



Some Perspectives on Immunosuppressive Drugs

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My coming here to Richmond to discuss immunosuppressive drugs is surely carrying coals to Newcastle, because the Medical College of Virginia has been a leader in this field, particularly with reference to transplantation of the kidney. I don't know what I can tell you that you already don't know about immunosuppression; nevertheless, you might be interested in learning of our own experience with these drugs.

The four main classes of cytotoxic drugs of interest to the immunologist are the *alkylating agents* such as nitrogen mustard and cyclophosphamide, *purine antagonists* (6-mercaptopurine and azathioprine), the *pyrimidine antagonists* such as 5-fluorouracil, and finally the extremely interesting and potentially versatile agent methotrexate, a *folic acid analog*. Our laboratory has chosen to focus its attention on a single class of these compounds, the purine antagonists, in an attempt to find out as much about their immunological properties as we can. I plan to discuss two aspects of this work: 1) Some of the effects of 6-mercaptopurine (6-MP) in experimental animals, and 2) some of the effects of its analogue, azathioprine, in man.

Purine Antagonists

6-Mercaptopurine, a rather simple analogue of hypoxanthine, has

very powerful effects on cellular metabolism. Azathioprine was synthesized with the hope that it would have a higher therapeutic index than the parent compound. Its imidazol ring was attached to the sulfur atom in the expectation that this would slow down the metabolic degradation of 6-MP. Azathioprine does in fact appear to have a higher therapeutic index when compared to 6-MP in mice, but this has not yet been established in man.

6-Mercaptopurine has two major immunological properties that can be demonstrated in experimental animals. The first of these is suppression of humoral antibody synthesis. Animals given only a one-week course of 6-MP fail to elaborate a normal primary immune response. The second major effect of this material is on transplantation immunity; a significant prolongation of homograft survival can be obtained in a variety of animals treated with 6-MP.

One of the fundamental problems in this field, in fact the problem which I believe to be central to rational and successful immunosuppressive drug therapy, is that despite the very specific biochemical sites of action of various antimetabolites, the final result in an organized cell is its death. Regardless how specific the biochemical effect of an antimetabolite may be, the end result is disintegration of the metabolic cycles of the cell. Therefore, the central question is

whether any specific immunological effects can be obtained by the use of materials which are really cell poisons. In my view, it is worthless to pursue a generalized destruction of the immune capability of an individual in order to achieve immunosuppression, whether in the treatment of an immunological disease or in the establishment of a functioning tissue graft. We would be trading a possible clinical effect for an immunological cripple.

Immunological Effects of Cytotoxic Drugs

Quite surprisingly, specific immunological effects can in fact be obtained by cytotoxic drugs. Depending upon the experimental design, it is possible to delete a specific immunological reactivity without affecting an immune response to a randomly selected antigen. Such an animal is not an immunological cripple. It has acquired immunological tolerance of an antigen used during the period of chemotherapy. If this can be obtained in an experimental animal, there is every reason to believe that it can be also achieved in man.

One other effect of 6-mercaptopurine, and probably of other agents, which is of considerable importance in attempting to assess the reason for their clinical effectiveness, is illustrated by experi-

ments on suppression of the Arthus reaction in hyperimmunized rabbits. In these animals the peripheral expression of immune injury has been eliminated without an effect on the synthesis of antibody. Or, to put it differently, 6-MP has, in addition to its capacity to suppress antibody synthesis, a very potent anti-inflammatory effect. This will be seen time and again in clinical material.

Mechanism of Action of Cytotoxic Drugs

The mechanism of action of these drugs in patients with diseases presumed to be on an immunological basis is far from clear. Some of the questions we have posed include: 1) Does immunosuppression in fact occur in patients treated with these agents? 2) Can selective immunosuppression be achieved in man? 3) Is there any correlation between the degree of immunosuppression achieved with these agents and the clinical response? In order to gain some insight into these questions, the immune responses of a group of patients treated with either azathioprine or amethopterin were measured. Keyhole limpet hemocyanin (KLH), a powerful antigen long used in experimental animals, but never before applied to the study of human immunity, was used to evaluate the primary response. In normal subjects it provokes both a circulating antibody response and classical delayed hypersensitivity. Diphtheria toxoid was used to study the secondary response. In about a third of the patients, both primary and secondary immune responses were completely ablated during chemotherapy. In another third of the patients the primary immune response was completely suppressed, but a relatively normal secondary immune response occurred. Another third of the patients had a most interesting type of immune response while on continuous or

even intermittent drug therapy. This can be called the "accordion" effect. When compared to the normal immune response, the induction period is greatly prolonged. However, once antibody synthesis occurs, there is a very rapid burst of antibody formation. This occurs even while the patient is on continuous immunosuppressive drug treatment.

One of the interesting observations that came out of this study was the effect of these drugs on two classes of immunoglobulins, IgM and IgG. In two-thirds of the patients on immunosuppressive drug therapy a greatly prolonged, but quantitatively normal IgM response occurred in the absence of any detectable IgG antibody synthesis. Thus, an apparently selective suppression of one molecular class of antibody may be obtained with both azathioprine and methotrexate in man.

Clinical Results

The question whether continuous immunosuppression is required to maintain a clinical remission in patients with immunological diseases probably has a negative answer in light of the "accordion" effect mentioned previously. This is another reason for believing that treatment with the currently available immunosuppressive drugs need be pushed to the point of destruction of all immune capabilities of the patient.

The third question, is there any correlation between the degree of immunosuppression and the actual clinical result, is extremely difficult to answer. In many patients there is no such correlation. Extensive depression of immunity does not indicate that a patient will respond clinically. Furthermore, some patients with a minimum or no immunosuppression have dramatic improvements. We believe that many of the effects of antimetabolites we have seen in man may be due to their important, but poorly

understood, anti-inflammatory actions.

Conclusion

In conclusion, the antimetabolites have proven extremely interesting in the laboratory for the exploration of the mechanism of antibody synthesis and related problems. They have also proven to be extremely useful and interesting materials in the clinic. Whether they are going to *replace* any other standard forms of therapy, such as the corticosteroids, is, in my view, doubtful. Their use at the moment is experimental and their ultimate place in clinical medicine is by no means settled. They appear to have two important effects in man: 1) Suppression of antibody formation which can be, in many individuals, selective; and 2) Very important anti-inflammatory properties which may account for their effects on immune injury and for some of the very rapid responses seen in individuals treated with these agents.