

Editorial

We take great pride in announcing that three Swedish members of our Society, actually the three members of the organizing committee of our forthcoming 6th Congress in Hälsingborg, namely Dr. STIG BENGMARK, Dr. SVEN-ERIK BERGENTZ and Dr. BENGT ZEDERFELDT all have been appointed full *Professors of Surgery* by the Swedish king at the beginning of this year.

STIG BENGMARK (42), our president elect, is now chairman of the Department of Surgery in Lund. He has been associated for many years with Prof. RAGNAR ROMANUS, at the second University Clinic in Gothenburg. With a very strong background in anatomy his main interest in recent years has centered around the pathophysiology and surgery of the liver, his main clinical activities covering gastrointestinal surgery in general.

Like STIG BENGMARK, SVEN-ERIK BERGENTZ (44) is also one of the editors of our journal. He too comes from Gothenburg and is internationally known for his important contributions in the field of rheology and blood coagulation as related to surgery. His thesis on fat embolism which he worked out under Prof. LARS GELIN at the first Surgical Department has become a standard reference. During the past 7 years he has been very active in clinical kidney transplantation, now overlooking one of the largest and finest series in the world. He will continue his important work as transplantation- and vascular surgeon as head of one of the departments of Surgery and Director of Experimental Surgery in Malmö.

BENGT ZEDERFELDT (42) also has been associated for many years with Prof. GELIN. During the last 2 years he has been working with Prof. YNGVE EDLUND in the newly formed third University Department of Surgery in Gothenburg. His field of interest, apart from rheology, is wound

healing, and has published several outstanding papers of great practical significance relating to suture materials. He too is heading one of the Departments of Surgery in Malmö with a strong interest in general and endocrine surgery.

We heartily congratulate our three colleagues in Sweden for their great success. We are looking very much forward to meet you, dear friends, in Hälsingborg, and I may certainly speak in the name of all members of the European Society for Experimental Surgery in stating that we want to bring our best wishes for yourselves, your families and your future activities.

For the Editorial Board:

W. BRENDL, U. F. GRUBER

Modern Trends in Experimental Organ Transplantation¹

Specific immunological tolerance. A great deal of basic immunological research work dedicated to organ transplantation is aimed at inducing transplant tolerance. The prerequisite to attain such a goal is knowledge about the fundamental cellular interaction in the immune response. Recent studies in this field provide evidence that the immune response is based on the cellular cooperation of two distinct kinds of small lymphocytes: First the long-lived, thymus-derived cells and the short-lived bone marrow (bursa Fabricii)-derived cells. The stem cell of both cell lines is probably located in the bone marrow. The precursor cells of the thymus-derived cells migrate into the thymus, where they become special cells (thymus-processed cells), whereas the precursors of bone marrow-derived cells do not migrate through the thymus (not thymus-processed cells). Both cell populations possess antigen-binding antibody receptors (IgM, IgG) on their cell surface and are able to react with the antigen (antigen-reactive cells). Moreover both cell lines are precursors of antibody-forming cells and both – important in this context – can be rendered tolerant. These 2 cell lines can be differentiated only by different intensity and potency in exerting various immunological functions (Discrimination). Thymus-derived cells are especially equipped for antigen recognition, bone marrow derived cells (as precursors) for differentiation and proliferation to those cells which secrete the bulk of humoral antibodies (MITCHISON).

¹ Summing up of a symposium held from January 18th to 21st 1971 in Kitzbühel under the patronage of Prof. LONGO, President of the European Society of Experimental Surgery and organized by the Institute for Surgical Research, Munich (Prof. BRENDL).

One way to make immunocompetent cells tolerant to transplant antigens is to introduce antigens in ALS-treated recipients. Principally, transplantation tolerance (across a weak histoincompatibility barrier) can be induced by treating skin-grafted mice with ALS and subsequently injecting i.v. donor-specific lymphoid cells or hemopoetic stem cells as tolerance-conferring antigens. This principle of tolerance induction using viable bone marrow cells has been proven effective as far as the tolerance conferring capacity is concerned (LANCE). Although the experimental data look rewarding it seems too dangerous at the moment to apply this method of tolerance induction in transplant patients, because of the risk of serious secondary disease (CALNE, ALEXANDRE, MYBURGH, LARGIADER).

One problem of this type of tolerant state is its limited duration. A possibility which may account for this phenomenon is the presence of tissue differentiation antigens which are not existing on lymphoid or hemopoetic cells.

So, rats made chimeric with infusions of hemopoetic cells after irradiation, rejected allografts from the cell donor (LANCE). This observation suggests that tissue differentiation antigens are important considering tolerance production as a means of abetting the survival of organ transplants.

Another kind of non-reactivity of immunocompetent cells to transplantation antigens – without the maintenance of a chimeric state – has been observed in pigs: after liver allografting grafts of skin, heart, pancreas and kidney survive permanently. Thus, the liver graft provide some protection for donor tissues. This phenomenon could be interpreted as a special kind of immunological tolerance (rather than the expression of the action of enhancing antibodies) so that one could assume that antigen secreted out of the liver allograft acts as a tolerogen (CALNE).

One example of an accomplishment of a tolerant state to a (non-transplantation) antigen in man, is the successful induction of immunological tolerance to the xenogenic serum protein antigen horse IgG in order to prevent foreign serum reaction in patients to be treated with ALG. In spite of the difficulty in setting up an adequate experimental design in these patients as to prove the real tolerance state (challenge of patients), all data received so far suggest that the lack of any antibody formation against horse IgG under ALG treatment in those patients is due to the induction of immunological tolerance (BRENDDEL, LAND, SEIFERT).

Enhancement. Although it is sometimes in question to differentiate this from tolerance (MITCHISON), enhancement seems to be another pos-

sible approach to achieve long-term survival of tissue allografts. Thus, the induction of enhancing antibodies in prospective recipients by means of pretreatment with donor-specific antigens may be advantageous for both allogeneic and xenogeneic organ transplantation. Pre-treatment of recipients (dogs and rats respectively) with subcellular soluble tissue antigens from various donor tissue sources resulted in marked prolongation of the survival time of subsequent kidney allografts. One optimal pre-treatment schedule seems to be the i.v. injection of the 100,000 g supernatant of donor liver homogenate (WILSON). A reasonable effect of enhancing antibodies is supposed to be correlated with a certain level of circulating antibodies, as detectable *in vitro*. Low amounts of anti-donor antibodies provide an enhancing effect; in contrast, higher amounts provoke accelerated graft rejection (WILSON).

Another kind of effective donor-antigen pre-treatment of prospective recipients (rats) providing long-term survival of allografts is represented by the i.v. injection of whole donor blood prior to grafting. But the effectiveness of this form of active enhancement is strictly confined to certain organ tissue (kidney, heart, not skin!) and a successful effect depends on what strain combinations were used (VAN BEKKUM). Pre-treatment of prospective recipients with soluble donor-tissue antigens also influences the hyperacute xenogenic graft rejection in widely divergent species. Pre-treatment of dogs with soluble pig liver antigens over a period of 6 weeks leads to a significant prolongation of the survival time of pig kidneys connected with the canine circulation (HAMMER, LAND, BRENDL). On these findings it can be concluded, as a matter of fact, the induction of enhancing antibodies is a reasonable procedure to obtain significant prolongation of the survival time of allografts as well as of xenografts. Although the data available at this time are sufficient to explain a certain effectiveness of enhancing antibodies, there is no doubt that a great deal of questions are unsolved, because no adequate experiments have been performed yet.

These problems include: knowledge of the exact action of this kind of antibodies; the optimal schedule of antigen-pre-treatment; development of an adequate *in vitro* test for the evaluation of the potency of enhancing antibodies; and methods needed for optimal separation of antibodies with enhancing activity from those with cytotoxic activity (MITCHISON, WILSON, VAN BEKKUM, CALNE, VAN ROOD).

Bone marrow grafting. In the past 2 years remarkable progress has been obtained in the field of clinical bone marrow transplantation, concerning especially the avoidance of the fatal secondary disease (GvH disease)

and the facilitation of a take of bone marrow cells. Pre-treatment of the recipient with cyclophosphamide or (in recent time) with ALS alone has resulted in a number of complete takes in patients suffering from leukemia or aplasia without the occurrence of severe acute secondary disease. The improved incidence of takes as well as the decreased incidence of fatal graft versus host reactions is largely attributed to improved donor selection (HLA-identical donors, MLC-negative combinations) (VAN ROOD, ALBERT), to the pre-treatment of the recipient with ALS, and to the improved methods of separating hemopoietic stem cells from immune competent cells (VAN BEKKUM). Under these circumstances, in the future long-lasting states of chimerism without persistent graft versus host diseases following bone marrow transplantation can be expected in man. For instance, recent clinical results of the group of MATHÉ (Paris) showed that bone marrow transplantation in man becomes more and more promising. This group attempted allogenic marrow grafts in patients with total bone marrow aplasia after conditioning the recipient with ALS alone, administered prior to the transfusion of allogenic bone marrow cells. As judged by the absence of serious signs of secondary diseases in nearly all cases, a real strong immunosuppressive effect of ALS could be established. These observations showed that bone marrow transplantation after conditioning the recipient by ALS alone is a non-dangerous therapy which can be efficient for bone marrow aplasias (SCHWARZENBERG). New experimental approaches to this field are under way. In weak histoincompatibility systems (H_2 -compatible mice, analogous to HAL identity) it is possible to get a take of bone marrow cells with subsequent long-lasting chimerism when the recipient is simultaneously conditioned with ALS treatment and semicorporeal irradiation (THIERFELDER).

Xenografting. There is no doubt that cross species transplantation is that field in transplantation research which has been explored only scantily. Recently, however, there has been made some progress in setting up a new definition regarding the mechanism of xenograft rejection and prevention of responses. Discussing the various problems of xenografting one should *a priori* differentiate between xenografting in closely-related species (intra-order xenografting) or in widely divergent species (inter-order xenografting) (LAND). So, the behaviour of xenografts in closely related species is similar to that of allografts as far as any immunological, pathophysiological and histological parameters are concerned. Immunosuppressive agents are effective in modifying this type of xenograft rejection (concordant xenografting [CALNE]).

The xenografts in widely divergent species are determined by the accelerated rejection in a hyperacute fashion within minutes or hours. Immunosuppressive agents are ineffective in modifying this type of xenograft rejection (discordant xenografting [CALNE]). The hyperacute rejection of xenografts in widely divergent species is supposed to be due to the primary action of preformed (natural) humoral antibodies in the circulation of the recipient species. These antibodies (hemagglutinins, leucoagglutinins, complement fixing tissue antibodies) which are acting with tissue from other species outside the same order, can be found in a variety of species of the orders Carnivora, Ungulata, Rodentia, Primates, etc. (BRENDDEL). The hyperacute xenograft rejection is initiated by the primary antigen-antibody reaction between donor tissue antigens (endothelial cell antigens?) and recipient preformed anti-donor antibodies. The predominant signs of the hyperacute rejections (increase of flow resistance with rapid cessation of blood flow, hemorrhage and congestion of the xenogeneic organ) however, presumable are mainly secondary to the involvement of recipient cells (thrombocytes, leukocytes) in this antigen-antibody reaction. There is evidence that in addition to the formation of antigen-antibody complexes and cell aggregates respectively the release of pharmacological mediator substances from destroyed cells play an important role as pathogenetic factor in this complex rejection reaction (LAND). Further attempts to explain the whole complexity of this reaction must include considerations about the participation of non-immunological factors being able to initiate the hyperacute rejection (CALNE, LAND, BRENDDEL, MESSMER).

To date an effective modification of this hyperacute xenograft rejection is only provided using either the methods of inducing 'xeno-enhancing antibodies' in the prospective recipient (HAMMER) or of removing actively the responsible blood elements (preformed antibodies, complement, thrombocytes and leukocytes, etc.) from the circulation of the recipient. The latter procedure can be performed during extreme hemodilution in dogs with subsequent substitution of the autogenic red blood cells, which leads to profound depletion of recipient γ -globulins, complement and cells. Under these circumstances (in combination with a lymph drainage) a pig kidney can function over 20 h after the connection with the canine circulation (MESSMER).

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