ISO-TOLERANCE—A HYPOTHESIS*

A. LEVER, M.B., B.CH. (RAND), *Krugersdorp, Transvaal*

During a course of postgraduate study 2 years ago, a certain line of thought became evident to me, which I wish to present below. As I am not a research worker, no new experimental findings are offered. It is my hope that this discussion will stimulate further work in the field involved.

Since the days of Koch and Pasteur, medical science has developed the concept that the body is able to protect itself by the recognition of alien antigens and to dispose of them by various means, e.g. the formation of antibodies and the development of immunity. To suggest that the body can tolerate foreign antigenic material may at first appear to contradict our basic concepts. Natural tolerance has been described in chimaeras and in experimental conditions as shown by Howard and Mitchie in 1962.[1] They found that small doses of spleen cells, irradiated to prevent multiplication, would elicit immunity. If the dose was increased, the recipient became tolerant.

The purpose of this hypothesis is to suggest that nature itself has breached the immunological barrier in 2 conditions that have as yet not been defined as states of immunological tolerance, viz. pregnancy and malignancy.

PREGNANCY

With conception a new organism that is somatically antigenically different is harboured within the body. A reaction similar to a homograft reaction should logically occur, as the foetus is antigenic.[2] A skin graft between any random male and female would not normally be tolerated, and yet this alien antigenic mass of conception is usually successfully tolerated. One is immediately confronted with the present-day concept of anatomical and physiological separate circulations and it has been put to me that no phagocytic contact takes place. Chorionic villi, lying in maternal blood lakes, are exposed to millions of lymphocytes in a vigorous circulation, and would appear to be eminently antigenic. Woodruff has postulated that the placenta is an anatomical barrier,[3] but if that were so the ABO- and Rh-reactions would not occur.

Cauchi[4] points out that evidence is accumulating to indicate that the passage of cells from mother to foetus is probably a common event. Maternal red cells have been found in the foetus, and massive amounts of blood may be transfused in cases of neonatal plethora; and maternal white blood corpuscles labelled with quinacrine have been found in the foetus. Cancer cells present in the maternal blood have, on occasion, become established in the foetus.[5] Kadowaki *et al.*[6] have described a case in which they postulated that an infant had received a dose of maternal lymphoid cells across the placenta, and was unable, because of immunological incompetence, to get rid of this unwanted homograft. Epstein[7] reported that the normal foetus is capable of immune reaction against micro-organisms, and at birth the cord blood contains antigens of foetal origin.

To explain why maternal rejection of the foetus does not normally occur, it is my hypothesis that a state of iso-tolerance is established by the foetus, and that it is produced by a specific factor, which I shall call the iso-tolerance producing factor (ITPF). This factor would affect the mother and the foetus and could explain why the foetus is immunologically incompetent until shortly after birth. The possible mode of function of ITPF could be: (*a*) depression of the level of antibody formation, (*b*) inhibition of antibody formation, or (*c*) reaction and neutralization of formed antibodies. ITPF could possibly be similar to hydrocortisone, and be produced initially by the trophoblast. It is interesting to note that the foetal adrenal cortex has a histological structure different from the adult one, and that its function is not yet known.[8]

Medawar[9] has postulated that immunological tolerance was probably equatable with immunological paralysis, which denoted the specific suppression of an animal's ability to respond to an antigen that had been administered in a large dose. Immunosuppression has been achieved by massive X-ray irradiation and large doses of hydrocortisone, and Hellman[10] has shown that thalidomide possesses a similar property.

Evidence of maternal tolerance has not been widely sought, but the experimental evidence by Prehn,[11] Breyere and Burhoe,[12] and Lengerova and Vojtiskova[13] should stimulate further research. In these experiments it was found that a female who had borne progeny by the same mate became tolerant to grafts from that same mate. The induced tolerance to male incompatibility was probably permanent. Prehn has also pointed out that the incidence of erythroblastosis foetalis is very low, even when antigenic differences between mother and child are marked, and that a tolerance phenomenon in the human similar to that in the mouse may be a factor in the prevention of erythroblastosis foetalis.

A somewhat related finding by Robinson and his coworkers[14] was that 2 women with choriocarcinoma exhibited specific tolerance to skin grafts from their husbands, but promptly rejected grafts from unrelated donors in patients with chorionepithelioma.

The next point that arises is whether early abortions may be homograft reactions. This was originally propounded by His.[15] Hellman[10] noted that histocompatibility is also associated in some degree with sex chromosomes, and it would not be surprising to find a preponderance of male abortuses. This has been claimed more than once.

If pregnancy be postulated to be a state of iso-tolerance, one could also suppose spermatozoa to produce ITPF. Repeated pregnancy would be impossible if there was sensitization and rejection of spermatozoa. In a preliminary communication, Nelken *et al.*[16] report some success in modification of homograft rejection patterns with sperm-treated rabbits. However, the late Professor Becker of Johannesburg[17] pointed out that spermatozoa are normally shielded from the blood and lymphatic systems, and are therefore not 'accessible' antigens. If they escape from their environment (e.g. following trauma or testicular disease) antibodies readily develop against them and sterility results. He doubted the possibility of ITPF being produced by spermatozoa.

*Date received: 15 August 1968.

Another reason to suggest that immunological tolerance is present is the experiments that have been carried out in animals, where the embryo or foetus from one animal has been implanted in another of the same species.

Toxaemia of pregnancy, of which the aetiology is at present unknown, may perhaps be related to disturbance of the iso-tolerance mechanism. If ITPF has fluid-retaining properties, it would explain the oedema and perhaps the hypertension.

MALIGNANCY

Here again a mass of tissue exists that is probably antigenically different, because the nuclear structure differs from the normal cell. The chromosomal count is not constant, and varies from one malignant cell to the next. Abnormal mitotic divisions occur, and an abnormal DNA pattern is postulated. Malignant cells produce specific antigens to which antibodies are produced. Cancer-specific antibodies have been produced against both experimental and spontaneous human tumours, but there is little evidence that they have any inhibitory or destructive effect on tumour cells *in vivo*.[18]

Orthodox concepts relating immunity to serum antibodies are inadequate to understand whatever response to cancer cells may in fact exist.[19] The reason for introducing the hypothesis of production of ITPF by cancer cells is the evidence of immunological depression in malignancy, and it is logical to postulate that immunological depression is in fact produced by the malignancy in the early as well as the late stages, where immunological paralysis may be produced by overwhelming antigenic doses.

Prehn[20] reports that depression of immunological response is important in carcinogenesis. Berrian and McKhan[21] found that in women with choriocarcinoma favourable results have been obtained with tissues derived from the husband, used as antigens to increase resistance to this trophoblastic tissue. Paternal tissues would, of course, contain antigens in addition to those in the tumour, and a possibility is suggested from studies in mice that these additional antigens of paternal origin may increase the resistance to those antigens shared by the tumour. It is also reported that semen is the antigen source in maternal tolerance to male tissues.

As noted earlier in this paper, Robinson *et al.*[14] reported 2 cases of choriocarcinoma who exhibited specific tolerance to skin grafts from their husbands.

It has been demonstrated that patients with established cancer have a reduced capacity for forming humoral antibodies for rejecting homografts or for delayed hypersensitivity reactions.[22-24]

An ingenious method of treatment has been attempted by Nairn *et al.*,[25] whereby specific antibody has been linked with a radioactive substance, with excellent results. It would suggest a method of treatment other than trying to bolster the defences of the body.

The formation of metastases is an important consideration in malignancy. Several probabilities have been put forward:[26]

(*a*) The natural antitumour immunity of the host develops too late.

(*b*) There are so many migrating tumour cells that the immune mechanisms cannot reject them all.

(*c*) A selection of tumour cells non-susceptible to the immune reaction takes place during the development of metastases—the antigens of the tumour may be masked, but not lost.

(*d*) Immunofluorescent studies have shown the deletion of certain antigens from the primary growth and the metastases are probably immunologically different from the primary.

Possibly absorption of antibodies on cells is the first phase in the antigen loss, and prolonged growth of a tumour containing the antigen in the presence of corresponding antibodies could lead to a selection of a cell population in which synthesis of transplantation antigen is depressed. This would be defined as the adaptive modification of tumour cells in the immune organism.

SUMMARY

It is postulated that pregnancy and malignancy are states of iso-tolerance. Recognition of this concept would change our ideas and approaches to the problems facing us in these related spheres.

REFERENCES

1. Howard, J. G. and Mitchie, D. (1962): Transplant. Bull., **29**, 91.
2. Bellingham, R. E., Brent, L. and Medawar, P. B. (1956): Nature (Lond.), **178**, 514.
3. Woodruff, H. A. (1960): *The Transplantation of Tissues and Organs*. Springfield, Ill.: Charles C. Thomas.
4. Cauchi, M. N. (1967): Brit. Med. J., **1**, 111.
5. Bellingham, R. E. (1964): New Engl. J. Med., **270**, 667 and 720.
6. Kadowaki, J.-I., Thompson, R. I., Zuelzer, W. W., Woolly, P. V. jnr, Brough, A. J. and Gruber, G. R. (1965): Lancet, **2**, 1152.
7. Epstein, T. W. V. (1964): Science, **148**, 1591.
8. Guyton, A. C. (1961): *Textbook of Medical Physiology*, 2nd ed., p. 1125. Philadelphia: W. B. Saunders.
9. Medawar, P. B. (1961): Folia biol. (Kraków), **7**, 1.
10. Hellman, K. (1966): Lancet, **2**, 1136.
11. Prehn, R. T. (1960): Nat. Cancer Inst. Res. Rep., **25**, 883.
12. Breyere, E. J. and Burhoe, B. O. (1963): J. Nat. Cancer Inst., **31**, 179.
13. Lengerova, A. and Vojtiskova, M. (1962): Folia biol. (Kraków), **8**, 21.
14. Robinson, E., Shulman, J., Ben-Hu, N., Zuckerman, H. and Neuman, Z. (1963): Lancet, **1**, 300.
15. His, W. (1891): Int. Beitr. Wissen. Med., **1**, 177.
16. Nelken, D., Gabriel, M. and Boss, J. H. (1966): Israel J. Med. Sci., **2**, 75.
17. Becker, B. J. P.: Personal communication.
18. Leading Article (1966): Brit. Med. J., **2**, 185.
19. Wade, L. (1964): S. Afr. Cancer Bull., **8**, 21.
20. Prehn, R. T. (1963): Nat. Cancer Inst. Res. Rep., **31**, 791.
21. Berrian, J. H. and McKhan, C. J. (1960): Ann. N. Y. Acad. Sci., **87**, 106.
22. Lytton, B., Hughes, L. E. and Fulthorpe, A. J. (1964): Lancet, **1**, 69.
23. Southam, C. M. and Pillemer, L. (1957): Proc. Soc. Exp. Biol. (N.Y.), **96**, 596.
24. Hughes, L. E. and Mackay, W. D. (1965): Brit. Med. J., **2**, 1346.
25. Ghose, T., Cerini, M., Carter, M. and Nairn, R. N. (1967): *Ibid.*, **1**, 90.
26. Deichman, G. I. and K'uchareva, T. E. (1966): J. Nat. Cancer Inst., **36**, 647.