The Defence Mechanism on Malignant Disease

R.D. Hunter B.Sc.

Abstract
From a dissertation read before the Society on November 6th, 1968.
The original suggestion implicating immunological factors in the natural history of malignant disease has been ascribed to Paul Ehrlich (1). Confirmation of this concept has waited fifty years for developments in knowledge and technique but its application allows not only some understanding of observed phenomena, but speculation on a rational approach to treatment and on a scientific establishment of the aetiological factors involved.

Traditional teaching defines this group of conditions by the type of tissue change involved, the degree of differentiation and extent of spread. From these a prognosis is assessed and the clinical picture tends to be one of steady progression, interrupted by therapeutic endeavour, but culminating in the death of the patient. Variations on this picture are seen in clinical practice.
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CLINICAL PHENOMENA

Everson(2) has collected a series of 130 fully documented cases in which unequivocal regression of the neoplasm was observed in spite of no effective treatment. Histologically proved metastases have been seen to regress after treatment of the primary lesion (3), and metastatic deposits from breast neoplasms often recur many years after treatment of the primary lesion (4).

Considering the opposite end of the spectrum, transplantation of tissue containing neoplastic cells in the face of immunological suppression has resulted in the rapid proliferation of the neoplasm within the new host (6, 7) and apparent reversal of this phenomenon has been seen when the suppression was discontinued(8).

These examples, implicating immunological reactions between the host mechanism and the neoplastic cell, imply some alteration in the antigenicity of the neoplastic cells. Specific tolerance, by the host, of its own tissue antigens is a very well substantiated thesis(9) and the absence of them has been demonstrated for a variety of neoplastic tissues(1). Evidence for the development of new antigens has been sought for in investigations examining both specific effector mechanisms of the immunological system; humoral antibody and the immunologically competent cells(11).

In human disease there are examples of the detection of specific antibody to neoplastic cells(10) and of the qualitative relationship between them and the extent of the disease process(11). A strong case has been made on the basis of animal experiments, implicating humoral antibody in the natural history of neoplasia(12) but the cellular nature of the infiltration, when viewed in the light of the lack of role for antibody in the homograft reaction(13), and recent concepts of the possible role for humoral antibody in the consequences of cell death(14) makes any interpretation of the results impossible at present.
ANIMAL EXPERIMENTS

Unfortunately the function of the immunologically competent cells has proved more difficult to study and no reliable direct test of this mechanism has become available. The method which has given rise to the breakthrough in this field has been the transplantation of neoplasms between members of allogeneic strains of animals. Their genetic similarity allows tissue to be transplanted from one to another within the strain with impunity, but Foley (15) demonstrated that a carcinogen induced neoplasm would be rejected if the animal had previously been exposed to the same neoplasm. This rejection was shown to be a function of sensitized lymphocytes (16), thus conforming to the criteria for a homograft reaction, i.e. different antigens must have been present. The work has been confirmed with different animals and different carcinogens (17, 18) with the additional demonstration of the antigenic independence of each individual neoplasm.

Repetition of this work with viral induced neoplasms in animals has allowed the demonstration of tumour specific antigens (19) as before but a very significant difference became apparent when the new antigenicity was shown to be identical in all the neoplasms induced by the same group of viruses (20) and different when various groups were contrasted (21).

In view of the artificial method of neoplasm induction used in these experiments the results might be viewed with some suspicion but the demonstration of this rejection phenomenon in a spontaneous tumour arising in an allogeneic strain of animals (21) and in recent sophisticated experiments involving human neoplasms (23) makes the acceptance of the general concept much easier.

IMPLICATIONS ON EARLY NEOPLASM GROWTH

While the reality of neoplasm specific antigens accords with experimental results and explains clinical phenomena, the presence within an immunologically mature individual of a viable antigenically distinct clone of cells demands some explanation. The dose of antigenic neoplastic cells necessary to stimulate graft rejection is critical and overwhelming by large implants (24) has its corollary in infectious disease. However the viability of a minute implant of antigenic neoplastic cells (25) and the possibility that neoplasms are the descendants of a single mutant cell (26, 27) complicates the picture.

The lack of association between antigenic change and malignant change, as evidenced by the carcinogen experiments (17), suggests that loss of cell specific antigenicity may not be a universal concomitant of malignant transformation. The antigenic change may be small and not provide the necessary stimulus to summate in a homograft reaction (13) or produce physiologically poor antigenic groupings (1).

It has also been pointed out that serum infusions may stimulate neoplasm growth and the possibility that antigen expression may be prevented by blockage of the sites must be entertained (28).

Looking to the defence side, the possibility of poor immunological competence in patients with neoplastic disease has been considered but, using the present rather crude methods, no defect has been found in patients with early neoplastic disease (5) defects only appearing as the disease progresses (29).

The growth of antigenically distinct cells in the face of apparently good immunological function remains, at present, unexplained but it seems probable that it is a manifestation of a multifactorial system invoking many of the above factors, and others as yet undiscovered, in different proportions under different circumstances.

CLINICAL CONSEQUENCES

1. Theoretical

One consequence of these findings has been the concept of Immunological Surveillance (26) in which the antigenically distinct mutant cell is picked out and destroyed by the immunological mechanisms. Indirect evidence suggesting that this should be seriously considered comes from the recent reports of the appearance of reticulooses quite out of proportion to the expected incidence, in patients on continuous immunological suppression (30, 31). It has also been pointed out that the incidence of neoplastic disease rises as immunological function falls in old age (26).

This exciting concept may not stand the test of time but it seems likely that with the realisation of the ability of one challenge to
influence general immunological responses for some time(32) and a better understanding of the phenomenon of specific tolerance(3) host factors may find some place in the explanation of the successful growth of the early neoplasm.

2. Treatment

A logical consequence of these results has been the suggestion that immunological methods might be used in the treatment of malignant disease. Infusions of splenic tissue (33) and sensitized lymphocytes(34) have been tried in terminal patients with some apparent success. This is an interesting phenomenon but the lack of overt impairment of the immunological response in patients with early neoplasia(5) militates against such an approach being of any help when curative procedures are being considered. There are also dangers of the selection of non-antigenic mutants, antibody blockage of antigen sites, and the induction of tolerance, all of which have been seen in the experimental model(28), and which call for a better understanding before methods of specific response stimulation can be used in man. Further developments are to be expected as the specific nature of the response of the immunological system when contrasted with the systemic administration of a drug makes this the theoretical method of choice.

Preventive procedures also call for some attention. Immunosuppression is the accepted treatment of the rejection of human homografts but the recent appearance of neoplasia (30, 31) soon after the onset of treatment, in what is a young population, must give rise to concern. Advances in tissue typing should soon eliminate the necessity for this approach but it must be remembered that the therapeutic arsenal of malignant disease contains many immunosuppressive agents(35). One of these, 6-mercapto-purine has been shown to cause tolerance induction to neoplastic antigens(36) and, in therapeutic doses, to convert a tumour rejection reaction into acceptance with consequent death of the animal(37). The relative importance of the immunosuppressive effect and the therapeutic effect is probably weighted heavily in favour of the latter but this should not allow the former effect to be ignored.

3. Aetiology

One final aspect of neoplasia which has been influenced by the study of antigens on neoplastic cells has been the consideration of the aetiologic factors in human disease. With the difference between the neoplasm specific antigens following carcinogen induction and the group specific antigens seen after viral induction in mind one group of workers, led by Kleine(12), have studied the human disease process in which the possibility of a viral aetiology has been most entertained — Burkitt's Lymphoma. Their results showed cross-reactivity between the cellular antigens of different patients. Interpretation has been complicated by the demonstration of the presence of three different viruses in lymphoma tissue(38), the recognition of the parasitism of neoplastic tissue by viruses, and the implication of one of the viruses in a common benign lymphoreticular disease(39) but the methods involved may lead to a breakthrough in knowledge when these phenomena are better understood.

CONCLUSION

It would be foolish to claim that the demonstration of neoplastic cell antigenicity has contributed significantly to the treatment of human disease to date but, apart from offering tremendous hope of advance in the near future, it allows consideration of the problem, not as a one-sided invasion, but as a dynamic situation in which host mechanisms may be playing a significant part.

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