone of cells; secondly, that a clone of cells producing antibody is formed when the antigen reacts with antibody-like receptors on the surface of a resting immunocyte. Thirdly, that the rate of proliferation of a given clone increases as the affinity of these receptors is increased, because stimulation is proportional to the firmness of binding. Using the probability curve, we see that the initial response to an antigen will be polyclonal and will involve mainly cells producing antibodies of moderate

affinity. Low-affinity cells will not be stimulated sufficiently, whereas there will be too few high-affinity cells to make a noticeable contribution to the total amount of antibody. Provided antigenic stimulation is continued, selection will occur in favour of the antibody producers of the high-affinity classes. This is because the latter are more actively stimulated to proliferate and also because high-affinity antibody present in the circulation will compete with the low-affinity receptors of the cells producing weak antibodies so that these cells will no longer be adequately stimulated. Hence, given enough time, a single clone of cells—the one producing the best-fitting antibody—will overcome all its competitors and become the sole producer of what is now a monoclonal antibody. Nevertheless, when there is more than one antigenic determinant the outcome will be an antibody pattern of "restricted heterogeneity" rather than a single monoclonal band.

Restricted Heterogeneity

The time required to achieve the "monoclonal limit" will be shortened if competition is restricted to a few clones. This may be the explanation of the restricted heterogeneity patterns of the serum immunoglobulins observed in the following states: immunological deficiency; immunologically incompetent patients who are treated with limited number of foreign lymphoid cells; and in the cerebrospinal fluid of patients with chronic infectious or autoimmune disorders of the central nervous system (since the brain is poor in lymphoid cells).

If it is assumed, firstly, that oncogenesis is a loss of control mechanisms governing cell division which occurs in several stages; secondly, that the risk of oncogenesis is related to the proliferative activity of the type of cells involved; and, thirdly, that antigen has an affinity for immunocytes which produce immunoglobulins with potential antibody affinity, then there is a simple explanation for the observed high incidence of myeloma proteins with antibody affinity to antigens from the internal or external environment. The proposed mechanisms may also explain why lymphoma so frequently occurs in immunological deficiency diseases.

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