of primary sarcomas in rats if the amount of residual tumour was small.¹¹ A similar phenomenon also occurs with some murine leukaemias, but again a detectable therapeutic effect can be observed only if there are few malignant cells. Possibly the local node draining a tumour becomes impaired by the massive quantity of antigen flowing into it and no longer discharges cytotoxic immunoblasts.⁸ This defect is local; by autoimmunization other nodes are stimulated and they release immunoblasts into the circulation, which are then able to attack the tumour. Whether this is the correct explanation or not, autoimmunization with irradiated tumour cells is effective in experimental animals in increasing their reaction to the tumour.

Non-specific Stimulation of the Immune System

The pioneering studies of Halpern and his associates showed that some unidentified components of Gram-negative organisms increase the resistance of animals against infection with bacteria and against increased resistance to a challenge with tumour cells. The best agents appear to be living B.C.G. or killed *Corynebacterium parvum*. Mathé showed in mice that these stimulants of the reticuloendothelial system are not only prophylactic (in other words, pretreatment with them increases resistance to a subsequent challenge) but that they can be used therapeutically in helping the host to eliminate a few tumour cells.¹² We and others have confirmed these observations and a combination of treatment with B.C.G. and irradiated cells appears to act synergistically in some murine lymphomas.

We are testing the hypothesis that sometimes enough cytophilic antibody is formed but the capacity of the animal to reject tumour is limited by too few suitable macrophages. Non-specific stimulation by B.C.G. may increase the number of such macrophages. Tumours at or near the skin have been shown to disappear if inflammation is induced in the vicinity of the tumour. This was first observed by Gorer, who found that following infection such tumours sometimes disappeared.⁶ In man cutaneous melanomas respond to vaccinia

and basal cell carcinomas to painting with dichloronitrobenzene. All such procedures will bring macrophages into the vicinity of the tumour.

Conclusions

In carefully manipulated experiments various immunological procedures have a definite antitumour action, but it is quite premature to speak of clinical immunotherapy. With the exception of one study by Mathé there is no evidence that immunological procedures are useful in controlling malignant disease in man.

Since all the available cancer chemotherapeutic agents are immunosuppressive, it has been suggested that chemotherapy may be harmful. This I believe to be nonsense; so long as there is massive disease immunity can play no part. The first essential before immunological factors have the slightest chance of being effective is to reduce the amount of tumour present. If it were possible to achieve extensive cyto-reduction without immunosuppression obviously this would be the procedure of choice. However, even with the presently available agents it is much more important to kill tumour cells than to restrict chemotherapy in an attempt to preserve the immune system, especially since once the drugs have been withdrawn or reduced immune reactivity quickly returns.

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Immunotherapy of Cancer

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The questions we have to consider in this session may be stated as follows: "In so far as tumours possess associated antigens which are capable of evoking an immunological reaction in the patient or animal in which the tumour originated, can this be turned to therapeutic advantage, and if so, how?"

As a preliminary it is clearly important to consider how such tumours manage to survive at all. Fortunately Professor Klein has already dealt with this question very thoroughly, so I will content myself with one comment. The list of possible "escape mechanisms" which he proposed is not very different from lists put forward several years ago.^{1,2} What has changed, thanks largely to the work of Klein himself, and some of his former associates like the Hellströms and the Möllers, is that we are today very much better equipped than we were to determine what particular escape mechanisms are operating in given animal models and even, to some extent, in individual patients.

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Possible Immunotherapeutic Procedures

The list of possible immunotherapeutic procedures one might consider has also not changed very much over the past few years. In an Almroth Wright lecture in 1964,¹ for example, I suggested that tumours which possessed specific antigens but had somehow escaped from control might be attacked by measures designed to intensify the host reaction, by passive immunization with antiserum, or by adoptive immunization with lymphoid cells from normal isogeneic donors or immunized donors of any strain or species. I went on to suggest that while, if a tumour lacked specific antigen, an attack could not be directed in the same way, it might perhaps be directed in a non-immunological way by concentrating the agent (antibody or cells) in the tumour, or by preliminary subsidiary procedures designed to make the tumour more susceptible than normal tissues to immunological attack. Alternatively, the immunological procedure might be nondirected (that is, might damage

tumour and host indiscriminately) but might be followed by some other type of directed attack.

The list of suggestions relating to tumours with specific, or as we should now say, associated antigens, can now be filled out a little. Following the work of Professor Alexander and his colleagues one should, for example, add injection of RNA extracted from immune lymphoid cells—but in general, with a little juggling, the procedures which have been enumerated by Professor Mathé can be fitted quite well into this framework.

Here again, however, while the list of theoretical possibilities remains much the same, considerable advances have been made, and we are in a much better position today than we were even a few years ago to choose the right strategy in planning experiments and even to some extent in treating patients.

Stimulating Immunological Defences

Serendipity operates in this as in other branches of medicine and, as I have argued elsewhere,³ possibly immunotherapeutic procedures have sometimes been employed inadvertently. The administration of Coley's fluid to patients with malignant lymphomas and bone sarcomas is a possible example. More recently the use of simple mastectomy followed later by radiotherapy in the treatment of breast cancer, which as all the world knows we owe to Professor McWhirter, may conceivably stimulate immunological defences against residual tumour cells. The same applies also to the use of preliminary high-dose radiotherapy in the treatment of osteosarcoma. This was introduced by Sir Stanford Code with the object of sparing the patient a mutilating operation that would have no chance of curing him if the tumour had already become disseminated, but the results suggest—though they certainly do not prove—that this method of treatment actually carries a slightly better prospect of curing this dreadful disease. It is only fair to add that the suggestion is mine;³ Sir Stanford and his colleague Mr. E. S. Lee, with exemplary caution, have refrained from making any such claim.

It is widely believed that immunotherapy, if it is to be of any value in cancer, should be used when the bulk of the tumour has been removed surgically, or destroyed by other means such as irradiation or chemotherapy, and the patient

(unless he has in fact been cured) has what I have called *minimal residual cancer*.⁴ Dr. Hamilton Fairley expressed this view yesterday and it is certainly supported by the work of Professor Mathé. As Professor Buttle pointed out in yesterday's discussion, however, if the augmented host resistance which appears to be concerned in the disappearance of Burkitt's tumours of maxi proportions following what one can only describe as mini-chemotherapy is immunological in nature, then in this respect (as, one might add in so many others) this tumour is exceptional.

If immunotherapy is to be used in patients with minimal residual cancer it is of paramount importance that the procedure should, at least, do no harm. Dr. Hamilton Fairley, in discussing his work on melanoma, told us he had found no evidence to suggest that the treatment used might stimulate the production of blocking antibody—and in consequence enhance the growth of the tumour—but this is still in my view a possibility to be seriously considered in every proposed clinical trial. When, several years ago, Boak and I⁵ found that the growth of intrastrain transplants of a mouse mammary carcinoma could be inhibited by treating the recipient by injection of killed cultures of *Corynebacterium parvum* we considered using this agent as an addition to standard procedures in the treatment of early human breast cancer. But the fear of producing enhancement held us back, and it is now proposed that the first clinical trials with *C. parvum* should be in patients with tumours carrying a much worse prognosis. Moreover, in my view, trials of this and other forms of immunotherapy should no longer be planned on a purely empirical basis. As I have already reminded you, the way is now becoming open to us to define the immunological defect operating in individual patients, and we should plan our attack accordingly. Of course, the immunological situation may change during the course of treatment, but this does not obviate the need for planning; rather, it imposes on us the task of continued reassessment and a readiness to change our protocol as the need arises.

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Immunological Treatment of Leukaemias

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Immunotherapy is the most recently introduced method for treating leukaemia, and probably it can be greatly developed during the next few years. Depending on whether antibodies or immunocompetent cells (lymphocytes) are administered or whether the body's own immune defences are stimulated, immunotherapy is called, respectively, passive, adoptive, or active.

Passive Immunotherapy

So far, valid trials of passive immunotherapy have not been made in man. For such trials to be acceptable cytotoxic

antibodies would have to be separated from the antibodies which "enhance" tumour growth, and then given alone. In patients with choriocarcinoma we have shown that enhancement antibodies do exist in man,^{1,2} and these could enhance the proliferation of neoplastic cells. From the results of studies at present being carried out in our laboratory,³ we hope that passive immunotherapy may eventually be used as a method of destroying tumour cells.

Adoptive Immunotherapy

Adoptive immunotherapy is based on the antitumour effect of the graft-versus-host reaction. We have shown this antitumour effect in studies on mice carrying the L 1210 grafted

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