PART VIII

WORKSHOP ON BIOCOMPATIBILITY

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BIOCOMPATIBILITY

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The Chairman started the workshop by pointing out that since the early 1950s devices made with synthetic biomaterials have been introduced into therapeutic medicine at an ever increasing rate. However, the blood compatibility of membranes used in extracorporeal detoxification devices, were not taken into consideration until recently, despite the fact that transient reduction of leucocytes has been known about for the past 20 years. This reflects one of the main problems in the development of artificial organs, since often the clinical success of using certain materials exceeds by far the degree of basic research. Most biomaterials in clinical use are derived from industrial developments for non-medical purposes and no generally accepted test procedures are available to judge the quality of this material on an international basis. The term 'biocompatibility' has been generally accepted as a quality concept but it has not been precisely defined yet. From the simple clinical point of view biocompatibility of a material is a 'negative' definition and requests the absence of thrombogenic, toxic, allergic or inflammatory reaction; no destruction of formed elements, no changes in plasma proteins and enzymes, no immunological reactions; no carcinogenic effect and no deterioration of adjacent tissue.

In dialysis the mechanism of biocompatibility and its clinical relevance is still a matter of controversial discussion to which this workshop should add some new aspects.

Wegmüller [1] compared the ability of three hollow fibre dialysis membranes: cuprophan, polymethylmethacrylate and polyacrylonitrile, to activate complement and to induce leucopenia. In cuprophan membranes he repeated the observation of the fall of blood leucocytes. This decrease in leucocytes correlated inversely with C_{3a}, C_{3d} and C_5 concentrations; polymethylmethacrylate and polyacrylonitrile membranes induced very little complement activation without significant leucopenia. From the clinical point of view, however, all patients tolerated the three different membranes equally without complications.

Bommer [2] presented interesting data, questioning the role of the dialysis membrane as the main reason in the genesis of anaphylactoid reaction in dialysis. He stressed earlier findings of reagenic antibodies against ethylene oxide, which is now widely used as a sterilizing agent in dialysers. The recent investigations of his group concentrated on the detection of cytophilic allergen-specific IgE – antibodies against ETO-haptens on a patient's own basophils. All dialysis patients with a history of anaphylactoid reactions had degranulation of their basophils in response to ETO conjugate.

Rumpf [3] supported the concern about the role of ethylene oxide in the genesis of hypersensitivity phenomena during dialysis. In patients with ethylene oxide-albumin complexes the incidence of eosinophilia and increased IgE was high. He concluded that the occurrence of ETO-Ab does not seem to be a rare event and may play a greater role in the anaphylactoid reactions on dialysis than hitherto suspected.

Mahiout [4] analysed the kinetic profiles of white blood cells in patients treated with cuprophan membranes. He found no difference in the kinetic profile of white blood cells during the very first blood-membrane interaction compared to those on routine long-term treatment.

The additional effect of different ultrafiltration rates on the circulating polymorphonuclear leucocytes was studied by Mori [5] by means of chemiluminescence. The observed increase of the chemiluminescence phenomenon with increased ultrafiltration indicates a secondary activation of the circulating polymorphonuclear leucocytes.

Falkenhagen [6] reported for the first time in the literature about the possibility of changing the biocompatibility of a basic membrane material (cuprophan) measured by leucopenia and complement activation, by only slight chemical modification of this basic material. A comparative clinical study between cuprophan and the new modified cellulose membrane (Enka-AG) showed excellent dialyser efficiency with especially high clearances for middle molecular weight substances for the modified cellulose membrane and a highly reduced complement activation indicative of a much better biocompatibility.

The results reported by Hemmeløff [7] about a newly developed polycarbonate membrane supported earlier reports about the efficiency and compatibility of the material when used as a dialysis membrane. Clinical trials demonstrated that allergic reactions which appeared in patients on cuprophan dialysis could be avoided when switched to polycarbonate dialysers.

An extremely interesting new idea was discussed by Bergström [8]. He referred to the clinically well-known fact that morbidity and mortality in dialysis patients are often associated with protein malnutrition, thus indicating a high protein requirement by these patients. To explore whether blood-membrane interaction triggers protein catabolism in muscle, the free aminoacid balance across the leg was investigated in fasting non-uraemic subjects before and after sham-dialysis, i.e. in vivo passage of blood through a cuprophan dialyser. The net release of free tyrosin increased by about 100 per cent in the dialysed subject, the enhanced catabolism of muscle protein was thus evident. This result indicates that blood interaction with cuprophan in man leads to

accelerated protein catabolism, raising the question of the influence of membrane biocompatibility on protein metabolism.

In his concluding remarks the chairman summarized the results of the workshop as a remarkable contribution to the ongoing discussion about the mechanism of biocompatibility in membrane-related blood purification procedures, stressing especially the central role of leucocytes and the complement system. He pointed out that as a result of scientific discussions new membranes with better biocompatibility parameters were developed for clinical use in a very short period of time. The workshop, however, also demonstrated very clearly that in judging a medical device for its clinical application, the individual material of that device should never be divorced from the total device.

Papers presented

1 **Wegmüller E**, Descoeudres C, Hodler J. *Biocompatibility of haemodialysis membranes: activation of complement and leukopenia*
2 Barth H, **Bommer J**, Wilhelms H, Ritz E. *ETO-induced IgE-mediated degranulation of basophils of dialysis patients*
3 **Rumpf KW**, Seubert S, Seubert A, Ippen H, Scheler F. *Eosinophilia (E), elevated IgE and antibodies to ethylene oxide-albumin complexes (ETO-AB) in patients on regular dialysis treatment (RDT)*
4 Albers F, **Mahiout A**, Kessel M. *Leukokinetics in long-term use (LTU) of cuprophan haemodialysers*
5 Mori R, Triolo R, **DeSole P.** *Effect of ultrafiltration rate on neutrophil metabolic activation.*
6 **Falkenhagen D**, Zinner G, Falkenhagen U, Ahrenholz P, Holtz M, Behm E, Klinkmann H. *A modified cellulose membrane (MC) with reduced complement activation*
7 **Hemmeløff KE**, Riede G, Konstantin P, Göhl H. *The performance and compatibility of a new copolymer membrane – gembrane – for haemodialysis*
8 Gutierrez A, Alvestrand A, Wahren J, **Bergström J.** *Blood-membrane interaction without dialysis induces increased protein catabolism in normal man*