EDITORIALES

Clinical relevance of biocompatibility. «The material cannot be divorced from the device»

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The clinical use of the artificial kidney has been one of the very first examples for the application of biomaterials in life-supporting therapies. During the last 20 years the clinical application of biomaterials has been extended to treatment or support of a vast array of bodily functions. Today the number of biomaterial implants is estimated to be hundreds of millions per year around the world [1].

Most biomaterials in clinical use are derived from industrial developments for non medical purposes. The term «Biomaterial» is applied to natural or synthetic material that is used in contact with living tissue and/or biological fluid. Each biomaterial considered for clinical application has unique chemical, physical and mechanical properties. Its clinical application causes numerous dynamic events at the tissue/material interface. Forecasting the biological performance of a biomaterial is therefore much more difficult than the prediction of functional performance of that specific material over a period of time. Unfortunately there is no international agreement on generally accepted standardized test procedures to assess the quality of such a biomaterial [2].

As a compromise the term «Biocompatibility» was introduced for a quality concept and represents today a rather wide collection of not always precisely defined effects of the biomaterial on the human body. Considering the biocompatibility as the interrelationship between nonbiological surfaces and a living system, the following description of biocompatibility is possible:

Biocompatibility includes

— The energetics and kinetics of all physical, chemical and biochemical processes at the interface between the biomaterial and biological system during the time of contact and the direct reaction of the biological system induced by these processes at the interface.

— The sum of changes of physical and chemical properties of material i.e., surface composition, surface free energy, corrosion, biodegradation, etc.

— The sum of changes of the biological system outside the interface, triggered or induced by the interaction (toxic or immune reactions, cancer; etc.).

For clinical purposes we reviewed in 1984 this interfacial problem of high complexity and introduced for practical use the so called NO-definition, which has gained wide acceptance in the medical and bioengineering community [2] (table I).

In the treatment of endstage renal failure with different detoxification devices a variety of biomaterials and bioactive agents is incorporated either in the dialysis equipment or in the dialysis procedure [3, 4] (table II + III).

Since our concern for RDT patients has shifted from mortality to morbidity with the goal of long-term survival the avoidance of treatment induced complications becomes more evident [6]. A considerable portion of acute and chronic symptomatology of patients during RDT might be related to poor biocompatibility or better, bioincompatibility of the device used for treatment.

Regrettably the poorly understood high complexity of the biocompatibility scenario has been misinterpreted and even misused in declarations of biocompatibility or bioincompatibility of treatment-devices just for reasons of marketing competition. In most cases this classification was based exclusively upon the biocompatibility parameters of a single material (the membrane) used in a device that incorporates a variety of different materials [7] (see tables II, III).

It is the aim of our paper to demonstrate that for the judgment of the biocompatibility of a given device the individual material can not be divorced from the device. Furthermore I would like to discuss different indexes of biocompatibility in blood detoxication devices and their possible clinical relevance.

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Table I. Definition of biocompatibility

Biocompatibility
No: — Thrombogenic toxic, allergic, inflammatory reaction.
— Destruction of formed elements.
— Changes in plasma-proteins and enzymes.
— Immunologic reactions.
— Carcinogenic effect.
— Deterioration of adjacent tissues.

Indexes of Biocompatibility

Coagulation Cascade:

The complex interaction between the patient and the biomaterial and thus its biocompatibility is summarized in a simplified manner in fig. 1. Until the late 70s the reaction of the coagulation cascade was almost exclussively the basis for judgment of the biocompatibility of a material. The well-known formation of a protein layer on the surface and the subsequent entrapment of cells leads to activation of blood coagulation. To characterize the surface induced coagulation process (platelet adhesion, thrombus formation, hemostasis) numerous physical and biochemical methods have been proposed [2].

However, for a device like a dialyser it can not be concluded if the observed event (degree of hemostasis, platelet adhesion or thrombus formation) is maincy influenced by the material and its interrelationship with the blood elements via the protein adsorption layer, the surface design or the hemorheological conditions of the dialyser [5].

Complement System:

The initial observation of neutropenia in the early phase of hemodialysis by Kaplow and Goffnet 1968 [8] did not cause any attention as a clinically relevant complication. In 1977 Graddock et al [9] suggested, that activation of the alternate pathway of complement would lead to granulocyte clumping in the pulmonary capillaries and may be responsible for acute dialysis dyscomfort.

The complement system consists of a series of plasma proteins with activation of early components inducing activation of later components in a cascading sequence. To date 11 protein factors are known and for brevity they are designated as C_1 for the first factor, C_2 for the second and so on. For complement activation two primary pathways, the classical and the alternative, are known. The classical pathway involves activation of the 11 proteins in a well characterised sequence, in contrast to the alternative pathway in which C_3 is activated independent of C_1, C_4 and C_2.

The alternative pathway can be fired by complexes of antibodies such as IgE which are incapable of activating the classical pathway and by substrates such as polysaccharides, lipopolysaccharides and endotoxin without requiring antigen-antibody complexes.

Detailed descriptions of the complement system and its activation can be found in reviews [10-12].

Although complement activation by synthetic materials has been known for years, it only recently gained wide interest in clinical medicine as a possible source of clinically relevant acute and chronic complications in the application of biomedical devices (table IV).

The reported clinical consequences have recently been reviewed [4, 5, 13, 14] and range from acute anaphylactic reactions, intradialytic hypotensive episodes, hypoxemic and acutely induced protein breakdown to long term complications like amyloidosis, joint problems, pulmonary fibrosis, extranstion of the reticuloendothelial system and muscle breakdown. Table V summarizes possible immunologicall mediated acute and chronic complications related to complement activation with hemodialysis. It is generally accepted that for example-complement split products such as C_3a and C_5a can cause anaphylactoid reactions, known as an acute complication in dialysis patients. As an example for chronic complications, special susceptibility to infections are the main cause of hospitalization of the RDT-patient. The combination of granulocytopenia, decrease in phagocytosis and exhaustion of the complement system by repeated activation may

Table II. (Toxic?) substances being used for production of cellulose hollow fibers dialyzers

Hollow fiber production			**Dialyzer + Blood line production**		
Extrusion medium	**Care fluid**	**Regeneration step**	**Care fluid removal**	**Polymer (resin)**	**Sterilization**
aqueous cooper ammonia Glyerin Carbon disulfide	isopropyl myristate other organic liquids	acid or alkaline bath	organic solvent	Isocyanate Polyole plasticizer	ethylene

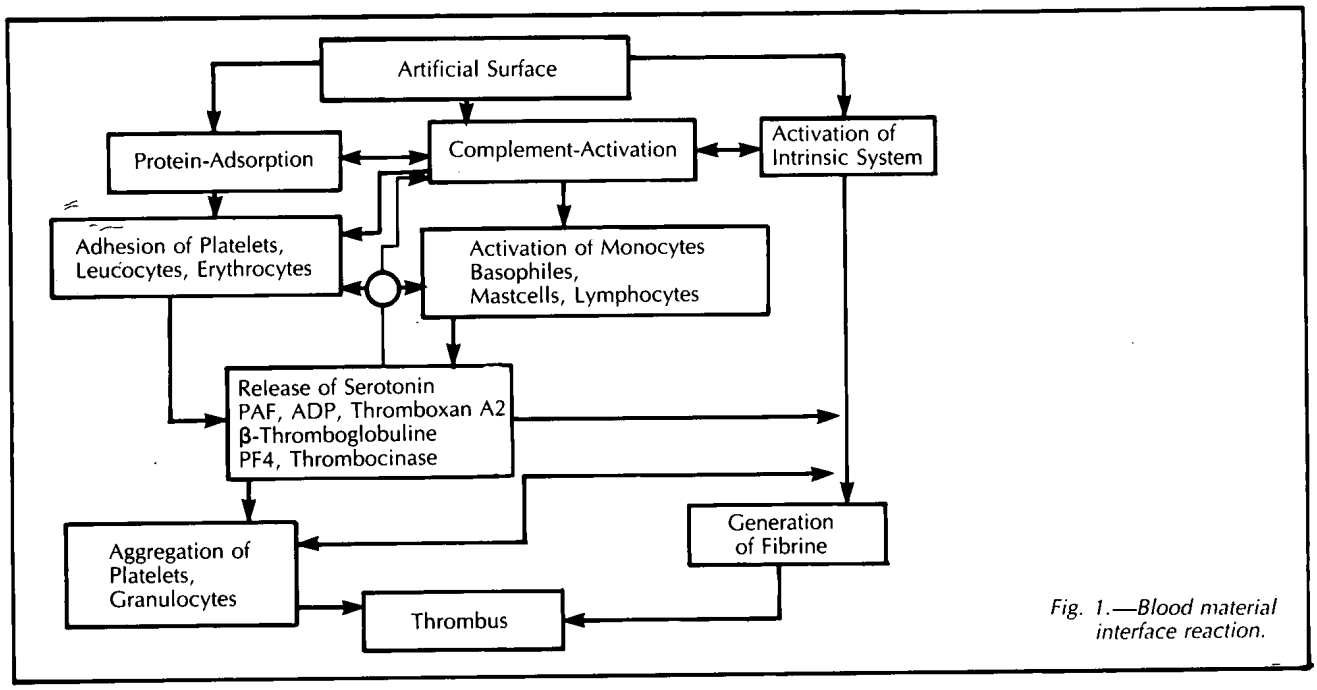

Fig. 1.—Blood material interface reaction.

Table III. (Toxic?) substances being used for the hemodialysis procedure (hemofiltration)

Dialysate	Heparin, Drugs Infusion solutions (Substituate)	Reused dialyzer
Nitrate	Bacteria and pyrogens	Formaldehyde
Sulfate	Viruses	Bacteria
Chloramines		Pyrogens
Heavy metals		Viruses
Bacteria and pyrogens		

Table IV. Direct biological activity of complement activation

Releasing of
- — Biological active substances form cell granules.
- — Thrombokinase from platelets.
- — Lysosomal enzymes from granulocytes and B-lymphocyles (collagenase, elastase).

Opsonization of bacteria and viruses.
Immune adherence of neutrophile, monocytes, B-lymphocytes macrophages.
Stimulation of antibody production of lymphocytes.
Membrananalysis of bacteria, viruses, tumor and endothelial cells.

predispose bacterial infections. Alterations of the immune system induced by interaction between blood and material in dialyzers are becoming one of the most convincing evidence for many symptoms and complications in dialysis patients.

In dialysis the extent of complement activation obviously depends on the type of membrane used [15, 16].

Several case reports appeared in literature, describing dialysis related acute and chronic complications such as fever, chest pain, hypotensive episodes, respiratory distress etc. in relation to the type of dialysis membrane used (reviewed in 14).

The classical dialysis membrane Cuprophane has been charged with the highest incident of complement activation. Obviously the chemical structure of the membrane material (polysaccharide structure) and the hydroxyl groups (OH^-) seem to be associated with the activation of the complement cascade via the alternative pathway and the production of C_5a [17].

Theoretically a reduction in the hydroxyl groups could result therefore in a diminished complement activation.

We recently reviewed the possibilities to reduce complement activation in cellulosic membranes [7] (table VI).

Examples for reducing complement activation

a) *Membrane modification*

In an attempt to block the reactive hydroxyl groups of cellulose without altering the solute properties of the membrane a modified cellulose membrane (Hemophan ®) was recently developed and tested clinically [7, 18, 19]. This modification replaced some of the hydroxyl groups with amino-groups (NH_3^+) (fig. 2).

The significant differences in leucocyte-drop and complement activation between different cellulosic membranes are demonstrated in fig. 3 and fig. 4.

Table V. Possible clinical relevant. Biological activity of complement activation

Acute

— Anaphylatoxic reaction.
— Smooth muscle contraction.
— Microcirculary disturbances.
— Pyrogenic reactions.
— Hypotension.

Chronic

— Pruritus, deficiency of host defence mechanism.
— Disturbances of protein metabolism.
— Production of amyloid like substances.

b) *Larger pore size*

Clinic evaluation demonstrated, that contrary to cellulosic membranes dialysers with different polymeric membranes like polyacrylonitrile, polysulfone, polycarbonate and polymethylmethacrylate cause a lesser degree of transient leucopenia and complement activation [20].

The same observation was made by us in different detoxification devices like hemofilters and plasmafilters, equipped with different polymeric membranes with larger pore size.

The molecular weight of 10.000 dalton of the C_3a complement factor indicates the possibility for filtration of complement components or fractions in certain membranes with larger pore size. The results of our study, published earlier [21] are summarized in fig. 5. There is clear evidence, that complement components generated by different membranes, are abandoned by filtration through the membrane before entering the patient. In our opinion the final input of activated complement components into the patient is a summary of a rather complex mechanism including generation, absorption and filtration.

We therefore suggest to consider for further studies the differences between the total generation rate of a substance (complement factors) and the amount, that finally reaches the organism, termed effective generation rate (fig. 6).

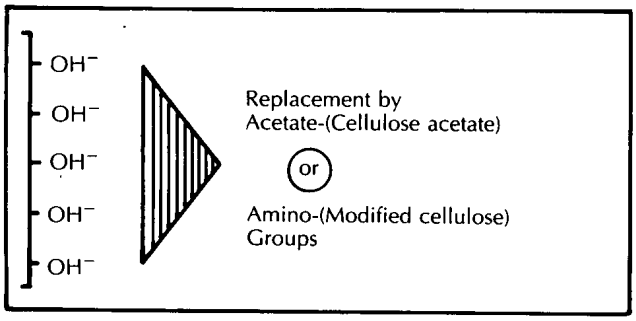

Fig. 2.—Membrane modification.

Table VI. Possibilities to diminish the activation of the complement system in dialysis

— Membrane Modification.
— Reduction of Surface Area.
— Larger Pore Size.
— Reuse.
— Decrease of Dialysate Temperature.
— Application of Complement Inhibiting Anticoagulation.

In a blood purification system, only the effective generation rate will be of clinical relevance and should be used for judging the biocompatibility of the device.

Our study in blood purification device, equipped with a polysulphon membrane (F 60, Fresenius) reveal clearly, that the biocompatibility of the same device can be different if used in different modes of application. In the mode of dialysis, where the larger pore size of the membrane is less effective, the effective generation rate comes close to the total generation rate. Using the F 60 as a hemofilter with high pressure gradients, the larger pore sizes becomes more, effective. Obviously more complement factors are filtered through the membrane. This results in a much bigger difference between the total and effective generation rate, making the F 60 even more biocompatible when used as hemofilter (figs. 7 + 8).

Alternative Mechanism

Although many data support the importance of the complement system for the clinical relevance of biocompatibility, some findings do not fit well into this concept and suggest, that alternative mechanism might play an equally important role. Activation and alteration of the blood coagulation cascade with release phenomena, granulocytopenia and leucostasis, changes in oxydative metabolism of polymorphonuclear leukocytes, release phenomena of cationic and granular proteins and involvement of humoral factors such as kallikrein, leukotrienes, prostaglandines and interleukin have been studied as possible factors for biocompatibility [22-24]. In the search for easily accessable screening parameters for biocompatibility there has been an interest in the already mentioned release reactions. These reactions are induced by adhesion of cells to biocompatible foreign surfaces during which active chemicals or enzymes are released from cells into the surrounding. The development of techniques for measuring these products of the release reaction and their sensitivity has drawn attention to their potential use in blood compatibility assessment. In our experiences the platelet release-reaction products Beta-thromboglobulin (BTG), platelet factor 4 (PF_4) and thromboxane B_2 (TBX_2) are reliable markers of biocompatibility.

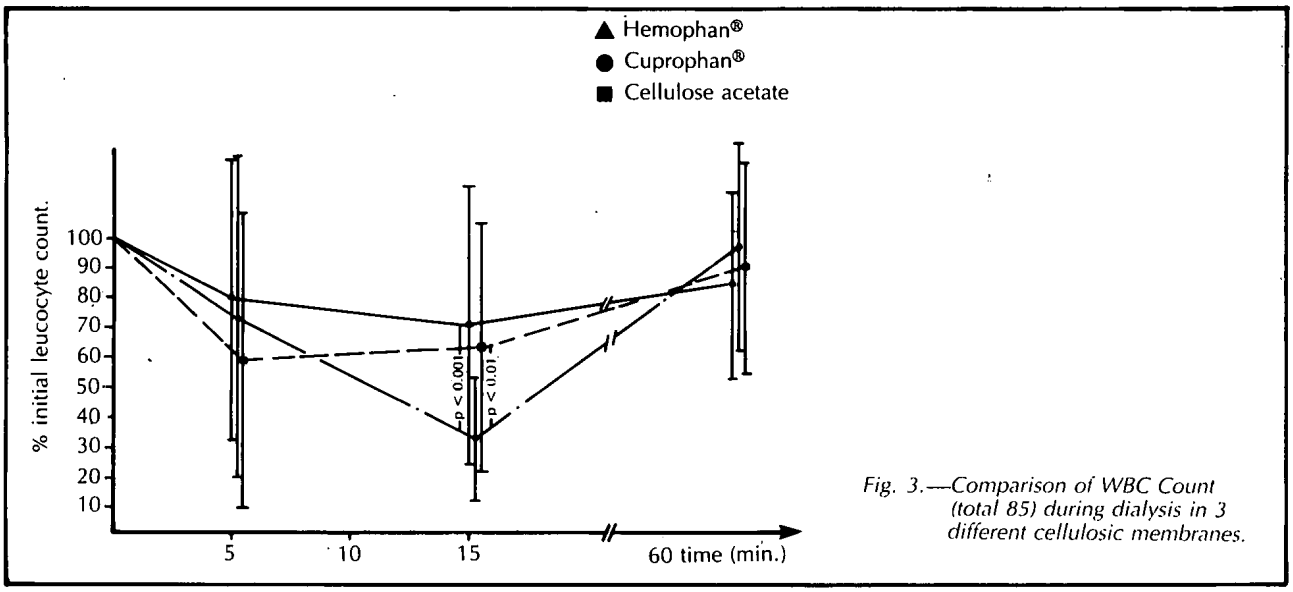

Fig. 3.—Comparison of WBC Count (total 85) during dialysis in 3 different cellulosic membranes.

Table VII. Influence of different dialysis membranes and anticoagulants on beta-thromboglobulin (BTG) release

Membrane	Anticoagulant	BTG (ng/ml.) 3 min.	6 min.	9 min.
Cuprophan	None	70	101	154
Cuprophan	Heparin (1 IU/ml.)	89	102	103
Cuprophan	Citrate (15 mmol/l.)	42	40	37
An 695	None	74	105	205
An 695	Heparin (1 IU/ml.)	61	71	85
An 695	Citrate (15 mmol/l.)	44	38	48

Our data with different membranes confirm the validity of this method showing significant differences between regenerated cellulose and polyacrylonitrile-type membranes (table VII).

Among the humoral factors interleukin-1 (IL-1) has gained much interest and has recently been revieved by Shaldon et al. [25, 26].

Chenoweth et al. [17] demonstrated, that purified human C_5a was capable of inducing interleukin-1 release from human monocytes. This lead together with the clinical observation that the body temperature rose during dialysis to the postulation of the Interleukin hypothesis [25].

Interleukin-1, formerly known as endogenous pyrogen, designates the monocyte hormone, mediates fever and influences the acute phase response resulting in hepatic synthesis of C-reactive protein, amyloid-A-like substances and muscle breakdown with hypercatabolism. This hypothesis today assumes that during dialysis with regenerated cellulose membranes monocytes adhere to the membrane. They are then exposed to activated complement components (most likely C_5a) and aggregated granulocytes from the blood-side. Also under discussion is a possible influence of endogenous pyrogens and possible other inducers directly deriving from the dialysate. Besides acutely induced vasodilatation with hypotension, sleep tendency and protein catabolism may result. A repeated stimulation of IL-1 during regular dialysis treatment could be responsible for several chronic complications as osteopenia, fibrosis and amyloidosis [26] (fig. 9).

Table VIII. Main factors influenting the biocompatibility of a dialyzer

Biocompatibility of a dialyzer:
- — Membrane.
- — Sterilization.
- — Flow-geometry.
- — Material.
- — ?
- — ?

Additional Mechanism

1. *Sterilisation*

In the late 1970s Takahashi et al. [27] observed eosinophilia and allergic-type reactions in patients treated with ethylenoxyd (ETO)-sterilized hemodialysers. They also showed a high serum IgE concentration and a positive IgE-RAST for antibodies to ETO. Eosinophilia as well as allergic reaction disappeared with the introduction of steam sterilized dialysers.

Recently this observation was confirmed by different investigators [28-30]. Bommer [31] reported on the high incidence of ETO-specific IgE antibodies in dialysis patients. Furthermore, he observed a good quantitative

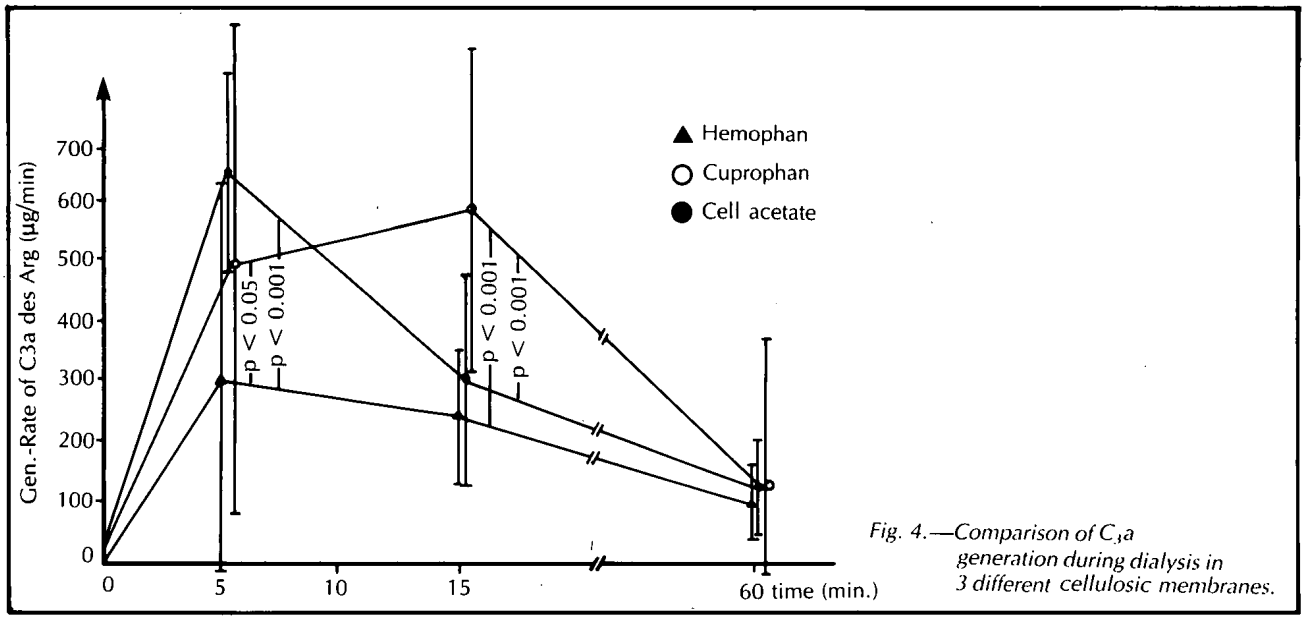

Fig. 4.—Comparison of C_3a generation during dialysis in 3 different cellulosic membranes.

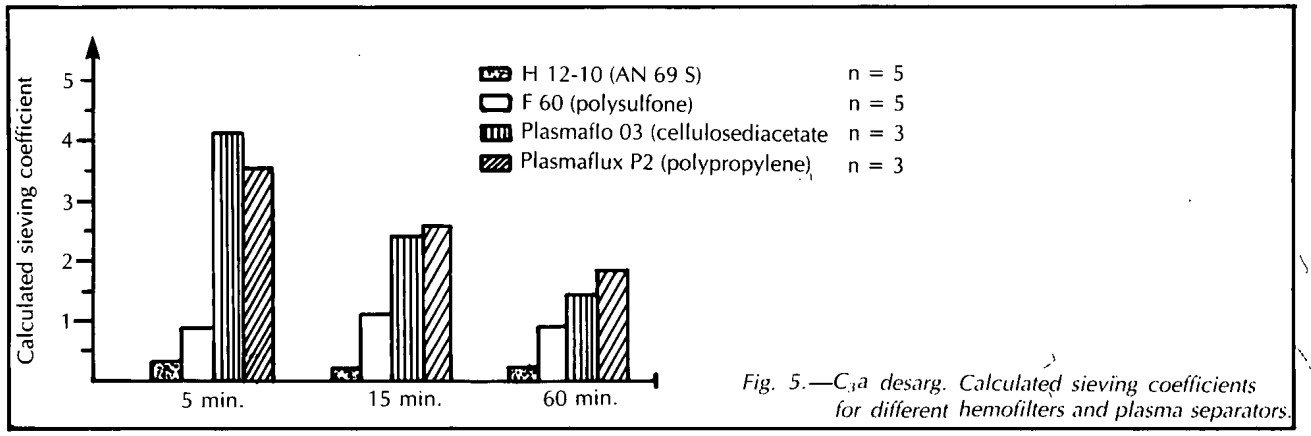

Fig. 5.—C_3a desarg. Calculated sieving coefficients for different hemofilters and plasma separators.

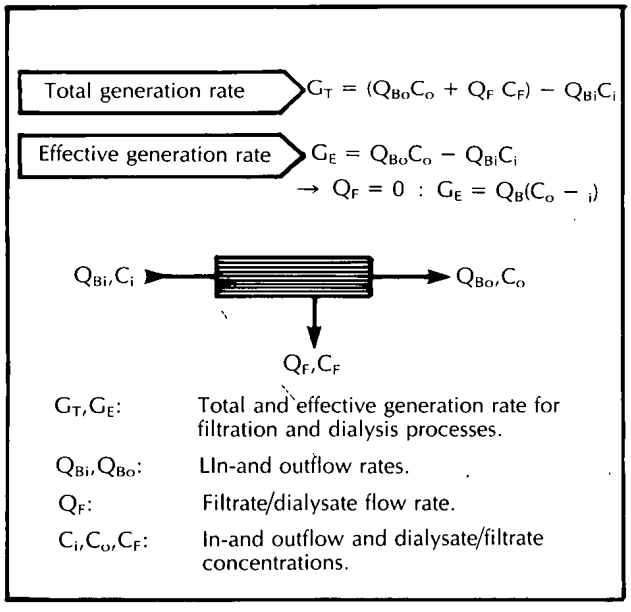

Fig. 6.—Total and effective generation rate.

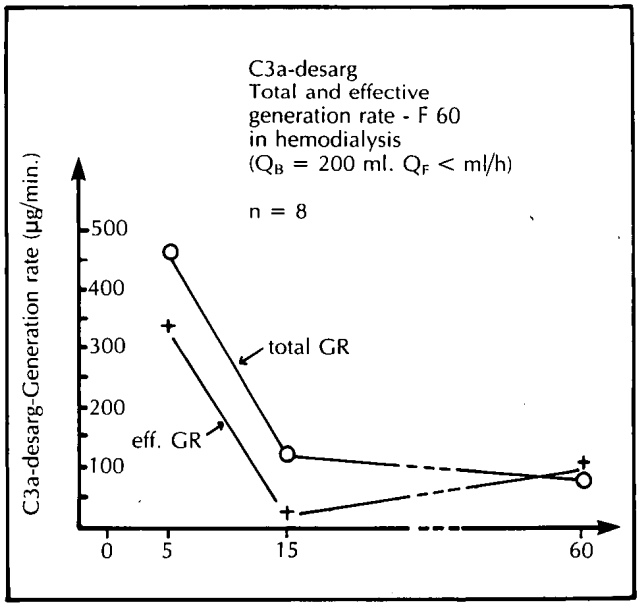

Fig. 7.—Total and effective generation rate of C_3a-desarg. in F 60 used as dialyzer.

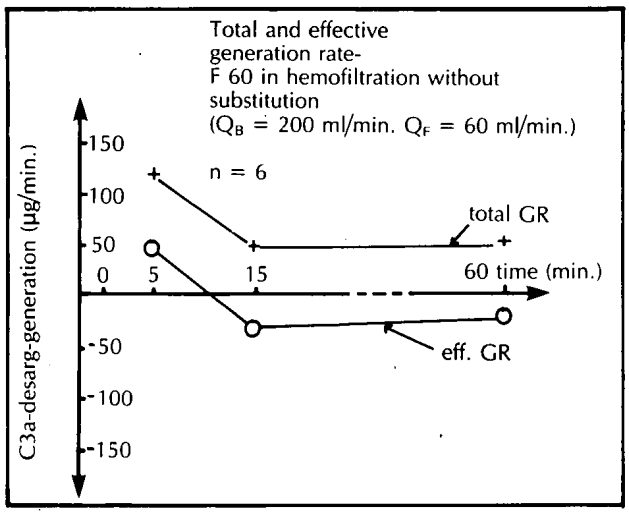

Fig. 8.—Total and effective generation rate of C_3a-desarg. in F 60 used as hemofilter.

correlation between ETO-induced protease release and anaphylactoid symptomes. By comparing the frequency of complications between plate-dialysers and hollow-fibre-dialysers Henne et al. [32] found convincing evidence that ETO-release was correlated to dialyzer-design and its flow geometry. In hollow-fiber kidneys, residual ETO was trapped in the potting material of the device. This underlines again the importance of careful preparation of a dialyser by sufficient rinsing before its clinical application [33].

Baurmeister et al. [34] reported a significant correlation between the anaphylactoid symptoms and the prevalence of ETO-antibodies in serum.

Since γ-radiation is also known to produce biological active radicals and these radicals may activate the complement cascade, further studies are required to elucidate the influence of different modes of sterilisation for acute and chronic complications in dialysis patients. From the present knowledge it seems justified to propose steam-sterilisation as the most biocompatible procedure.

2. *Dialyser geometry*

An often ignored impact on biocompatibility is that of the geometric design of a dialyser. Shear stress is different in hollow fiber or flatsheet dialysers. As a consequence of shear an increased aggregation of preferably white cells as well as a cell damage up to a lysis in blood cells was reported [35, 36]. The data on shear stress available today do not permit a final estimation about its importance on biocompatibility of a dialyser, it must however be seriously considered for further investigation.

3. *The patient*

In the vast number of recent studies an biocompatibility the most important factor for the clinical relevance of biocompatibility has been almost neglected - the patient. We see convincing evidence, that the actual characteristic of the patient at the time of application of the device will have an important effect upon the actual and chronic reaction of the organism. This wide variety even in one individual during the course of treatment may well explain the big differences in clinical observations in regard to biocompatibility.

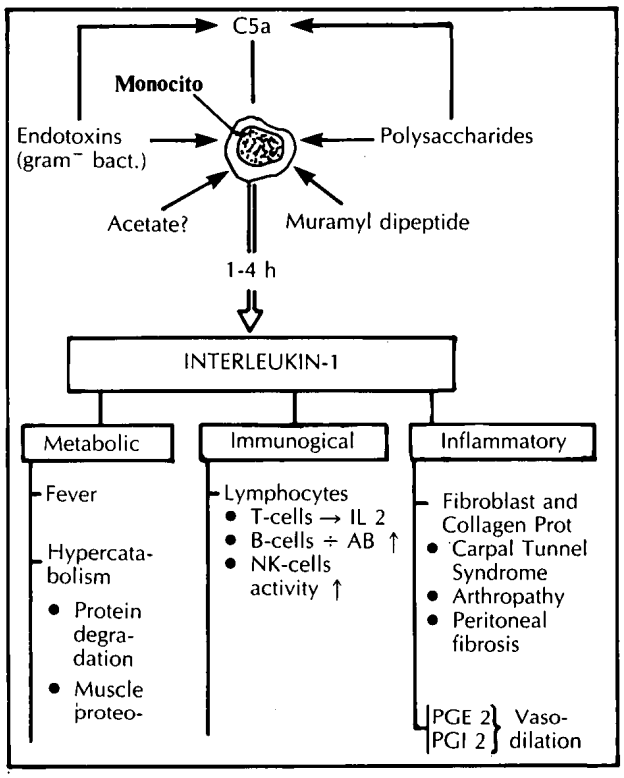

Fig. 9.—Biological activity of Interleukin-1.

Conclusions

It is apparent from literature, that the clinical relevance of biocompatibility relies on numerous reactions of the host (patient) - material (dialyser) interrelation. Given the complexity of these reactions and the incomplete knowledge of its interaction with the human body, it is completely unjustifiable to either employ a single parameter as the only criterion for final judgement of the compatibility of the material nor would it be justified to judge a multi-material device like a dialyser by the biocompatibility of a single component of this device. The multifactorial sources for different reactions are listed in table II + III.

Furthermore performance and compatibility of the same biomaterial depends on numerous characteristics, f. e. the environment of its application, the device design, the interaction with other materials used in the same device, the anatomic site of its application, etc. A biomaterial, that fails in a specific

application should not automatically be excluded from consideration for a different setting and, on the contrary, the successful use of a biomaterial in a special application does not always guarantee for its multipurpose use.

Table VIII summarizes the main factors which are known today to influence the biocompatibility of a dialyser.

In the future the biocompatibility of a material will be the basis of artificial organs development. However, for the final judgement of the compatibility of a biomaterial product like an artificial kidney the single material should never be divorced from the device.

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