Leukocyte Dynamics during Haemodialysis

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After the initial article by Kaplow and Goffinet in 1968 we reported profound changes in the leukocyte count during the first hour of haemodialysis with three types of dialyzers (Gral et al., 1969). In the present study we supplemented our experiments with other types of dialyzers and tried to further elucidate the mechanism of the leukocyte dynamics during haemodialysis.

METHODS
Thirty chronic haemodialysis patients were studied. All had indwelling teflon silastic arterio-venous cannuae and had no apparent shunt or systemic infection at the time of the study. The patients were on regular intermittent dialysis and their uraemic state was stable. Dialysis was performed with the Ultra Flo 145 (Coil) Dialyzer [Travenol] in 12 patients, with the Hollow Fiber Artificial Kidney (HFAK) [Dow Chemical] in 6, with the two layer Kill Parallel Flow Dialyzer (Kill) [Western Gear] in 6 patients, with the EX-01 Dialyzer (EX) [Extracorporeal] in 6 and the Ultra Flo 100 Coil (Coil 100) Dialyzer [Travenol] in 3 studies. More than one type of artificial kidney was utilized in most patients. Blood for leukocyte counts was drawn before dialysis from the arterial cannula of the arteriovenous shunt, then 20, 40 and 60 minutes after starting dialysis from the arterial (in some studies also from the venous) line of the blood tubing. Additional hourly leukocyte counts were taken until the end of dialysis on two studies with the Coil, HFAK and Kill dialyzers each. A leukocyte count was drawn at the end of haemodialysis with all EX and Coil 100 dialyzers. The technique of leukocyte count was described previously (Gral et al., 1969). The coil dialyzers were used only once; in 8 Kill studies the same membranes were reused after properly cleaning and sterilizing (Sodium hypochlorite 500 ppm and 2% Formalin) the dialyzer. In the Kill and EX experiments also a 10 minute leukocyte count was performed.

RESULTS
In 22 studies including 10 Coils (Ultra Flo 145), 6 HFAK and 6 EX-01 dialyzers
the mean leukocyte count decreased from 6400/cmm to 2600/cmm (60% drop) at 20 minutes after the start of haemodialysis, then came back to predialysis levels at 60 minutes and stayed stable without major decrease or rebound until the end of dialysis.

Since there was practically no change in the mean lymphocyte count, the leukocyte fall consisted entirely of a decrease in neutrophil population (Figure 1).

In Figure 2 the findings from four types of artificial kidneys are depicted. The Kiil Parallel Flow two layer dialyzers are divided into studies with seven new and eight reused membranes. Whereas the fall in leukocytes at 20 minutes of haemodialysis is fairly uniform with the Coil, HFAK, EX and new Kiil dialyzers, the leukocyte drop at 20 minutes with the reused Kiil is less.

In Figure 3 the Coil, HFAK, EX and new Kiil data are compiled together, since the difference in the leukocyte fall between them is at no time significant (p>0.5). If plotted against the reused Kiil dialyzer the difference in the 20 minute leukocyte fall is significant (p=0.05). However, at 40 and 60 minutes the results are similar in all dialyzers.

The difference between the (new and reused) Kiil and EX dialyzers seems to be in the earlier onset and somewhat greater magnitude (at 10 minutes) of the leukopenia especially with the reused Kiil dialyzer. Since the volumes of

![Figure 1. Mean leukocyte counts (±S.E.) during first hour of dialysis](image-url)
Figure 2. Percent change in mean leukocyte count (± S.E.) with four types of dialyzers. First hour of dialysis.

Figure 3. Percent change in mean leukocyte count (± S.E.) during first hour of dialysis with new and reused dialyzers.
both types of dialyzers are about equal, the earlier leukocyte fall in the reused Kiil is possibly caused by the washout and sterilization techniques (Figure 4).

In six studies with the Coil as well as in four experiments with the HFAK, Kiil and EX artificial kidneys there was no arterio-venous (pre and post dialyzer) difference in the leukocyte count. Intravenous isotonic saline rinse from four Coil, two Kiil and two EX dialyzers did not induce leukopenia in the patient; neither did a 5% AlbumisolR (5% albumin in 0.9% saline) rinse of two Coils and four EX dialyzers, nor a blood prime of the dialyzers (Table I).

In vitro recirculation of isotonic saline through the dialyzer for 15 minutes and infusion into the patient did not alter the leukocyte count at 10–20 minutes of haemodialysis. However, recirculation of blood or AlbumisolR through the dialyzer caused profound leukopenia (four Coils and two EX dialyzers in the blood recirculation study; two Coils and four EX dialyzers in the Albumisol study). Table II is a summary of these experiments.

Recurrent or persistent leukopenia was observed also with exchange of dialyzers at the nadir of the leukocyte fall. Intravenous hydrocortisone, 100 mg administered two to six hours prior to haemodialysis did not prevent the leukocyte fall at twenty minutes after initiation of dialysis in three Coil, one Kiil and two EX studies (Table III).
### TABLE I. Leukocyte dynamics

<table>
<thead>
<tr>
<th>Pre and post-dialyzer (A-V) leukocyte study</th>
<th>Number of dialyses with</th>
<th>Leukocyte count 10-20 min after starting haemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological saline rinse from dialyzer</td>
<td>UF* 6 HFAK** 4 Kill*** 4 EX**** 4</td>
<td>No difference</td>
</tr>
<tr>
<td>Phlebotomy into dialyzer then return to patient</td>
<td>4 2 - 2</td>
<td>No change</td>
</tr>
<tr>
<td>5% Albumisol rinse from dialyzer</td>
<td>2 2 - 4</td>
<td>No change</td>
</tr>
<tr>
<td>Physiological saline recirculated 15 min through dialyzer then given to patient I.V.</td>
<td>2 - 1 2</td>
<td>No change</td>
</tr>
</tbody>
</table>

* Ultra Flo 145 Coil Travenol  
** Hollow Fiber Artificial Kidney Dow  
*** Kill Parallel Flow Dialyzer Western Gear  
**** EX-01 Low Volume Coil Extracorporeal

### TABLE II. Leukocyte dynamics

<table>
<thead>
<tr>
<th>Number of dialyses with</th>
<th>Leukocyte count 10-20 min after initiation of haemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular dialysis</td>
<td>12 6 15 6 2</td>
</tr>
<tr>
<td>100 mg hydrocortisone I.V., 2-6 hr prior to dialysis</td>
<td>3 - 1 2 -</td>
</tr>
<tr>
<td>Exchange of dialyzer at low point of leukopenia</td>
<td>4 - 2 2 1</td>
</tr>
<tr>
<td>Phlebotomy into dialyzer, in vitro recirculation 15 min then return to patient</td>
<td>4 - - 2 -</td>
</tr>
<tr>
<td>5% Albumisol into dialyzer, in vitro recirculation 15 min then given I.V.</td>
<td>2 - - 4 -</td>
</tr>
</tbody>
</table>

* Ultra Flo 145 Coil Travenol  
** Hollow Fiber Artificial Kidney Dow  
*** Kill Parallel Flow Dialyzer Western Gear  
**** EX-01 Low Volume Coil Extracorporeal  
***** Ultra Flow 100 Coil Travenol

### DISCUSSION

Several substances can induce transient leukopenia; the best known being intravenous colloids, bacterial endotoxin and etiocholanolone. The latter two may cause leukopenia prior to increasing the white blood cell count (Vogel et al, 1967; Perry et al, 1968). Haemodialysis induced leukopenia can now be added as an established but poorly understood phenomenon. The most striking feature of this leukocyte fall is its rapidity, making it somewhat dissimilar to the previously mentioned leukopenic agents which tend to act much more slowly. The immediate onset of leukopenia suggests leukocyte trapping. Since the dialyzer is probably not the site of the leukocyte sequestration (no AV difference in leukocyte count in vivo and in vitro),
the leukocytes (granulocytes) have to be trapped or pooled elsewhere. Indeed, the patient's (or experimental animal's) presence is necessary to show evidence of dialysis-induced leukopenia, since in vitro dialysis of human (and dog) blood did not cause any change or difference in the leukocyte count of the pre- and post-dialyzer samples. In fact, the venous counts (post-dialyzer) tended to be somewhat higher, which readily can be explained by ultrafiltration in the dialyzer.

However, isotonic saline rinse from the dialyzer and even a 15 minute in vitro recirculation of normal saline through the dialyzer did not induce leukopenia after intravenous infusion into the patient. This indicates that the patients' blood is necessary as a contact medium for the leukopenic effect of the dialyzer. To our surprise, however, a blood prime of the dialyzer (patient's own blood or blood bank blood) did not evoke leukopenia, and in order to induce a 10-20 minute leukocyte fall, the blood had to be recirculated through the dialyzer for 15 minutes. The confirmation of this phenomenon with Albumisol would indicate that a substance or factor from the dialyzer membrane — for which the name 'leukokinetin' was offered — is carried and activated by protein (but not by saline), and this in turn initiates the profound leukopenic response (Table II). The question remains, where the leukocytes (granulocytes) actually disappear and from where they reappear. Since there are several organs which may act as granulocyte filters or reservoirs and there is an intricate interrelationship between the circulating and marginal leukocyte pools, the query is not easy to answer. Furthermore, the human organism is able to respond to various leukokinetic stimuli with an increased production and mobilization of leukocytes. Leukopoietin is believed to play a role in the release of granulocytes from the bone marrow and also in the increased maturation of leukocytes from the stem cells of the bone marrow (Essers, 1967). A scheme of a possible pathway for the

![Substance from Dialyzer](Leukokinetin ?) ↓
Circulating Neutrophils
Margination
Mobilization
Sequestration
Neutropenia
Leukopoietin
Marginal Pool (Mature Neutrophils)
Bone Marrow (Bands)
Return of Neutrophils to Predialysis Values

Figure 5. Possible pathway of dialyzer induced neutropenia
dialyzer-induced leukopenia (neutropenia) is given in Figure 5. 'Leukokine-
tin' from the dialyzer activated by protein, would induce a sequestration and
margination of leukocytes (neutrophils). The ensuing neutropenia as a strong
stimulus for a second enzymatic substance — 'leukopoietin' — would in return
influence the marginal leukocyte pool and the bone marrow, and hence both
mature neutrophils and young cells from the marrow would replenish the low
circulating leukocyte pool.

More studies are indicated to evaluate these rather interesting questions
which may have an important bearing on the poorly understood problem of
leukokinetics.

SUMMARY
In 30 patients, the leukopenic effect of haemodialysis was examined with
several types of dialyzers. The profound leukocyte fall at 20 minutes after
initiation of haemodialysis was in neutrophils; the number of lymphocytes
did not change.

The leukocyte count returned to normal within the next hour of haemo-
dialysis and did not change significantly throughout the rest of dialysis.

The leukocytes were probably not sequestered in the dialyzer but trapped
and/or marginated in the patient.

A factor from the dialyzer (leukokinetin) activated by protein, but not
saline, may be responsible for the leukokinetic-leukopenic effect.

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