SOMETIMES excess fluid accumulates in the lung primarily because of changes in the lung circulation (Brigham et al., 1974). When humans develop pulmonary edema while lung vascular pressures are low, it is inferred that lung exchanging vessels are leaking too much fluid and protein (increased permeability; see Robin et al., 1968, 1973). Diagnosing increased permeability in this way poses two problems. First, the diagnosis cannot be made until enough lung fluid has accumulated to make pulmonary edema obvious on chest x-ray or physical examination. Second, the diagnosis does not involve a measurement of lung vascular permeability per se, because there has been no way to make that measurement.

In animals, we found a multiple-indicator method useful for measuring lung water and vascular permeability (Harris et al., 1976; Brigham et al., 1977; Harris et al., 1978; McKeen et al., 1978b). We have now used the method in humans with normal and increased pulmonary vascular pressures due to stable heart failure. We found that the lung permeability-surface area product (PS) correlated well with alveolar volume (VA). ¹⁴C-Urea PS correlated well with VA+VA (r = 0.62, P = 0.019). Urea PS/VA did not correlate with Pmv (r = -0.36, P = NS), hematocrit (r = -0.07, P = NS), or cardiac output (r = 0.36, P = NS). EVLW/TLC correlated with Pmv (r = 0.51, P = 0.02) and even better with Pmv - plasma oncotic pressure (r = 0.63, P = 0.007). We therefore conclude that ¹⁴C-Urea PS is a measure of lung vascular permeability in humans, and that, as in animals, permeability is unaffected by Pmv. EVLW may be a more useful measure of lung water in humans than previously thought, when interpreted in light of the measurable forces affecting fluid exchange. Circ Res 44: 523-530, 1979
vascular pressures, and that extravascular lung wa-
ter, when normalized to total lung capacity, corre-
lated well with the difference between lung micro-
vascular pressure (P_{mv}) and plasma oncotic pres-
sure. This is consistent with the results of our
studies on animals, and suggests that the multiple-
indicator method may help determine both the kind
and amount of lung edema in humans.

Methods

General

We studied subjects of both sexes, aged 19-71
years, who were hemodynamically stable and were
undergoing cardiac catheterization for diagnosis
and evaluation of heart disease. Each subject lay
supine on a table in the catheterization laboratory
while catheters were placed under fluoroscopic ob-
servation through an antecubital vein into the pul-
monary artery and through a femoral artery into the
abdominal aorta. In three subjects, the left atrium
was catheterized transseptally to record pressure there. Strain gauges were zeroed at the
midthoracic level, and pulmonary artery (P_{pa}) and
pulmonary arterial wedge (P_{paw}) or left atrial (P_{la})
pressures were recorded. P_{mv} was calculated [P_{mv} = P_{pa} + 0.4 (P_{pa} - P_{la} or P_{paw}); Brigham et al., 1974]. The venous catheter was then withdrawn
into the right atrium. Three milliliters of a mixture
of 51Cr-erythrocytes, 125I-human serum albumin,
14C-urea, and 3H-water in saline were injected as a
bolus through the venous catheter, and 30 arterial
blood samples were collected at 1.5-second intervals
by allowing blood to flow from the arterial catheter
into heparinized tubes mounted on a rotating disc
collector. Total protein concentration (biuret) and
hematocrit were measured on samples of heparin-
ized arterial blood drawn prior to the study.

Isotopic Methods

Ten milliliters of venous blood were drawn from
each subject into acid-citrate-dextrose anticoagu-
lant prior to the study. To label erythrocytes, the
blood was incubated with 51Cr-sodium chromate for
30 minutes, and the cells were washed once with
0.89% sodium chloride solution (normal saline). The
labeled cells were resuspended in normal saline to
30 minutes, and the cells were washed once with
blood was incubated with BICr-sodium chromate for
prior to the study. To label erythrocytes, the
each subject into acid-citrate-dextrose anticoagu-

The time-concentration curves, normalized to
the injected activity for each isotope, were plotted.
The details of analysis are discussed in the Appen-
dix. Cardiac output was calculated as the inverse of
the area under the 51Cr curve, corrected by extrap-
olation for recirculation (Chinard et al., 1962). We
used a Krogh-convolution circulatory model to cal-
culate extravascular lung water (EVLW) volume
and 14C-urea PS. We have described these calcula-
tions in detail in the literature (Harris et al., 1976;
Rowlett and Harris, 1975) and compared them with
several other methods for interpreting indicator
dilution data (Harris et al., 1976). For comparison,
we also calculated EVLW volume by the more
standard mean transit time method (Chinard et al.,
1962), and 14C-urea PS from the integral of extrac-
tion to the peak of the reference curve (Crone and
Garlick, 1969). In all calculations, the intravascular
reference curve was a composite of the red cell and
albumin curves, weighted for hematocrit and water
content of red cells and plasma (Goresky et al.,
1969; see Appendix).

Other Methods

We measured lung volumes using a Collins spi-
rometer, functional residual lung capacity by a
closed-circuit helium dilution method (Hathirat
et al., 1970), and single-breath carbon monoxide dif-
fusing capacity in the Pulmonary Function Labo-
atory within 24 hours of the indicator study. From
these data, we calculated total lung capacity and V_{A}
using the equation of Cotes (1975). Plasma oncotic
pressure was calculated by the formula of Landis
and Pappenheimer (1963) from the measured total
plasma protein concentration.

Statistics

We calculated means, standard errors, and cor-
relation coefficients by standard formulas (Snede-
cor and Cochran, 1967). The coefficient of variation
(CV) for the curve fitting was computed as follows:

\[ CV = \sqrt{\frac{\sum (D_{DO} - D_{DP})^2}{n \cdot P}} \left( \frac{\Sigma C_{DO}/n}{1} \right) \]  

where n is the number of points, and P is 2 for 3H-
water data and 1 for 14C-urea. C_{DO} and D_{DP} are the
observed and predicted diffusing tracer relative concentrations, respectively.

Results

Figure 1 shows a typical set of indicator curves. The relationships among the four indicators are like
those we have previously reported for animals and
humans (Harris et al., 1976; Brigham et al., 1977b;
Harris et al., 1978; Brigham et al., 1976a). There is
some intravascular separation of red cells and albumin reflected in a higher peak and steeper downslope for the red cell curve. The urea curve falls between the intravascular curves and that of the flow-limited tracer, tritiated water. Figure 2 shows the indicator curves (composite intravascular, $^{14}$C-urea, and $^{3}$H-water) for subject VCH-6. The ability of the mathematical model to fit concentration data and extraction is shown by the dotted lines. The CV for the two fits was 0.104 for $^{3}$H-water data and 0.0232 for $^{14}$C-urea data. The model fits all but the earliest extraction point where the relative concentrations were very low (0.05 for reference indicator and 0.039 for $^{14}$C-urea data).

Table 1 lists the clinical data for all of the subjects studied. Table 2 lists the pressure, plasma protein, and pulmonary function values. Table 3 lists the indicator dilution data. Values for $P_{mv}$ ranged from 4-35 torr. There was also a broad range of cardiac outputs, hematocrits, EVLW volumes, $^{14}$C-urea PS, and total lung capacities.

Although the primary data show widely varying urea PS values, these values correlated quite well with measured total lung capacity ($r = 0.52, P = 0.03$ for model PS values). The best normalizing variable for PS would be exchanging vessel surface area, as has been suggested (Weibel, 1973), then PS should correlate best with $V_{A}^{2/3}$ as a result of the relationship between volume and surface area of a sphere. In fact, urea PS did correlate better with $V_{A}^{2/3}$, as is illustrated in Figure 3. When normalized to $V_{A}^{2/3}$, urea PS did not correlate significantly with hematocrit ($r = -0.07, P = NS$), cardiac output ($r = 0.39, P = NS$), or $P_{mv}$ ($r = 0.36, P = NS$). The relationship between urea PS and $P_{mv}$ is illustrated in Figure 4.

Although mean transit time extravascular water space is significantly correlated with model-based values, ($r = 0.79, P < 0.001$), there is an average difference of 25% between the two values. This variation is quite different from the close agreement between the two techniques in a series of multiple-indicator studies on sheep (Harris et al., 1978). The probable cause is illustrated in Figure 5, in which normalized composite intravascular and $^{3}$H-water concentrations are plotted as a function of dimensionless time for sheep and human data. The intravascular curves match except on the downslope. The $^{3}$H-water curves are dissimilar. There are five points past the peak before recirculation in the curves for sheep, but only three in the curve for humans. This is because human and sheep cardiac outputs are similar (60 ml/sec in VCH-10 vs. 63.8 for the sheep), but their water volumes are quite different (for the sheep, model EVLW volume was 236 ml and the mean transit time value was 241 ml). This results in fewer downslope points from which to extrapolate the curves for humans and compromises the accuracy of the mean transit time calculation.

When indicator dilution EVLW volume (EVLW model values) was normalized to total lung capacity, it correlated significantly with $P_{mv}$ ($r = 0.51, P = 0.016$). The correlation of EVLW with pressure was improved by including plasma oncotic pressure. Figure 6 shows EVLW as a function of the difference between $P_{mv}$ and plasma oncotic pressure, illustrating the good correlation between those variables.

**Discussion**

At least in animals, when lung vascular permeability to fluid and protein is increased, there may
be very large increases in transvascular fluid filtration without substantial lung fluid accumulation (Brigham et al., 1974). Pulmonary edema (increased lung water content (Visscher et al., 1956)) occurs late in the pathogenetic sequence of events (Staub, 1974). If a reliable measure of the integrity of exchanging vessels could be made in humans, it should be possible to detect increased vascular permeability early, before alveoli flood and lung function deteriorates.

We have shown that the lung vascular 14C-urea PS calculated from single pass indicator dilution curves is unaffected by increased pulmonary vascular pressures in dogs (Harris et al., 1976) and sheep (Harris et al., 1978), but increases after injecting alloxan in dogs (Harris et al., 1976) or his-

---

**Table 1 Clinical Data for All Subjects**

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Ht (inches)</th>
<th>Wt (kg)</th>
<th>Duration of symptoms (years)</th>
<th>Diagnosis</th>
</tr>
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<tbody>
<tr>
<td>VCH-1</td>
<td>60</td>
<td>M</td>
<td>72</td>
<td>80.0</td>
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<td>Cardiomyopathy</td>
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<td>F</td>
<td>62</td>
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<td>5</td>
<td>Mitral stenosis</td>
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<td>64</td>
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<td>6</td>
<td>Mitral insufficiency</td>
</tr>
<tr>
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<td>M</td>
<td>70</td>
<td>65.5</td>
<td>1</td>
<td>Mitral insufficiency</td>
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<td>63.6</td>
<td>0.5</td>
<td>Pericardial effusion</td>
</tr>
<tr>
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<td>M</td>
<td>66</td>
<td>48.6</td>
<td>14</td>
<td>Mitral stenosis</td>
</tr>
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<td>M</td>
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<td>72.3</td>
<td>6</td>
<td>Mitral stenosis</td>
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<td>0.25</td>
<td>Cardiomyopathy</td>
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---

**Table 2 Pressure, Hematocrit, Plasma Protein, and Pulmonary Function Data for All Subjects**

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<tr>
<th>Subject no.</th>
<th>Pulmonary artery</th>
<th>Pulmonary artery wedge</th>
<th>Left atrium</th>
<th>Hct</th>
<th>Concentration (g/dl)</th>
<th>Oncotic pressure (torr)</th>
<th>VC (ml)</th>
<th>TLC (ml)</th>
<th>DLco (ml/min x torr)</th>
<th>VA (ml)</th>
</tr>
</thead>
<tbody>
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<td>—</td>
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<td>4.9</td>
<td>4970</td>
</tr>
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<td>11</td>
<td>—</td>
<td>0.50</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
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<td>—</td>
<td>—</td>
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<tr>
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<td>7.35</td>
<td>27.6</td>
<td>3010</td>
<td>4574</td>
<td>16.6</td>
<td>4402</td>
</tr>
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<td>25</td>
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<td>4192</td>
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<td>7.80</td>
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<td>0.55</td>
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<td>7</td>
<td>0.50</td>
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<td>4470</td>
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</tr>
</tbody>
</table>

VC = Lung vital capacity; TLC = total lung capacity; DLco = lung carbon monoxide diffusing capacity; VA = alveolar volume; Hct = hematocrit; — measurements not made.
tamine in sheep (Harris et al., 1978). Alloxan causes pulmonary edema in dogs due to increased vascular permeability (Staub et al., 1967), and lung lymph measurements in sheep indicate that histamine increases pulmonary vascular permeability (Brigham and Owen, 1975; Brigham et al., 1976a). Thus in animals the 14C-urea PS detects increased permeability in the lung circulation and distinguishes edema due to high pressure from that due to increased permeability (Harris et al., 1978). Pulmonary vascular 14C-urea PS also is quantitatively consistent with protein permeability calculated from lung lymph measurements (Harris and Brigham, 1977).

The first step in evaluating the utility of the indicator dilution lung vascular urea PS in humans was to demonstrate its feasibility and to see whether it was affected by pulmonary vascular pressures. Thus we chose subjects with apparently normal lung vascular permeability, but with a broad range of pulmonary vascular pressures due to various degrees of heart failure. Although the actual urea PS values varied widely in this group, there was good correlation with $V_{A}^{2/3}$. When urea PS was normalized to $V_{A}^{2/3}$, there was no significant correlation with pulmonary vascular pressures. This result suggests that, as in animals, urea permeability is unaffected by vascular pressures in humans. Since indicator dilution methods measure only diffusive transport [i.e., "true" permeability (Kedem and Katchalsky, 1958)], hydrostatic pressure should have negligible effects unless permeability actually increases in response to high vascular pressures (Pietra et al., 1969). The bulk of available evidence

![Figure 3](https://example.com/figure3.png)  
**Figure 3** 14C-urea PS (Krogh-convolution model values) as a function of $V_{A}^{2/3}$ in human subjects.

![Figure 4](https://example.com/figure4.png)  
**Figure 4** 14C-urea PS (model values) normalized to $V_{A}^{2/3}$ as a function of lung $P_{mo}$ (see text for calculation).
suggests that this does not occur with pressures in the range seen in intact organisms (Brigham and Owen, 1975a; Brigham et al., 1976a; Erdmann et al., 1975; Brigham and Owen, 1975b). Recruitment of more microvessels at higher pressures also might increase PS due to an increase in surface area. Our data do not show this, possibly because we studied supine subjects for whom, even at normal pressures, none of the lung is in zone I.

The best normalizing variable for PS would be exchanging vessel surface area in each subject, but that cannot be measured. Although the relationship between lung volume and exchanging vessel surface area may not be linear, they should relate; that is, bigger lungs should have more surface area. If alveolar surface area approximates exchanging vessel surface area, then, given a spherical lung model, PS ought to correlate with $V_A^{2/3}$. The good correlation of $^{15}N$-urea PS with $V_A^{2/3}$ in these studies gives us some confidence in the accuracy of the PS measurement and provides a good normalizing variable in this group. Unfortunately, $V_A$ measured by gas inhalation methods may not be a good estimate of exchanging vessel surface area when there is substantial alveolar flooding or collapse.

Urea has been criticized as a permeability indicator because of the possibility that red cell transport affects the PS calculation (Chinard et al., 1965). Basing our views on extensive theoretical (Roselli et al., 1977) and experimental (Brigham et al., 1977a; Harris et al., 1978; Brigham et al., 1977b) work, we do not believe red cell effects are important in the lung. The fact that, in the present studies, urea PS did not correlate with hematocrit supports this view.

Indicator dilution methods have been used to measure EVLW in humans (Brigham et al., 1976; Brigham et al., 1971; McCredie, 1967; Biddle et al., 1974; Goresky et al., 1975), but the correlation of the lung water with $P_{paw}$ has not been very good (Biddle et al., 1974). There are several reasons why this might be true: (1) The indicator method measures different fractions of total extravascular water under different circumstances (Pearce et al., 1965), presumably because of differences in the fraction of lung perfused. (2) Vascular hydrostatic pressure is only one of five variables that may govern microvascular filtration rate; the other four are perimicrovascular hydrostatic pressure, microvascular and perimicrovascular oncotic pressure, and the porosity and surface area of exchanging vessel walls. (3) Under some circumstances lung water content may be increased when actual filtration rate is low (Bowers et al., 1977; McKeen et al., 1978a). (4) Neither $P_a$ nor $P_{paw}$ may relate consistently to pressure in exchanging vessels (Grega et al., 1971). (5) The denominators for normalizing measurements among patients may be inaccurate.

Recently reported clinical studies suggest that lung water content correlates better with the difference between plasma oncotic pressure and $P_{paw}$ than with $P_{paw}$ alone (Stein et al., 1975). In our studies in subjects with stable heart failure, inclusion of plasma oncotic pressure improved the correlation substantially. But why should this be true when the oncotic driving force is not plasma oncotic pressure but the difference between plasma and interstitial oncotic pressures (Staub, 1974)? The reason may be that, at higher microvascular hydrostatic pressures, interstitial (lymph) protein concentrations fall relative to that of plasma (Erdmann et al., 1975), so that plasma oncotic pressure contributes more to the sum of filtration forces. Since many of our subjects had high pulmonary vascular pressures, inclusion of plasma oncotic pressure might be expected to improve the pressure-lung water correlation.
Normalizing variables for EVLW have included height, weight, and body surface area (Brigham et al., 1971; McCredie, 1967; Biddle et al., 1974). It would be more accurate to normalize to some index of the mass of lung perfused at the time the study was done, but such an index is difficult to measure. We chose to normalize extravascular water to total lung capacity as an estimate of lung size. Our subjects with normal vascular pressures had values similar to those reported in the literature (Goresky et al., 1975). Normalized extravascular water correlated significantly with Pmv and even better with the difference between Pmv and plasma oncotic pressure. Total lung capacity might not be a good normalizing variable when there is substantial alveolar flooding or collapse.

These studies demonstrate the feasibility of measuring lung vascular permeability in humans by a multiple-indicator dilution technique. They also demonstrate that 14C-urea permeability measured in this way correlates well with an estimate of exchanging vessel surface area based on the measurement of alveolar volume. This finding lends credence to the urea permeability measurement. As in animals, urea permeability was unaffected by vascular pressure. Indicator dilution estimates of EVLW, when normalized to total lung capacity, correlated significantly with Pmv and plasma oncotic pressure. These studies encourage us to think that lung 14C-urea PS may distinguish pulmonary edema due to increased vascular permeability from that due to increased pressure in humans, and may permit clarification of the pathogenetic role of altered vascular permeability in several human diseases. Also, the indicator dilution lung water measurement may be more useful than previously thought (Staub, 1974), when appropriately normalized and interpreted in light of the measurable factors affecting fluid exchange.

**Appendix**

**Methods for PS Computation**

We calculated 14C-urea PS by two methods (both of which assume that vascular endothelium is the only significant barrier to tracer diffusion): (1) the integral extraction technique, which integrates the extraction of diffusible indicator from appearance to the peak of the reference curve, but neglects the effects of back diffusion from the extravascular space; and (2) by fitting a mathematical model to the 14C-urea concentration curve, which explicitly includes the effects of back diffusion.

The integral extraction was defined as:

\[
E_s = \frac{\int_0^t \left( C_R - C_D \right) \, dt}{\int_0^t C_R \, dt}. \quad (A1)
\]

Here \( C_R \) is the reference tracer and \( C_D \) is the diffusing tracer. The time of the peak of the reference curve is \( t_p \).

In the mathematical model, the Sangren-Sheppard equation for capillary transport was assumed to hold:

\[
\frac{\partial C_D}{\partial t} + \frac{F_c}{V_e} \frac{\partial C_D}{\partial X} = - \frac{PS}{V_e} (C_D - C'_D), \quad (A2)
\]

\[
\frac{\partial C'_D}{\partial t} = \frac{PS}{V_e} (C_D - C'_D), \quad (A3)
\]

where \( C'_D = \) concentration of tracer in the radially mixed extravascular space, \( F_c = \) capillary blood flow, \( V_e = \) volume of the extravascular space, \( V_v = \) volume of the intracapillary space, \( X = \) normalized capillary length, \( X/(\text{length of a capillary}) \), and \( t = \) time in seconds.

We further assumed that:

\[
C_0(t,0) = C_R(t - \frac{V_e}{F_c}). \quad (A4)
\]

This assumption implies that all capillary transit times are equal (Goresky, et al., 1970). It further implies that \( PS/V_v \) and \( PS/V_e \) are equal for all capillaries. Under these assumptions, the diffusing tracer curve is the convolution of the reference curve \( C_R \) and the impulse response of the capillary transport model, Equations A2 and A3. Because of this, we have called this entire model the "Krogh-convolution model" (Rowlett et al., 1975). The quantity \( F/V_v \) is eliminated in the calculus leading to the expression based on Equations A2, A3, and A4, which is used in the curve fit and is not evaluated explicitly in the model fitting (Rowlett et al., 1975).

Since all tracers are preequilibrated with whole blood before injection, the intravascular composite concentrations and flows of 3H-water and 14C-urea are based on the total intravascular water space:

\[
0.7 \times (\text{Hct.}) \times (51\text{Cr conc}) + 0.94 \times (1 - \text{Hct.}) \times (125\text{I conc})
\]

\[
0.7 \times (\text{Hct.}) + 0.94 \times (1 - \text{Hct.})
\]

\[
F = \left[ 0.7 \times (\text{Hct.}) + 0.94 \times (1 - \text{Hct.}) \right] \times \text{(cardiac output)}. \quad (A6)
\]

Cardiac output (C.O.) was based on the formula:

\[
\text{C.O.} = \frac{\text{Mass of injected tracer}}{\int_0^\infty (51\text{Cr concentration in whole blood}) \, dt} \quad (A7)
\]

Recirculation artifact was eliminated by the standard exponential extrapolation method.

The quantity \( F \), computed from Equations A6 and A7, was fixed in the algebraic solution of the
model, and the quantities $PS$ and $V_e$ were determined for $^3$H-water by nonlinear regression analysis. Since water $PS$ is most likely a minimum value and not true permeability surface area, it has not been reported. Regression was then applied for the $^{14}C$-urea data. Here $PS$ for urea was computed, but $V_e$ was fixed at the value for $^3$H-water as discussed in an earlier publication (Harris et al., 1978). For both sets of diffusible tracers, only those data to the point prior to the appearance of recirculation in the $^{51}Cr$ curve were used for regression analysis.

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