Improving Contact Area between the Peritoneum and Intraperitoneal Therapeutic Solutions

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Abstract. A general assumption in peritoneal dialysis or intraperitoneal chemotherapy has been that a volume of 2 to 3 L in the human is sufficient to make contact with the entire anatomic peritoneum. On the basis of our previous experimental work and that of others, it was hypothesized that only a fraction of the anatomic peritoneum was in contact with the therapeutic solution in the cavity over a short period of time. It was also hypothesized that use of agitation of the experimental animal or a surfactant in the dialysis fluid would increase the contact area of the intraperitoneal solution. These hypotheses were tested by developing a method to measure the peritoneal contact area simultaneously with the anatomic peritoneal area. Anesthetized mice (25 to 35 g) received an injection of a relatively large volume (10 ml) of isotonic solution containing a radiolabeled protein that adhered to the peritoneum with which it came in contact. After a dwell of 1 to 24 h, the animal was killed and frozen. Cross sections of the abdominal and pelvic cavities were cut and placed against film to develop into autoradiograms, which represent the linear dimension of fluid contact in each sampling plane. The tissue sections that corresponded to the autoradiograms were stained to display the linear dimension of the anatomic peritoneum in the sampling plane. By imaging both the autoradiogram and the corresponding histologic slide, an estimate of the ratio of the contact area to anatomic area in each plane can be calculated (Rmean = average of all ratios). Applying this method to mice that were dialyzed with an isotonic salt solution under quiescent conditions for 1 h produced Rmean = 0.43 ± 0.03. With rapid shaking of the animal, Rmean = 0.54 ± 0.03 (P < 0.05). Addition of the surfactant dioctyl sodium sulfosuccinate (DSS) 0.5% to the solution under quiescent conditions increased Rmean to 1.07 ± 0.03 (P < 0.001). Lengthening the dwell of the isotonic solution to 24 h increased Rmean to >0.90. In further study of the effect of the concentration of DSS on contact area, there was a direct correlation of Rmean with concentrations ranging from 0.0005 to 0.05% DSS. It is concluded that less than half of the mouse peritoneum is in contact with a large volume of solution in the peritoneal cavity. Maneuvers such as agitation and use of surfactant in the intraperitoneal solution increase the fraction of contact area. Also demonstrated was a direct dose-response of contact area versus intraperitoneal concentration of DSS, which may be useful in intraperitoneal therapies of peritoneal dialysis or intraperitoneal chemotherapy.

The area of contact between a large volume (2 to 3 L) of therapeutic solution in the peritoneal cavity and the anatomic peritoneum of humans is unlikely to be equal to the total anatomic area. Determinations of peritoneal area by cadaveric dissection and measurement of paper overlays of the tissue by early researchers (1, 2) produced estimates that were close to body surface area, whereas more recent measurements have produced numbers that vary from 8000 cm² (3) to 10,000 cm² (4). Many have assumed that a large volume (2 to 3 L) in the cavity would be in contact with the entire peritoneum. Using a new stereographic technique coupled to computed tomography of the peritoneal cavity with 2-L solutions containing a contrast agent, a group of researchers estimated the area of contact in six dialysis patients to be 5500 cm², a fraction of previous anatomic measurements from the cadaveric studies (5). Results of animal studies (6) in our laboratory indicate that a much smaller area than the total area found on dissection is available for transport. Individual mass transfer coefficients (MTC) of different surfaces of the peritoneum were multiplied times the area (A) of each of the surfaces measured after killing the animal and dissecting the abdominal cavity. By summing the MTC x A products of all of the tissues surrounding the cavity, we calculated an estimate of the mass transfer-area coefficient (MTAC) for the whole cavity. In a separate set of animals, the MTAC for the entire cavity was measured in intact rats with a large volume of dialysis solution (50 cc in 300-g rat) and was found to be 25 to 30% of the sum of the MTC x A. This discrepancy between calculated MTAC and measured MTAC suggested that much of the area was not available for transport during a large-volume dialysis. A separate set of animals were then dialyzed with an intensely staining dye for 1 h to detect those surfaces that came in contact with the solution. Large parts of the peritoneal surface had no staining, i.e., one side of the cecum, colon, and the stomach and large parts of the abdominal wall and diaphragm. Although qualitative, this observation demonstrated that large portions of the peritoneum were untouched by solution while the animal was in an anesthetized, quiescent state.
Vigorous shaking of anesthetized animals or surface active agents that were added to the peritoneal solution has resulted in marked increases in mass transfer. Levitt et al. (7) measured the rate of transport of urea, creatinine, and glucose in rats at rest or agitated with an orbital shaker and found a fourfold increase in MTAC in good agreement with our studies. Others (8) have carried out studies analogous to Levitt’s and have found similar results. Penzotti and Mattocks (9) used diocetyl sodium sulfosuccinate (DSS) in rabbits and were able to demonstrate a three- to fourfold increase in the mass transfer of uric acid. If we presume that the maneuvers of agitation or surface active agents primarily affect the A of the MTC \times A, then all of these studies in animal models provide indirect evidence that fluid in the quiescent peritoneal cavity comes in contact with only approximately 25 to 30% of the total peritoneal area.

Our hypothesis in this study is that even with relatively large volumes, only a fraction of the peritoneal surface is available to physiologic salt solutions in the cavity. We hypothesized further that maneuvers such as use of a surface-active agent or severe agitation result in an increase in surface area in contact with the fluid. To address these hypotheses, we carried out a study in mice to measure the area of contact relative to the peritoneal area under a variety of conditions.

**Materials and Methods**

**Animals and Surgery**

C-576J mice, 25 to 35 g in weight, were used in all experiments. Anesthesia was induced with an intramuscular injection of sodium pentobarbital (60 to 90 mg/kg). Anesthetized mice were maintained at 37 ± 2°C with an overhead heating lamp. All procedures were reviewed and approved by the University of Rochester Committee on Animal Resources.

Surgery was carried out after loss of the blink reflex and withdrawal reflex. A trocar was used to make a midline penetration in the lower abdominal wall, and a small catheter was passed into the peritoneal cavity. This was sutured closed with a purse stitch. Leyboldt (10) carried out experiments with 0.005% DSS in rabbits and calculated a 50% increase in mass transfer of creatinine. If we presume that the maneuvers of agitation or surface active agents primarily affect the A of the MTC \times A, then all of these studies in animal models provide indirect evidence that fluid in the quiescent peritoneal cavity comes in contact with only approximately 25 to 30% of the total peritoneal area.

The goal of protocol I was to determine what proportion of the peritoneal surface area is actually in contact with the dialysis fluid during a relatively short dialysis (1 h) and to investigate what effect the following maneuvers might have on the contact area: (1) vigorous movement of the animal or (2) a surface active agent in the peritoneal cavity after 24 h. The reason for this is that the level of amylase present in rodent tissue is 2 orders of magnitude higher than in humans (15). To verify this, we collected 4-h effluents from six peritoneal dialysis patients who were undergoing peritoneal equilibration tests with 2.5% glucose solutions and from three mice that were dialyzed with the KRB solution. The amylase activity was determined with Sigma Kit 577 (purchased from Sigma-Aldrich Co.). Amylase cannot be determined directly in Icodextrin solutions with this assay, which depends on the metabolism of a starch labeled with a marker; the Icodextrin would compete with the reagent and the resulting determination would be low. Amylase activity in the peritoneal effluent at 4 h was zero in humans, whereas the activity in mice was 168 ± 41 U (mean ± SD).

**Experimental Protocols**

The Icodextrin solution was used because human studies (13) demonstrated that the volume would remain constant for up to 48 h. It was assumed that holding the volume constant would result in a higher value for peritoneal contact area than an isotonic solution that would be absorbed over time (14). However, the 10-ml volume of either Icodextrin or KRB was completely absorbed from the mouse peritoneal cavity after 24 h. The reason for this is that the level of amylase present in rodent tissue is 2 orders of magnitude higher than in humans (15). To verify this, we collected 4-h effluents from six peritoneal dialysis patients who were undergoing peritoneal equilibration tests with 2.5% glucose solutions and from three mice that were dialyzed with the KRB solution. The amylase activity was determined with Sigma Kit 577 (purchased from Sigma-Aldrich Co.). Amylase cannot be determined directly in Icodextrin solutions with this assay, which depends on the metabolism of a starch labeled with a marker; the Icodextrin would compete with the reagent and the resulting determination would be low. Amylase activity in the peritoneal effluent at 4 h was zero in humans, whereas the activity in mice was 168 ± 41 U (mean ± SD).

**Materials and Methods**

**Isotopic Tracer and Solutions**

To mark the peritoneum that is in contact with the intraperitoneal solution, we dissolved 125I-IgG (anti-rabbit IgG, no. IM-134; Amer sham Corporation, Arlington Heights, IL) in all peritoneal solutions (25 μCi/10 ml). Four different batches of labeled IgG were used in the study. Each batch had a specific activity of 12 to 14 μCi/μg, and each batch was used within 2 to 3 wk, with little change in the specific activity. We previously tested various batches of this antibody, and there is very little variation in its nonspecific binding characteristics from batch to batch. As in our previous studies (12), before use of the isotope, the free 125I was removed by dilution with saline and successive ultrafiltrations to limit the free isotope to <1%. The approximate loss of label from tracer over the time of use of each batch was typically 5 to 8%. Samples of peritoneal fluid were collected at the end of each experiment, and the free isotope was determined by precipitation with 10% TCA (see reference 12) to be <1.5% at 1 h and <3% at 24 h.

Solutions included an isotonic Krebs-Ringer-Bicarbonate (KRB; see reference 12 for makeup of solution), pH 7.4, 290 mosm/kg, or Dextran (Icodextrin 4%, 278 mosm/kg, a kind gift from ML Laboratories, PLC, Liverpool, England). In some cases, a surface active agent, the sodium salt of DSS (purchased from Sigma-Aldrich Co., St. Louis, MO), was added to these solutions in concentrations of 0.0005 to 0.5%.

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with the other solutions, but this did not affect the analysis because all images are weighted equally (see the section Data Collection and Analysis).

Three animals each were dialyzed with (1) KRB under quiescent conditions, (2) KRB under conditions of vigorous shaking at the "shaking speed" (>60 cpm) on a vortex mixer (Model G560; Scientific Industries, Bohemia, NY), and (3) KRB with 0.5% DSS. All solutions contained the 125I-IgG, which labeled the peritoneum in contact with the solution. After dialysis for 1 h, each animal was killed, the cavity was drained, and the carcass was frozen. Tissue samples were collected and analyzed as below.

Protocol II was designed to answer the question, "Does the time of dwell change the contact area?" Presumably, peristalsis would distribute the fluid to different regions of the peritoneum and broaden the overall exposure. Under anesthesia, the animals (n = 3 for each solution) received an injection of the following solutions, each containing the labeled IgG: (1) KRB or (2) the solution containing 4% Icodextrin. After injection of the 10 ml, the mice were allowed to wake up and ambulate freely around the cage and eat and drink ad libitum. At the end of 24 h, each animal was killed, the cavity was opened to check for residual fluid, and the carcass was frozen. Tissue samples were collected and analyzed as below.

Protocol III was designed to establish the dose response of the additive DSS: how much surface area was in contact with the solution versus the concentration of DSS. Because the use of surfactants has been associated with increased protein loss (10), the total protein concentration of the peritoneal effluent was determined with Sigma Diagnostic Kit 690-A. The procedure was the same as in protocol I, but the solutions were made up of KRB with (1) 0.0005% DSS, (2) 0.005% DSS, and (3) 0.05% DSS, but the solutions were made up of KRB with (1) 0.0005% DSS, (2) 0.05% DSS, (3) 0.005% DSS, and (4) 0.0005% DSS. All solutions contained the 125I-IgG, which labeled the peritoneum in contact with the solution. After dialysis for 1 h, each animal (n = 3 for each DSS concentration) was killed, the cavity was drained, and the carcass was frozen. Tissue samples were collected and analyzed as below.

Data Collection and Analysis

The frozen carcass was sliced in whole cross sections, 20 µm thick, with a Hacker-Bright Cryotome (Model OTF; Fairfield, NJ). After three to four sections were collected, the entire block was sliced 2 mm down to the next sampling point, where several cross sections again were collected. This was repeated for a total of 10 sampling points, which spanned the entire peritoneal and pelvic cavities. These sections were then placed against x-ray film (Kodak Biomax MR film; Kodak Corp., Rochester, NY) for 1 to 3 wk to develop autoradiograms. It was assumed that the autoradiograms of each sampling level represent the linear measurement of tissue in contact with the solution in the cavity in the plane of sampling. The tissue sections that corresponded to the autoradiograms were stained with standard hematoxylin and eosin to highlight the anatomic peritoneum.

To quantify the area of contact (or "wetted area") and the area of the anatomic peritoneum, we imaged individual autoradiograms and the corresponding histologic slides (MCID; Imaging Research, St. Catharines, Ontario, Canada), and the linear measurement of each area was determined by manual tracing within the digital image. All portions of the autoradiogram that corresponded to peritoneal surface were included in the analysis irrespective of the optical density. No attempt was made to quantify the amount of radioactivity at different surfaces. If the optical density was above background and represented a tissue surface, then its linear dimension was determined. The principle of measurement is based on the assumption that the surface of the peritoneum is made up of a complex collection of cylinders, each of which has an area equal to the product of the tissue dimension d (2 mm) between sampling points (equivalent to the height of the cylinder) times the circumference of the cylinder C as determined from the linear dimension in each image. Figure 1 gives a simplified depiction of the principle. To estimate the area of the irregularly shaped light bulb, cross-sectional circumferences (Ci) through the light bulb are measured at intervals of d. The area of the light bulb may then be approximated by the following equation:

$$\text{Area} = d \sum C_i$$

In the same way, we can determine the area in each of 10 sampling levels of the mouse peritoneal cavity. The ratio (R) of the wetted area to that of the anatomic peritoneum at each sampling point is calculated by the following equation:

$$R = \frac{\text{Area}_{\text{wetted}}}{\text{Area}_{\text{anatomic}}} = \frac{d \times C_{\text{wetted}}}{d \times C_{\text{anatomic}}} = \frac{C_{\text{wetted}}}{C_{\text{anatomic}}}$$

The average of R at all sampling levels (Rmean) and the R from the sum of all Ci (Rsum = \sum C_{\text{wetted}}/\sum C_{\text{anatomic}}) were calculated for the purposes of analysis. No significant difference was found between Rmean and Rsum; therefore, only Rmean ± SEM is reported. Results are compared with the unpaired t test or one-way ANOVA in NCSS (Number Cruncher Statistical Systems, Provo, UT). A statistic is considered to be significant if the probability of a type 1 error is P < 0.05.

As a check on this measurement technique, direct measurements of the peritoneal area were compared with anatomic areas calculated from the first equation. The comparison cannot be carried out in the same animal because our technique requires the carcass to be frozen and sliced to create thin cross sections of the cavity. Therefore, the peritoneal tissues of six separate animals with similar weights to six animals in protocol III were dissected, and their areas were measured directly. The Areaanatomic of each of six animals of protocol III was calculated with the first equation. The mean of these six areas was

![Figure 1. Illustration of the sampling technique used to measure the surface area of an irregularly shaped object.](https://example.com/figure1.png)
then compared with the dissected areas with the unpaired \( t \) test (NCSS, see above).

**Results**

The technique is based on the assumption that the convoluted peritoneal area can be represented by a series of short cylinders, each with a height of 2 mm. This is an approximation that we assume to be appropriate over a 2-mm distance. To verify that the technique provides a reasonable estimate of the total peritoneal area, we used the first equation to calculate the histologic area in six animals from the protocol III experiments (DSS 0.05% and 0.005% concentrations). In six separate animals, we dissected the tissues of the peritoneal cavity and estimated the total area (not including mesentery) from direct measurement. The imaged histologic sections produced an estimated mean (±SEM) area of 5545 ± 194 mm\(^2\), whereas the direct measurement of similar-sized animals provided an estimate of 5949 ± 260 mm\(^2\) (not significant). The difference between the two techniques is less than 7%. We therefore estimate the errors associated with our technique to be on the order of ±5%.

The experiments in protocol I demonstrated that even with large volumes, the area of contact was limited in the quiescent animal but increased with shaking or with use of a surface-active agent. Figure 2A displays the histologic section of a quiescent mouse treated with KRB along with the corresponding autoradiogram (Figure 2B; presented with a reverse spectrum in which the bright areas are those in which the fluid is located or has made contact). Figure 2, C and D, shows an area at a similar sampling point in the mouse peritoneal cavity; however, the effect of DSS on the fluid contact is seen clearly in the autoradiogram when compared with that of Figure 2B. As shown in Figure 3, a large volume (10 ml) of isotonic KRB solution during a 1-h dwell in an anesthetized, quiescent mouse comes in contact with 0.43 ± 0.03 of the total peritoneal area. Vigorously shaking the animal increases R\(_{\text{mean}}\) (±SEM) to 0.54 ± 0.03 \((P < 0.05)\). Addition of 0.5% of an anionic surfactant, DSS, to the KRB in a quiescent animal increases the ratio of contact to 1.07 ± 0.03 \((P < 0.001)\). These findings uphold our hypothesis that only a fraction of the anatomic peritoneal surface is available to the typical salt solution in the cavity under quiescent conditions. The data also provide direct evidence that use of agitation or a surfactant increases the contact area in the peritoneal cavities of mice.

In protocol II, the effect of a 24-h dwell time was investigated with two different solutions. In all cases, there was less than 1 ml of the original 10 ml remaining in the cavity after 24 h. The results demonstrated no difference in surface contact ratios between two treatments: for KRB, R\(_{\text{mean}}\) = 0.88 ± 0.02; for 4% Icodextrin, R\(_{\text{mean}}\) = 0.92 ± 0.02. There was no statistical difference between these numbers, but they were significantly different from the KRB solution after 1 h (Figure 3). The data show that any solution, when given enough time in the cavity, will make contact with most of the peritoneal surface.

**Figure 2.** Images of the histology (A and C) and corresponding autoradiograms (B and D) at similar sampling points in the mouse peritoneal cavity. The edges of the tissue in the histologic image represent the peritoneum; the bright areas in the autoradiogram represent fluid contact. (A and B) After 1 h of dwell time of an isotonic salt solution. (C and D) After 1 h of dwell time of an isotonic solution containing 0.5% DSS.
The experiments in protocol III demonstrated a significant response of contact surface area ($R_{\text{mean}}$) and protein concentration in the peritoneal effluent with increasing concentrations of DSS in the peritoneal solution. Figure 4 displays the data from these experiments and includes complementary data obtained from protocol I (KRB with no DSS and with 0.5%). The one-way ANOVA that compared $R_{\text{mean}}$ with the DSS concentration was highly significant ($F = 68; P < 0.000001$). The surface area ratio ($R_{\text{mean}}$) increases significantly with addition of as little as 0.0005% DSS ($P < 0.05$ when compared with the control KRB). Likewise, the protein concentration in the fluid after 1 h increases proportionately to the concentration of DSS and proportionately to the area of contact (one-way ANOVA significant at $P < 0.0008$). That the ratio decreased slightly from 0.05 to 0.5% likely is because these experiments were run on separate lots of animals and were separated in time by several months. From the results, 0.05% DSS seems to produce total contact between the anatomic peritoneum and the solution in the cavity.

**Discussion**

**Technique**

The calculated anatomic areas found from imaging the histologic slides may underestimate the true area by approximately 5 to 10%. The areas as predicted by our technique seem to be 5 to 7% lower than the measured areas in animals of similar body size. In addition, the mean calculated contact areas exceeded the histologic areas by this amount (see Figure 4). This likely is due to the thickness of the sections. Most of the sections were 20 $\mu$m thick because thinner sections were too fragile and difficult to handle in the process of creating the autoradiograms. When imaged with a digital camera, these thick sections likely “hide” a small percentage of the peritoneum. The film, however, is exquisitely sensitive to any radioactivity in the specimen, which might be present in a portion of the tissue representing peritoneum but that is opaque to the imaging camera after staining. In the histologic sections, the mesentery is not measured in the estimation of surface area, whereas in the autoradiogram, a mesenteric fold with radioactivity might be included in the measurement. This may have produced the values of $R_{\text{mean}}$ that were greater than 1.

The $R$ values from 1-h dwells of the marker likely are higher than one would obtain if the experimental dwell were only 1 min in length (this likely would require a very large amount of radioactivity and be fraught with errors of contamination). Peristalsis over 1 h likely distributes the fluid to a larger total area than the contact area at a single point in time. This presumably is the mechanism that causes the $R$ for the control solution to increase from 0.4 at 1 h to 0.9 after 24 h. Despite the limitation in the interpretation of the absolute value of what is the “instantaneous” contact area of fluid in the peritoneal cavity, our findings uphold our hypothesis.

**Peritoneal Contact Area**

The general equation of mass transfer across the peritoneum is represented by the following:

$$\text{Rate of mass transfer} = MTAC(C_{\text{plasma}} - C_{\text{perit. cavity}})$$

where $C$ is the concentration of solute in either the plasma or the peritoneal cavity, MTAC is mass transfer-area coefficient, which represents the product of the mass transfer coefficient (MTC) and the contact area ($A_{\text{wetted}}$). If the concentration difference and the MTC are maintained constant, the rate of mass transfer is directly proportional to the $A_{\text{wetted}}$. In studies performed in patients or in intact animals, the MTC cannot be separated from the $A_{\text{wetted}}$.

We demonstrated that a relatively large volume of isotonic salt solution in the peritoneal cavity of the quiescent mouse makes contact with approximately 40% of the anatomic peritoneum during a period of 1 h. Furthermore, we showed that
shaking the animal or using a surfactant increases the proportion of the peritoneal surface area that is in contact with the solution. Unfortunately, there is no other study with which a direct comparison of results can be made. However, because MTAC = MTC × A, increasing A should increase the MTAC and therefore the rate of mass transfer. To relate observed MTAC variations by others (7–10) to our results, we assumed that the changes in the MTAC as a result of shaking or addition of surfactant most likely are due to variation in contact or “wetted” area. Unfortunately, the increases in MTAC observed by others do not correlate with our measurements in mice.

Differences in the magnitude of the effect of shaking on the MTAC (shaking rats increased the MTAC by two to four times) noted by Levitt et al. (7) or Zakaria et al. (8) and the surface area changes in our study likely are due to anatomic differences between rats and mice and to the relatively small volumes used in the rats. The 20 ml that these investigators used in the 300-g animals is much smaller than the 66 ml that we would have used with our scaling criteria. Thus, the relative contact area of the quiescent rats likely was much smaller than the area that we measured with 10 cc in 30-g mice. In the same way, early studies with DSS (9) in rabbits used volumes of 60 ml/kg (compared with 400 ml/kg in our study) and demonstrated increases in mass transfer that correspond to increases in contact area of three to four times the baseline. Our 1-h contact area likely represents a maximum attainable in the mouse, and therefore the observed changes are not expected to be as great as in other studies in which the initial contact area likely did not represent a maximum. Because our experiments were not designed to determine the MTAC, we cannot rule out an increase in the MTC portion of the MTAC calculated by other investigators.

There is a clear correlation of DSS concentration and the peritoneal contact area and protein transport, as demonstrated in Figure 4. A similar effect on the MTAC of urea was seen by Penzotti and Mattocks (9) in rabbits, with maximal MTAC at 0.05 to 0.5% DSS and diminished effect at 0.001%. As observed by Leypoldt et al. (10), the transport of protein is significantly enhanced with the use of 0.005% DSS and correlates with the surface area in contact with the fluid. In another study in rats (16), 25 ml of 3.86% dextrose with 0.005% DSS caused significant increases in fluid gain over 4 h (to 37 ml with DSS versus 33 ml without DSS) and 20 to 30% increases in urea and sodium clearance to the cavity. Our data showed that the surfactant DSS has a direct effect on the contact surface area. Although this provides a mechanism for the increases in MTAC observed with the use of DSS, it does not rule out the possibility that the MTC was changed simultaneously with the area.

Clinical Correlation

The single study in human dialysis patients has demonstrated that the contact area of the solution in the peritoneal cavity is 0.55 m² (5). Depending on the estimate used for the true anatomic area of the peritoneum (1–4), the ratio of contact area to anatomic area is 30 to 60% in 70- to 80-kg patients with a 2-L volume in the cavity. The area of peritoneum that is not in contact with the dialysis solution is a potential site for dialysis enhancement, because the MTAC = MTC × A, where A is the area of contact. In patients who are inadequately dialedyzed (weekly KT/Vurea < 2.1), a 20% increase in the MTAC may be enough to produce adequate dialysis and allow them to continue peritoneal dialysis.

As has been demonstrated in this study and by others (7–10), there are several methods of enhancing the surface area. Lengthening the duration of dialysis will increase the total surface area contacted presumably through the peristaltic movement of the hollow viscera. However, this slow movement may move the fluid from one location in the cavity to another, but it likely will not increase the contact area through which the transfer of solute and water occurs. Maneuvers, such as the violent agitation, that were imposed on the animals (7,8) may not be practical for human beings, but it is intriguing to consider recent data that showed a significant effect on small solute transport by the application of low-frequency vibration to the abdominal wall for three 20-min periods per day (17). Another possible method of contact area enhancement is the use of a surfactant added to the dialysate. Issues of toxicity must be considered carefully with these substances. We observed that 0.5% DSS in the peritoneal cavity of mice resulted in 100% lethality within 2 h. We also observed a direct correlation among DSS concentration, contact surface area, and the protein concentration in the dialysate fluid after 1 h of dwell; protein loss must be investigated before implementing this in long-term dialysis in patients. Another item that must be investigated before human implementation is the long-term effect on the peritoneum and the subperitoneal tissue space that forms the barrier between the dialysis fluid and the blood. Other investigators (18) observed fibrinoid material in the dialysis effluents of two of three rabbits in which a 0.04% DSS solution had been used; this finding suggests that DSS may set up or enhance conditions of inflammation within the peritoneal cavity. We would conclude that all of these maneuvers to increase the contact area during peritoneal dialysis are technically possible, but they require further study for potential complications during long-term use in humans.

The enhancement of the contact area in intraperitoneal therapy may be most beneficial to patients who receive regional (localized or, in this case, intraperitoneally) therapy for metastatic ovarian or colorectal cancers. These small tumor nodules are often not detected during surgical resection of the primary tumor and often result in the death of the patient due to obstruction of the gastrointestinal tract and inanition. An alternative to typical intravenous systemic therapy is the use of regional chemotherapy or immunotherapy, which minimizes the systemic side effects of traditional therapy. A major challenge in intraperitoneal therapy (19) is ensuring that the therapeutic agent reaches all sites of metastases with sufficient dose to treat the cancer. Because these patients typically are not in kidney failure, the agent is placed in 2 L of dialysis fluid and allowed to dwell in the cavity until it is entirely absorbed. From our data, this approach should ensure that more than 90% of the peritoneum comes in contact with the fluid during the first 24 h. However, contact with the therapeutic fluid for a variable
amount of time may or may not result in delivery of sufficient dose to treat the metastatic cancer. Use of a surfactant to increase the contact area to the complete peritoneal surface would ensure that the active agent is in contact with the target and can deliver a defined dose over the time of treatment. The potential benefit of using a surfactant in concentration sufficient to ensure contact between the therapeutic solution and all potential sites of metastasis within the peritoneal cavity may outweigh any toxicity of the agent. In contrast to daily dialysis, the peritoneum would be episodically exposed to the agent. Thus, the potential toxicity of the agent would be far less than in the case of dialysis, in which the exposure is continuous.

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References
2. Putiloff PV: Materials for the study of the laws of growth of the human body in relation to the surface areas of different systems: The trial on Russian subjects of planigraphic anatomy as a means for exact anthropometry. One of the problems of anthropology. Report of the Meeting of the Siberian Branch of the Russian Geographic Society, October 29, 1884, Omsk, 1886

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