5 Operating Characteristics of Hollow-Fiber Dialyzers

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INTRODUCTION

This survey of dialyzer characteristics is essentially limited to hollow-fiber devices (referring also to flat membranes when of theoretical importance only), as other dialyzer types are slowly disappearing from use.

This chapter will describe the basic mathematical tools needed to understand how to calculate dialyzer performance under various conditions, avoiding mathematical derivations (which can be found in literature). One application is in establishing computer programs that enable the dialyzer user to predict performance under special or modified operating conditions.

The present survey includes an approach for the optimization of hollow-fiber bundle dimensions developed by the author and successfully applied in dialyzer design. Some general information concerning various operating conditions is also presented, as well as considerations concerning cost-efficiency. Finally, operation of devices with high-flux membranes will be discussed.

Today, many types of hollow fibers are available. They not only differ in their permeabilities and (at least claimed) blood compatibilities, but also in mechanical properties, the latter of which have indirect influence on dialyzer characteristics. One mechanical factor, for example with impact on the performance of the dialyzer is the individual fiber's tear strength. A softer fiber material often requires a thicker fiber wall for sufficient strength and, furthermore, requires more careful handling in dialyzer assembly. As a result of the latter, fibers with lower tear strength cannot be as easily formed into well-ordered bundles as can strong fibers, which can be wound under considerable tension, e.g., on a polygonal wheel, keeping fibers straight, ordered, and well positioned in the bundle. Moreover, softer materials develop leaks more easily.

The need for a greater wall thickness when a weak or soft fiber material is used, influences permeability characteristics. For "middle molecules," the permeability is primarily determined by properties and structure of the membrane material. This is true for water permeability as well. For urea and other "small molecules," however, the permeability is roughly inversely proportional to fiber wall thickness, with a relatively small influence of the membrane material per se. As a general rule, therefore, one may say that softer membrane materials tend to result in lower urea clearances to the degree that they require greater wall thicknesses for sufficient strength.

When a high urea clearance is considered important, strong fibers, such as regenerated cellulose of the cuprammonium type (cuprophan and the similar membrane types of Asahi and Terumo) or viscose type are, therefore, preferable (raw, or saponified cellulose acetate is weaker). When "middle molecule" clearance is judged important or of special interest, other membrane materials may be advantageous, as they may be for treatment requiring high ultrafiltration rates.

The blood compatibility of the fiber material is improved by proper dialyzer priming. Differences in primary compatibilities claimed by manufacturers may be less apparent when the priming procedure is correctly performed, preferably with slight ultrafiltration in order to flush not only the dialyzer compartments and membrane surfaces, but also the membrane structure (membrane wash-through).

The first membrane materials used for hollow fibers were saponified cellulose acetate and cuprophan. The latter material, spun from cellulose via the cuprammonium or cuoxam process, originally used for textile fibers, results in the strongest hollow fibers available, far exceeding other materials in strength, except for cellulose hollow fibers spun via the viscose process (still more or less in an experimental phase).

The concept of the Cuprophan hollow fiber was conceived in 1969, by Heinz Ruck,[1] now professor at the University of Wuppertal (West Germany). His original drawing of a spinneret, shown in Fig. 5–1, is of great historical interest since it began a revolution in dialysis technology. Since the invention was privately developed, it was presented to and adopted by Bemberg

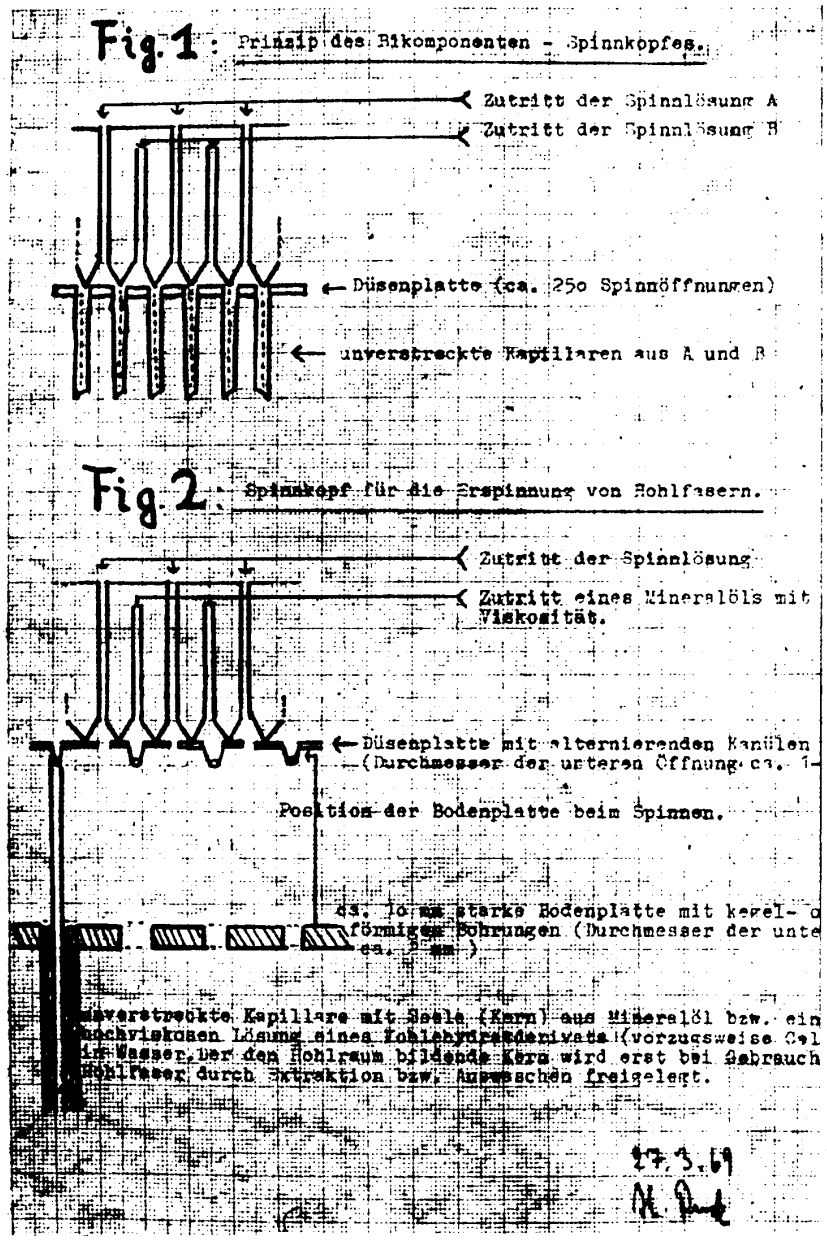

Figure 5–1. H. Ruck's original drawing of an arrangement for the extrusion of hollow fibers, using the cuprammonium process.

AG—later Enka AG—in Wuppertal by letter on March 27, 1969. It is anecdotal that the clearly documented inventorship has never been officially recognized by the manufacturer, who also did not comment on this in a statement concerning the inventorship in a book published in 1981.[2] The first Cuprophan hollow fibers were made by Dr. Ruck on June 27, 1969, as documented in a report of July 29 of the same year, in which the establishment of an experimental laboratory was also proposed. In the years 1970 to 1972, experimental extrusion took place with various oils as fillers and various types of spinnerets, from which the marketed fiber emerged.

Another interesting development is worth mentioning. In the mid-1970s, the Schott & Gen. Co. in Mainz, West Germany, presented a porous glass hollow fiber. Blood contact with glass generally promotes clotting, but this problem has been solved. The fibers were tested with

TABLE 5–1. AVAILABLE HOLLOW-FIBER MEMBRANES FOR DIALYSIS

Manufacturer	Description
Asahi	*Cuprammonium rayon*—a variety of Cuprophan (see Enka) *Biomembrane*—cuprammonium rayon with a 200–300 Å synthetic inner layer
CD Medical	Saponified cellulose ester Cellulose acetate
Enka	*Cuprophan*—cellulose regenerated by means of the cuprammonium process *Hemophan*—a modified cuprophan with improved biocompatibility
Gambro	*Gambrane*—an experimental polycarbonate copolymer
Hospal	Acrylonitrile-Na-methallyl-sulfonate copolymer
Kuraray	*EVAL*, ethylen-vinyl alcohol copolymer (various types)
Toyobo (Nipro)	Cellulose acetate
Teijin	Saponified cellulose acetate, including a version with longitudinal ribs on the outside surface for keeping distance between adjacent fibers.
Terumo	Cellulose regenerated by means of a modified cuprammonium process
Textilkombinat (Pirna, GDR)	Cellulose regenerated by means of the viscose process
Toray	Polymethylmethacrylate

interesting results by some dialyzer manufacturers, but never adopted as a marketable product. One reason for the interest in this fiber is that the reusability could be almost unlimited, as the fiber withstands even aggressive cleansing procedures. One could envision a situation in which each patient used one dialyzer per year, or even longer. Such an outlook is unattractive to a mass-product-oriented dialyzer manufacturer, whose products are labeled as disposable single-use devices. However, one day a manufacturer may market a dialyzer specifically designed for reuse. Such a device could eventually find wide acceptance even at a considerably higher market price than that spent today for conventional dialyzers.

Today, quite a wide variety of hollow-fiber types are used in dialyzers. A list is given in Table 5–1.

DIALYZER CLEARANCE

The clearance of a dialyzer may be defined as the portion of the blood flow from which a substance is completely removed. For purposes of illustration, suppose that the blood leaving the dialyzer could be split into two streams: one with unaltered concentration of a given substance and one with zero concentration. The flow of the latter stream is equal to the clearance for that substance. This is valid only for zero or negligible ultrafiltration.

If the blood concentration is C_{bi} at the inflow to the dialyzer and C_{be} at its exit, and Q_b is the blood-flow rate, one has at zero ultrafiltration[3,4]

$$Q_c = Q_b\left(1 - \frac{C_{be}}{C_{bi}}\right) \tag{1}$$

$$C_{be} = C_{bi}\left(1 - \frac{Q_c}{Q_b}\right) \tag{2}$$

$$\dot{M} = Q_c C_{bi} \tag{3}$$

where Q_c is the clearance (the notation Q being chosen because it has the physical dimension of flow, such as Q_b), and $\dot{M}$, the solute mass transfer out of the blood.

In the presence of ultrafiltration, the clearance may be more easily viewed as the portion, Q_c, of the input blood flow Q_{bi} from which the solute is elimated due to the mass transfer, $Q_c C_{bi}$. It equals the mass transfer, $\dot{M}$, divided by the input blood concentration C_{bi} of the given solute. Thus eq. (3) still holds in the case of ultrafiltration, but eq. (1) is replaced by[3,4]

$$Q_c = Q_{bi} - Q_{be}\frac{C_{be}}{C_{bi}} \tag{4}$$

where Q_{bi} is the input and Q_{be} the exit blood-flow rate. Because the difference between Q_{bi} and Q_{be} equals the ultrafiltration rate Q_u, this relation can also be written as

$$Q_c = Q_{co} + Q_u\frac{C_{be}}{C_{bi}} \tag{5}$$

where Q_u is the total ultrafiltration rate and Q_{co} the clearance at $Q_u = 0$. Equation (2) is in this case replaced by

$$C_{be} = \frac{Q_{bi} - Q_c}{Q_{be}}C_{bi} = \frac{Q_c - Q_{co}}{Q_u}C_{bi} \tag{6}$$

Equation (5) shows that the clearance is higher when ultrafiltration is taking place. This is not only a primary effect of the convective transport with the ultrafiltered plasma water as eq. (5) shows an increase in clearance even if one would extract Q_u as pure water, with zero concentration of the actual solute. Thus, the clearance increase also results from a concentration effect, tending to increase the blood concentration due to water extraction, which then, in turn, leads to a higher rate of solute diffusion through the membrane.

Simpler attempts to estimate the effect of ultrafiltration on clearance are based on eq. (5), assuming that the

change in C_{be} caused by ultrafiltration is negligible. In fact, however, this change in C_{be} can have an important effect, except in the case of a very small ultrafiltration rate. The more general case is treated in some detail later in this chapter.

MASS TRANSFER THROUGH A MEMBRANE

The mass transfer of a given substance through a membrane is governed by the diffusion equation. For a uniform flat membrane, the following equation applies[5]:

$$J = k(C_1 - C_2) \tag{7}$$

where J is the mass transfer rate per unit area (mass flux) and k the diffusive permeability coefficient. C_1 and C_2 are the concentrations of the substance at the two surfaces of the membrane and the mass transfer J goes from the higher to the lower concentration. Typical units for J and k are cm/s or cm/min, the concentration C being dimensionless (relative volume concentration). The concentration could also be expressed in, for example, mg/cm^3, in which case the unit for J becomes mg/sec,cm^2, or mg/min,cm^2.

This equation also applies to a hollow-fiber membrane; in such an instance, however, a specification is needed as to which of the two membrane surfaces one is referring. Because the membrane in this instance has a circular cross section, the mass flux is divergent (when flowing from inside to outside, as is usually the case). Therefore, the value of J is different at the two surfaces of the hollow fiber and, furthermore, varying inside the membrane. In the same manner, the value of k differs, depending upon which of the two surfaces one refers.

The coefficient k in eq. (7) can be related to a diffusion coefficient or constant for the membrane material. If the membrane is nonhomogenous, this is hypothetical and relates to an apparent or mean diffusion coefficient. Also, the actual solute concentration may exhibit a rapid change inside the membrane, at its surface. The diffusion coefficient in these circumstances is an apparent quantity, relating to external surface concentrations only.

Normally, the parameter measured for characterization of a membrane is k and not the diffusion coefficient. Nevertheless, the relation between the two parameters may be quantified. For a flat membrane, this relations is[5]

$$D_m = kh \tag{8}$$

where h is the thickness of the membrane. D_m is the (usually mean or apparent) diffusion coefficient of the membrane material, commonly expressed in cm^2/sec or cm^2/min.

For a hollow-fiber membrane of thickness h, having an internal radius r_i, the relation is[5]

$$D_m = kr_i \, ln\left(1 + \frac{h}{r_i}\right) \tag{9}$$

The *diffusion resistance* of the membrane is the inverted value of k,

$$R = \frac{1}{k} \tag{10}$$

usually expressed in min/cm or s/cm.

STACKED MEMBRANES

When calculating the clearance of a dialyzer, it is convenient to consider the membrane as composed of three layers: the actual or physical membrane and two hypothetical membranes representing the effects of the boundary layers of the fluids flowing over the two membrane surfaces. The total diffusion resistance of this hypothetically composed membrane is, for a flat configuration:[6,15]

$$R_t = R_d + R_m + R_b \tag{11}$$

where R_m is the diffusion resistance of the physical membrane, R_d of the hypothetical membrane representing the boundary layer on the dialysate side and R_b of the hypothetical membrane representing the boundary layer on the blood side. The corresponding relationship for the permeability coefficients is

$$\frac{1}{k_t} = \frac{1}{k_d} + \frac{1}{k_m} + \frac{1}{k_b} \tag{12}$$

These relationships also apply to a hollow-fiber membrane if all individual values of R or k, respectively, refer to the same radius, usually the internal radius r_i of the physical membrane. The general relationships are[15]

$$\frac{R_t}{r_t} = \frac{R_d}{r_d} + \frac{R_m}{r_m} + \frac{R_b}{r_b} \tag{13}$$

and

$$\frac{1}{k_t r_t} = \frac{1}{k_d r_d} + \frac{1}{k_m r_m} + \frac{1}{k_b r_b} \tag{14}$$

where r_t, r_d, r_m, and r_b are the corresponding radius values to which R and k, respectively, refer.

BOUNDARY LAYERS

The diffusion resistance of the boundary layer on the blood side can for a flat membrane be expressed as[15]

$$R_b = 0.25 \frac{h_b}{D_b} \tag{15}$$

where h_b is the thickness of the blood channel (from membrane to membrane) and D_b the diffusion coefficient in the blood (or, respectively, the test solution).

For a hollow-fiber membrane of internal radius r_i, the value can be expressed as[6]

$$R_b = 2\alpha \frac{r_i}{D_b} \tag{16}$$

referred to the internal fiber surface of radius r_i.

Herein

$$\alpha = 2\left(\frac{1}{p_1^2} - \frac{1}{4w}\right) \tag{17}$$

where p_1 is the first positive root of

$$\begin{aligned} &-p^{10}\,(0.421880 + w0.0926930)\,10^{-7} + p^8 \\ &\qquad (0.566862 + w0.145445)\,10^{-5} \\ &-p^6\,(0.450304 + w0.144043)\,10^{-3} + p^4 \\ &\qquad (0.0182292 + w0.00792101) \\ &-p^2\,(0.25 + w0.1875) + w = 0 \end{aligned} \tag{18}$$

and

$$w = \frac{r_i}{D_b(R_m + R_d)} \tag{19}$$

R_m and R_d are the diffusion resistances of the physical membrane and the dialysate boundary layer, respectively, as specified above.

The value of α falls between 0.229 and 0.274, so that a reasonable approximation is 0.25, the value in equation (15) (if h is taken as $2r_i$).

For a flat membrane, the value of R_b according to eq. (15) is only an estimate, as the blood-channel thickness varies, not only geometrically, but also with the local transmembrane pressure.

An expression for the diffusion resistance of the dialysate boundary layer in the case of a flat membrane arrangement is not known. It would have to be of the type[6]

$$R_d = \lambda \frac{h_d}{D_d} \tag{20}$$

where h_d is the mean thickness of the dialysate channel (from membrane to support) and D_d the diffusion coefficient in the dialysate. No value for λ has been found in the literature. Such a value would also depend on the membrane support structure. However, values of R_m given in the literature ~~approximate~~* the effect of R_d. Some works[15] on the determination of R_m are based on the erroneous assumption that R_d would approach zero if only the dialysate flow is high enough, or if the fluid is well stirred on the dialysate side. This is, however, basically impossible. As is seen, the value of R_b is *independent of the flow rate*. The same will necessarily hold for R_d, except for a rapid transition to another nonzero value, from there on, again constant, when the flow condition changes from laminar to turbulent. Observed effects of dialysate flow rates relate to dialysate flow distribution.

* more or less include

In other publications,[7] suitable experimental systems with vigorous stirring are used, for which the boundary layer permeability can be calculated—conditions entirely different from the laminar-flow condition in a flat-membrane dialyzer but yielding a fairly true value of R_m.

For a hollow-fiber membrane, an approximation for R_d is known. It is an approximation in that the expression is derived for the ideal condition of a regular, hexagonal array of equidistant parallel fibers. In the real case, the fiber arrangement can never be regular to such a high degree. However, if the cross-sectional area of the fiber bundle is the same for both the real and the hypothetical (perfectly ordered) case, the value calculated for the regular, hexagonal array will approximate the real case, because local deviations from the "perfect" arrangement will more or less average out.

The dialysate boundary–layer resistance for a hollow-fiber dialyzer with a "perfect" fiber arrangement is[6]

$$R_d = \frac{r_e}{72\,D_d}\frac{W}{V} \tag{21}$$

where

$$V = (3 - 4t^2 + t^4 + 4 \ln t)^2 \tag{22}$$

$$\begin{aligned} W = {} & -719 + 1680t^2 - 1296t^4 + 368t^6 - 33t^8 \\ & -120\,(19 - 24t^2 + 6t^4) \ln t - 288(9 - 4t^2) \ln^2 t \\ & -1152 \ln^3 t \end{aligned} \tag{23}$$

R_d in eq. (21) refers to the external membrane surface of radius r_e. If it is multiplied by r_i/r_e, it refers to the internal membrane surface of radius r_i, as does R_b of eq. (16) and usually also values of R_m as given in the literature.

Here, t is a parameter relating to the fiber packing density n in the bundle:

$$t = r_e \sqrt{\pi n} \tag{24}$$

where the packing density n (number of fibers per unit cross-sectional area) is

$$n = \frac{N}{A_b} \tag{25}$$

Here r_e is the external radius of the fiber, N is the total number of fibers in the bundle, and A_b is its cross-sectional area.

It should be noted, however, that values given in the literature for R_m of hollow fibers usually also include R_d of the test system[8] as above mentioned vigorous stirring effects (in test cells for flat membranes) are quite ineffective in hollow-fiber bundles. The agitation must take place very close to the membrane surface, a location unreachable in a hollow-fiber bundle. Observed influences of the dialysate flow rate relate obviously, therefore, to improved dialysate distribution in the bundle (or reduction of the influence of nonuniform distribution) at higher dialysate flow rates, and not to reduction of the dialysate boundary-layer permeability.

DIALYZER CLEARANCE UNDER NORMAL OPERATION

In this section, the effect of ultrafiltration is ignored. The normal operating condition is defined as one of countercurrent flow.

As has been shown in many publications, the clearance of a dialyzer with a total membrane resistance R_t (including boundary layer effects) and an active surface area A in countercurrent operation is[3,5,6,8–10]

$$Q_c = Q_b Q_d \frac{1 - \exp\left(-\frac{A}{R_t}\frac{Q_d - Q_b}{Q_d Q_b}\right)}{Q_d - Q_b \exp\left(-\frac{A}{R_t}\frac{Q_d - Q_b}{Q_d Q_b}\right)} \qquad (26)$$

where Q_d and Q_b are the dialysate and blood flow rates, respectively (usually in ml/min). For the clearance, the notation Q_c is used here, as it also has the dimension of flow (usually given in ml/min as with Q_d and Q_b).

This equation becomes "0/0" or incalculable when $Q_d = Q_b$. By means of a mathematical procedure (using l'Hôpital's rule), one finds for this special case[10]

$$Q_c = \frac{AQ_b}{A + R_t Q_b} \qquad (27)$$

valid only when $Q_d = Q_b$.

In a physical dialyzer, Q_c deviates somewhat from the theoretical value calculated by using eq. (26). This occurs because dialysate flow is not uniform over the entire membrane. In a hollow-fiber dialyzer, nearly conical sections at the bundle ends have low dialysate perfusion, approaching zero at the very ends of the active part of the bundle. Other deviations may, for individual dialyzers, be caused by such factors as a marked nonuniformity of the fiber arrangement, which can lead to dialysate channeling (preferred paths for dialysate flow).

"STANDARD CLEARANCE"

Traditionally, clearance values have usually been given for a dialysate-flow rate Q_d of 500 ml/min and a blood-flow rate Q_b of 200 ml/min. Therefore, the clearance under this condition could be regarded as a kind of "standard clearance," from which clearance values under other conditions can be calculated.

For this "standard condition," (26) gives a "standard clearance" value of

$$Q_{cs} = 1000 \frac{1 - \exp(-0.003\, A/R_t)}{5 - 2\exp(-0.003\, A/R_t)} \qquad (28)$$

Inverting this formula, k_t and R_t can be calculated for any dialyzer:

$$k_t = \frac{1}{R_t} = \frac{1}{0.003\, A} ln \frac{1 - 0.002\, Q_{cs}}{1 - 0.005\, Q_{cs}} \qquad (29)$$

From this, again, the clearance Q_c at any value of Q_d and Q_b, respectively, can be calculated, using eq. (26). An estimate can also be made of Q_c for another surface area A, if the fiber type, the fiber packing density, and the configuration remain the same.

DIALYZER CLEARANCE UNDER SPECIAL OPERATING CONDITIONS

Because the performance of a dialyzer is always lower in cocurrent and cross-flow operation modes, it is of minimal interest here to review the clearance equations for such conditions. (If desired, they can be found in the literature.) No dialyzer is designed for cocurrent operation and an earlier design for cross-flow operation disappeared from the market quickly.

The only special operating condition at least theoretically of some interest is one with dialysate recycling from the outlet to the inlet by means of a feedback pump, creating local recirculation. If the net dialysate flow rate is Q_d and the feedback pump returns a flow Q_p from outlet to inlet, the total dialysate flow inside the dialyzer is $Q_d + Q_p$. The resulting increase in the local flow rate has a positive effect on the clearance, which is, however, limited by the fact that the entering dialysate contains measurable concentrations of solutes to be removed. As shown in the literature, the clearance equation in this case becomes[3,4]

$$Q_c = Q_b Q_d \frac{1 - \exp\left[-\frac{A}{R_t}\frac{Q_d + Q_p - Q_b}{(Q_d + Q_p)\, Q_b}\right]}{\frac{Q_b Q_p}{Q_d + Q_p} + Q_d - Q_b \exp\left[-\frac{A}{R_t}\frac{Q_d + Q_p - Q_b}{(Q_d + Q_p) Q_b}\right]} \qquad (30)$$

If one calculates the limiting clearance as $Q_p \to \infty$, which is the maximum possible clearance under such operation, one finds a value between 0.7 $Q_{c\infty}$ and $Q_{c\infty}'$, where $Q_{c\infty}$ is the clearance value at infinite dialysate flow without feedback, that is, with zero inlet solute concentration.

As will be seen later in this chapter, suitable dialyzer operating conditions are such that little can be gained by a further increase in the dialysate flow rate Q_d. The clearance improvement resulting from dialysate feedback is even less, and the arrangement is hardly worth the effort and extra cost.

PRESSURE DROPS IN HOLLOW-FIBER DIALYZERS

The pressure drop on the blood side in the hollow-fiber bundle is easily calculated by means of Poiseuille's formula[5]

$$\Delta p_b = \frac{8\eta_b Q_b L}{\pi N r_i^4} \qquad (31)$$

where Q_b is the flow and η_b, the viscosity of the blood (or test solution), L is the fiber length, N, the number of fibers in the bundle, and r_i the internal radius of the fiber.

The dialysate side pressure drop can be calculated for an ordered hexagonal array of parallel equidistant fibers as[5]

$$\Delta p_d = \frac{8\eta_d Q_d L t^4}{\pi N r_e^4 F(t)} \tag{32}$$

where the parameter t is defined by eq. (24) and

$$F(t) = 4(t^2 - \ln t) - 3 - t^4 \tag{33}$$

Q_d is the flow of dialysate and η_d, its viscosity. r_e is the external radius of the fiber. N and L are as above. The parameter t is related to the fiber packing density n, as given by eq. (24) and (25), being an essential parameter in the optimization of bundle dimensions.

In real dialyzers, fibers are not so perfectly ordered. Nevertheless, deviations from the perfect hexagonal array of equidistant fibers will average out over the several thousand fibers in the bundle so that eq. (32) is valid as a good approximation.

ULTRAFILTRATION

The local transmembrane pressure varies due to pressure drop effects. If p_{bo} and p_{do} are the blood and dialysate pressures at the "venous" end of the active part of the hollow-fiber bundle (blood outlet/dialysate inlet end), the mean transmembrane pressure (taken positive from blood to dialysate) is[6]

$$\bar{p}_{tm} = p_{bo} - p_{do} + \frac{1}{2}(\Delta p_b + \Delta p_d) \tag{34}$$

For symmetrical designs, the same value $\bar{p}_{tm}$ results if p_{bo} and p_{do} are taken as the outlet blood port and dialysate inlet port pressures, respectively, and the pressure drop values are taken as the total pressure drops from port to port (including the pressure drop in potted and inactive fiber portions as well as in headers and dialysate distribution sections). The same relation holds for other types of symmetrical dialyzers, with corresponding additional pressure drops at the ends.

The ultrafiltration rate is

$$Q_u = k_u A \bar{p}_{tm} \tag{35}$$

where k_u is the ultrafiltration permeability coefficient and A, the active surface area of the membrane. The value of k_u is different for in vitro and in vivo operation, partly due to viscosity effects, and partly to a certain degree of protein deposition on the blood side of the membrane. A typical unit for k_u is cm/h, Torr (1 Torr = 1 mm Hg).

THE OPTIMIZATION OF HOLLOW-FIBER BUNDLE DIMENSIONS

The parameters to optimize are the fiber packing density n and the active fiber length L_a between the two resin plugs of the potting.

There are maximum values of n and t, in which the fibers are so tightly packed (without deformation of their round shape) in a hexagonal array that they touch all along their lengths. The centers of any three adjacent fibers then form equilateral triangles in the bundle cross section. From geometrical considerations, one finds in this case, as maximum values:

$$n_{max} = \frac{1}{2r_e^2\sqrt{3}} \tag{36}$$

and

$$t_{max} = \sqrt{\frac{\pi}{2\sqrt{3}}} \simeq 0.952313 \tag{37}$$

In Fig. 5–2, the relation between R_d, Δp_d, and t is represented graphically. For practical reasons, the values on the vertical axis in the diagram are proportional to $\sqrt[4]{\Delta p_d}$. The shaded areas in this diagram show ranges of values for common cuprophan fibers. Δp_b is calculated from eq. (31), using $\eta_b \simeq 2.4\ \eta_d$, as applies to hematocrit values typical for many dialysis patients.

From this diagram, one can conclude, as concerns the diffusion resistances, R_d, R_b, and R_m (see above):

- If Δp_d is of the order of 10% of Δp_b, R_d is of the same order of magnitude as $R_b + R_m$, which is unsuitable, as it is preferable to have R_d much lower than $R_b + R_m$;
- If R_d is of the order of 10% of $R_b + R_m$, Δp_d is of the same order of magnitude as Δp_b. This is an acceptable situation for clinical use.

Therefore, a "rule of thumb" for optimized design is to make the in vivo values of Δp_b *and* Δp_d *equal*. There is no sharp optimum, because deviations from equality in those values have relatively small effects on R_d in relation to $R_b + R_m$.

From eqs. (31) and (32), we thus find a relationship for an optimum packing density n and the corresponding parameter t

$$\eta_d Q_d t^4 r_i^4 \simeq \eta_b Q_b r_e^4 F(t) \tag{38}$$

irrespective of the fiber number N and the active fiber length L_a. $F(t)$ is given by eq. (33).

As is seen from the diagram in Fig. 5–2 (for common fiber dimensions), this leads to a t value of approximately 0.7, from which, with eq. (24)

$$n \simeq \frac{0.5}{\pi r_e^2} \tag{39}$$

For a more accurate and general calculation, one can write eq. (38) as

$$\left(\frac{r_i}{r_e}\right)^4 \frac{\eta_d Q_d}{\eta_b Q_b} \simeq \frac{1}{t^4}[4(t^2 - \ln t) - 3 - t^4] \tag{40}$$

from which the optimum value of t can be determined for

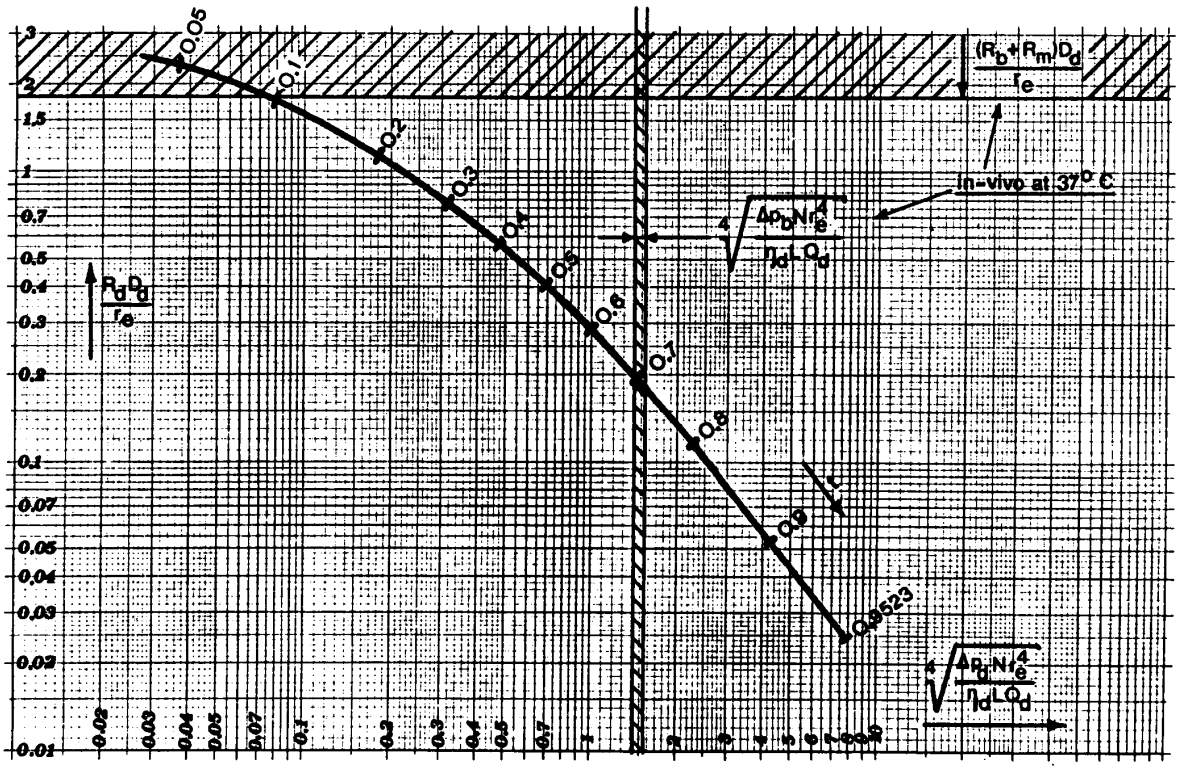

Figure 5–2. Diffusion resistance of the dialysate boundary layer versus dialysate pressure drop (curve) in comparison with corresponding values on the blood side (shaded areas) for common cuprophan fibers. The parameter t relates to the fiber packing density (see text).

any fiber dimensions and operating conditions with respect to fluid flows and viscosities. Equation (40) is best solved for t by means of iteration.

The choice of the active bundle length L_a depends upon the desired or tolerated value of the obligatory ultrafiltration rate, which is the lowest possible ultrafiltration rate under safe operating conditions. The operating condition is safe if the local transmembrane pressure is always positive (or zero), so that an accidental infusion of dialysate into the blood through a possible microleak ("pin-hole") in the membrane cannot take place. The obligatory ultrafiltration rate results when the transmembrane pressure is zero at the "venous" end of the active part of the hollow-fiber bundle, and hence amounts to

$$Q_{u\,min} = \frac{1}{2} k_u (\Delta p_b + \Delta p_d) \qquad (41)$$

according to (34), and (35), in which Δp_b and Δp_d are the pressure drops over the active fiber length L_a, only.

Inserting the pressure drop expressions of eqs. (31) and (32), L_a can be calculated from a chosen value of $Q_{u\,min}$. The longer the dialyzer is, the better the membrane utilization, as the nearly conical portions of poor dialysate perfusion at the bundle ends are smaller, not only in relation to the bundle length, but also because the resultant bundle diameter is smaller for a given surface area. On the other hand, the obligatory ultrafiltration rate is higher for a longer dialyzer (high pressure drops). It is, therefore, of interest to carefully consider the choice of $Q_{u\,min}$ from all medical aspects, so as to allow for the highest value tolerable under all relevant conditions.

FIBER SWELLING

All equations including fiber dimensions have to consider fiber swelling in water, that is, values for the wet fiber must be used.

Swelling is different for different kinds of fibers. For cuprophan, the manufacturer states that it is 8% in the internal diameter and 100% in the wall thickness. In the late 1970s, the values were given as 10% and 80%, respectively. However, neither of these two sets of values fits the swelling in the external diameter given in the data sheets. The author finds a close fit for 13.5% swelling in the internal diameter and 100% in the wall thickness for 200-μm fibers. However, the assumption that the swelling in the internal diameter would be independent of the wall thickness is not likely to be correct. Instead, there should be less swelling when the wall is thicker. Due to

the obvious influence of fiber swelling on the blood pressure drop (by the 4th power of the radius), this matter is of some importance and further investigation is needed.

The fibers may also tend to become slightly longer or shorter in water. The value and the direction of change depend not only on the fiber type, but also on the specific method of fiber processing during dialyzer manufacturing.

TOTAL FREE FIBER AREA AND DIFFUSION-ACTIVE FIBER AREA

Because there are nearly conical portions at the ends of the hollow-fiber bundle where dialysate perfusion is poor (approaching zero at the very end) the active surface area is lower for diffusion than for ultrafiltration. Ultrafiltration also takes place within the end sections mentioned, so that the corresponding area is approximately the same as the geometric free-fiber area, but diffusion primarily takes place outside of those end sections. An estimate of the diffusion-active free-fiber area can be obtained from clearance measurements if the diffusive properties of the fiber are well known, for example, from careful measurements on the same fiber type with a suitable test system. In that case, the ratio between the two surface areas may serve as a rough indicator of the quality of dialysate perfusion in the bundle.

DOUBLE DIALYZER OPERATION FOR LARGE SURFACE AREA DIALYSIS

It can be shown that the total clearance of two dialyzers operated simultaneously is the same as for a single dialyzer with a double surface area in the following two circumstances:

- Parallel flows for both blood and dialysate; and
- Serial flows for both blood and dialysate,

if the total flows are the same in all cases. This performance is further increased by less than 4% in serial operation for the blood flow and parallel operation for the dialysate flow (but reduced in parallel operation for the blood flow and serial operation for the dialysate flow).

ULTRAFILTRATION EFFECT ON CLEARANCE

A general equation for the dialyzer clearance during ultrafiltration is[6]

$$Q_c = Q_{bi} - \frac{Q_{be}}{\int_0^{L_a} [f(\xi)+g(\xi)]\exp[\int_0^{\xi} f(\eta)d\eta]d\xi} \tag{42}$$

in which

$$f(x) = \frac{A}{R_t L_a}\frac{Q_d - Q_c}{Q_d Q_b} - (1 - S)\frac{q_u}{Q_b} \tag{43}$$

and

$$g(x) = \frac{A}{R_t L_a}\frac{Q_{bo}}{Q_b Q_d} \tag{44}$$

Here, Q_b and Q_d are functions of x, the distance along the fiber bundle, from $x = 0$ at the blood inflow to the active part of the bundle up to $x = L_a$ at its exit from that bundle part. Q_{bi} is the inflow rate at $x = 0$ and Q_{be} the exit flow rate at $x = L_a$. S is the sieving coefficient of the membrane for the particular solute. q_u is the local ultrafiltration rate per unit length of the bundle. Hence[6]

$$Q_u = \int_0^{L_a} q_u(\xi)\, d\xi \tag{45}$$

$$Q_b = Q_{bi} - \int_0^{x} q_u(\xi)\, d\xi, \tag{46}$$

$$Q_d = Q_{de} - \int_0^{x} q_u(\xi)\, d\xi \tag{47}$$

where Q_u is the total ultrafiltration rate and Q_{de}, the exit flow of dialysate at $x = 0$.

In the most general case, one finds[6]

$$q_u(x) = a \exp(xu\sqrt{\rho_b + \rho_d}) + b \exp(-xu\sqrt{\rho_b + \rho_d}) \tag{48}$$

in which

$$2a = u^2 p_{tmo} - u\frac{\rho_b Q_{bi} + \rho_d Q_{de}}{\sqrt{\rho_b + \rho_d}} \tag{49}$$

$$2b = u^2 p_{tmo} + u\frac{\rho_b Q_{bi} + \rho_d Q_{de}}{\sqrt{\rho_b + \rho_d}} \tag{50}$$

$$u^2 = \frac{k_u A}{L_a} \tag{51}$$

$$\rho_b = \frac{\Delta p_b^0}{L_a Q_b^0} \tag{52}$$

$$\rho_d = \frac{\Delta p_d^0}{L_a Q_d^0} \tag{53}$$

Δp_b^0 and Δp_d^0 are the pressure drops over L_a, given by (31) and (32), and Q_b^0 and Q_d^0 the flows at zero ultrafiltration. p_{tmo} is the transmembrane pressure at $x = 0$.

When Q_u is much smaller than Q_b and Q_d, one finds an approximation for the clearance as follows[6]

$$Q_c \simeq Q_{co} + Q_u\left(1 - \frac{Q_{co}}{Q_{bi}}\right) + Q_{bi}\left(1 - \frac{Q_{co}}{Q_{bi}}\right)^2 \Delta\left(\frac{C_{bi}}{C_{be}}\right) \tag{54}$$

where Q_{co} is the clearance at zero ultrafiltration and

$$\Delta\left(\frac{C_{bi}}{C_{be}}\right) \simeq \frac{Q_u}{Q_{de}-Q_{bi}}\left\{\frac{Q_{de}-Q_{co}}{Q_{bi}-Q_{co}}\left[\left(\frac{Q_{bi}}{Q_{de}}\right)^2 - 1 + S\right] + 1\right\} - \frac{Q_u Q_{co}\left(S + \frac{Q_{bi}}{Q_{de}}\right)}{Q_{de}(Q_{bi}-Q_{co})\ln\left(\frac{Q_{bi}}{Q_{de}}\frac{Q_{de}-Q_{co}}{Q_{di}-Q_{co}}\right)} \quad (55)$$

C_{bi} is the inflow and C_{be} the outflow concentration of the solute in the blood.

As is seen, calculations of the effects of ultrafiltration become complicated, but once the formulas are programmed into a computer, the application is greatly simplified. It is found that the more exact calculation using the above formulas gives clearance values during ultrafiltration that differ from the estimate sometimes found in the literature, which, however, is not based on an exact mathematical study and neglects $\Delta\ (C_{bi}/C_{be})$ in eq. (54).

One complication in computer application of the above formulas is that the integral in eq. (42) cannot be expressed in elementary functions, so that numerical integration is needed.

ULTRAFILTRATION EFFECTS ON THE DIFFUSION RESISTANCE AND THE SIEVING COEFFICIENT

The diffusion resistance R_m of the membrane is a function of the local ultrafiltration rate per unit membrane length, q_u, as given by eq. (48), and hence also a function of x. For a flat membrane, this diffusion resistance is[6]

$$R_m = \frac{A}{q_u L_a S}\left(\exp\frac{q_u L_a S R_{mo}}{A} - 1\right) \quad (56)$$

where S is the sieving coefficient, L_a the total active length of the membrane, A the active surface area, and R_{mo} the diffusion resistance at $q_u = 0$. The same relation holds for a hollow-fiber bundle, in which case, however, a specification is needed as to which of the two surfaces of the fiber one is referring—usually the internal or blood-side surface.

A detailed study of the effect of ultrafiltration on hypothetical membranes representing the boundary layers has not yet been performed. It can likely be assumed that eq. (56) is valid as a first approximation for such hypothetical membranes, for which the sieving coefficient then is $S = 1$.

The calculation of total values for stacked membranes becomes a bit more complicated in the presence of ultrafiltration. In order to simplify expressions, one may introduce[6]

$$R' = \frac{AR}{A + q_u R L_a S} \quad (57)$$

valid for R_m and, with $S = 1$, also hypothetically valid for R_b and R_d (see above). The total diffusion resistance R_t, regarded as stacked up by three membranes with diffusion resistances R_d, R_m, and R_b, assuming that eq. (56) holds for all three membranes, is then

$$R_t = R_d + R_m\frac{R_d}{R'_d} + R_b\frac{R_m R_d}{R'_m R'_d} \quad (58)$$

Corresponding to eq. (57), one also finds

$$R'_t = R'_d\frac{R_m R_b}{R'_m R'_b} + R'_m\frac{R_b}{R'_b} + R'_b \quad (59)$$

from which, by analogy to eq. (57), the total sieving coefficient can be calculated as[6]

$$S_t = \frac{A}{q_u L_a}\frac{R_t - R'_t}{R_t R'_t} \quad (60)$$

HOLLOW-FIBER DIALYZERS WITH HIGH-FLUX MEMBRANES

If the clearance of a dialyzer with a high-flux membrane is to be calculated, the relatively complicated formulas of the last section are needed.

One problem is the question of safe operation of such devices. Safe operating conditions (defined above) result in very high obligatory ultrafiltration rates, which may be too high for easy management. Otherwise reversed ultrafiltration or back filtration of dialysate, which could lead to infusion of bacteria and particulate material through a membrane with microleaks and possibly even of pyrogens through the intact membrane, would be likely and of grave concern.[11] The author has carefully studied this problem from its very basis, beginning with the fundamental membrane equations of Kedem and Katchalsky[12]. The following is found:

- The net volume flow through the membrane is the sum of a solvent (water) volume flow and a solute volume flow.
- At a net flow of zero through the membrane, both solvent and solute flows pass the membrane, but in opposite directions, and at equal values, so that a partial inflow through the membrane is present.
- Contrary to what has been proposed, the colloid concentration in the blood at the site of a microleak does not become zero, except for the unlikely case that the local sieving coefficient is exactly 1, because the concentration is sustained by a constant feed from the blood flow; thus, colloid osmotic pressure can increase reversed filtration where there is a microleak.

As a result, the obligatory ultrafiltration rate may be of the order of three times higher[13,14] than claimed in certain publications which overlook the fact that the net flow is the sum of two partial flows and assume that the colloid osmotic pressure would be of negligible effect at the site of a microleak. Certain information about clinical

problems in the use of, for example, polysulfone fiber dialyzers with very high ultrafiltration factors, seem to confirm these results. As an example, a high-flux device with an ultrafiltration factor of 40 ml/hr, Torr could have an obligatory ultrafiltration rate of the order of 1000 ml/hr. Unless such high ultrafiltration rates can be maintained, the only safe operation of a high-flux device is, therefore, when it can be guaranteed that the dialysate is sterile and free from particles and pyrogens.

ECONOMIZING DIALYSATE CONSUMPTION IN DIALYSIS

It may be tempting to increase dialysate flow to gain more solute clearance at a given blood flow. However, from a certain point on, the dialysate flow needed per percent increase in clearance rises sharply, rapidly approaching an infinite flow value, so that any gain in clearance will require a large increase in dialysate consumption. In a detailed study, the author, together with B. Tersteegen, has shown that[10]

- A practically feasible upper limit of dialysate flow is twice the blood flow rate (as any attempt for a further substantial increase in clearance requires a disproportionate increase in dialysate flow),
- A practically feasible value for dialysate flow in most situations is the same value as that of blood flow.

When $Q_d = 2Q_b$, solute clearance falls less than 11% below the theoretical value at *infinite* dialysate flow. When $Q_d = Q_b$, it falls less than 23% below that value. At Q_b = 200 ml/min, Q_c falls *less* than 2.2% below the "standard clearance" value Q_{cs} (see above) in the case $Q_d = 2Q_b$, and *less* than 14% below Q_{cs} when $Q_d = Q_b$. (see Table 5–2.) In addition, the relative change in total solute mass transfer from the body during a dialysis session may amount to nearly half the relative change in dialyzer clearance, so that at $Q_d = 2Q_b$, the total solute mass transfer may fall less than 6% below the theoretical value at infinite dialysate flow.[10]

TABLES FOR DIALYZER CLEARANCE

Tables 5–2, 5–3, and 5–4 give theoretical values of dialyzer clearance under various conditions.

Table 5–2 relates clearance values at Q_d = 500 ml/min,$Q_d = Q_b$, $Q_d = 2Q_b$, and the hypothetical case $Q_d = \infty$ for a blood flow of 200 ml/min.

Table 5–3 relates clearance values at blood-flow rates Q_b of 200, 300, and 400 ml/min under two conditions of dialysate flow: Q_d = 500 ml/min and $Q_d = 2Q_b$

Table 5–4 relates clearance values at double-dialyzer operation for large surface dialysis to the corresponding single-dialyzer clearance at standard flow rates in all cases. Effects of flow rates can be judged from Tables 5–2 and 5–3.

TABLE 5–2. DIALYZER CLEARANCE UNDER VARIOUS BLOOD-FLOW CONDITIONS.[a]

Clearance at Q_d = 500 and			Clearance at $Q_d = 2Q_b$ and		
Q_b = 200	Q_b = 300	Q_b = 400	Q_b = 200	Q_b = 300	Q_b = 400
10	10.1	10.1	10.0	10.1	10.2
20	20.3	20.5	19.9	20.4	20.7
30	30.8	31.2	29.8	30.9	31.6
40	41.4	42.2	39.6	41.7	42.8
50	52.3	53.5	49.4	52.7	54.5
60	63.3	65.1	59.2	64.0	66.7
70	74.6	77.1	68.9	75.5	79.3
80	86.2	89.5	78.6	87.4	92.5
90	98.1	102.4	88.3	99.6	106.3
100	110.2	115.8	97.9	112.1	120.8
110	122.7	129.7	107.5	125.1	136.0
120	135.6	144.3	117.2	138.4	152.0
130	149.0	159.7	126.8	152.3	169.1
140	163.0	176.0	136.5	163.0	187.3
150	177.6	193.1	146.2	182.1	206.9
160	193.1	212.3	156.0	198.2	228.3
170	209.9	233.4	166.0	215.6	252.3
180	228.7	257.8	176.2	234.9	280.0
190	251.3	289.1	186.9	257.7	315.1
195	266.1	311.4	192.8	272.2	339.1
198	278.5	332.2	196.7	283.8	360.2
199	284.6	343.7	198.1	289.1	370.8

[a]All values are in ml/min. Q_d is the dialysate and Q_b the blood flow.

TABLE 5–3. DIALYZER CLEARANCE UNDER VARIOUS DIALYSATE FLOW CONDITIONS AT 200 ML/MIN BLOOD FLOW[a]

$Q_d = 500$	$Q_d = 200$ ($Q_d = Q_b$)	$Q_d = 400$ ($Q_d = 2Q_b$)	$Q_d = \infty$
10	9.9	10.0	10.1
20	19.4	19.9	20.4
30	28.7	29.8	30.9
40	37.8	39.6	41.6
50	46.6	49.4	52.4
60	55.2	59.2	63.4
70	63.6	68.9	74.6
80	71.9	78.6	85.8
90	79.9	88.3	97.2
100	87.9	97.9	108.6
110	95.7	107.5	120.0
120	103.4	117.2	131.4
130	111.0	126.8	142.6
140	118.7	136.5	153.5
150	126.4	146.2	164.0
160	134.2	156.0	174.0
170	142.4	166.0	183.1
180	151.1	176.2	190.9
190	161.5	186.9	197.0
195	168.4	192.8	199.0

[a]All values are in ml/min. Q_d is the dialysate and Q_b the blood flow.

TABLE 5–4. DOUBLE-DIALYZER CLEARANCE: TWO DIALYZERS IN SIMULTANEOUS OPERATION[a]

Single-Dialyzer Clearance	Double-Dialyzer Clearance, Both Flows Parallel or Serial	Double-Dialyzer Clearance, Serial Blood Flow and Parallel Dialysate Flow
10	19.3	19.4
20	37.3	37.9
30	54.2	55.5
40	69.9	71.1
50	84.6	87.5
60	98.3	102.0
70	111.1	115.5
80	123.1	128.0
90	134.2	139.5
100	144.4	150.0
110	153.9	159.5
120	162.6	168.0
130	170.5	175.5
140	177.5	181.9
150	183.9	187.5
160	189.2	192.0
170	193.7	195.5
180	197.0	198.0
190	199.2	199.5
195	199.8	199.9

[a]Clearance values in ml/min at 500 ml/min total dialysate flow and 200 ml/min total blood flow versus single dialyzer clearance at the same flow values.

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The Chapter further contains an extensive list of available hollow-fiber dialyzers on pp. 109-116, here left out as being no more actual.

Some minor corrections have been introduced in the text.