Mouse model of foreign body reaction that alters the submesothelium and transperitoneal transport

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Peters T, Potter R, Li X, He Z, Hoskins G, Flessner MF. Mouse model of foreign body reaction that alters the submesothelium and transperitoneal transport. Am J Physiol Renal Physiol 300: F283–F289, 2011. First published October 13, 2010; doi:10.1152/ajprenal.00328.2010.—To address the hypothesis that sterile intraperitoneal (ip) catheters alone promote a progressive foreign body reaction (FBR), silicone catheters were surgically implanted in C57BL mice. Controls (CON) underwent sham operations. After 1–5 wk (E1–E5 for catheter-bearing mice), catheters were recovered, and the adherent cell layer (ACL) was separated and cultured to demonstrate sterility. Transperitoneal transport experiments were performed to determine the mass transfer coefficients of mannitol (MTCM) and albumin (MTCA) and the osmotic pressure of the catheter-bearing mice. A fluid bolus was injected, and the adherent cell layer (ACL) was demonstrated to be intact. After 1–5 wk, the ACL demonstrated strong staining for all treated animals and correlated with the submesothelial thickness, angiogenesis, and cytokine immunohistochemistry (IHC). Progressive increases with time were observed in submesothelial thickness (μm): CON, 18.8 ± 12.3; E1, 46.1 ± 20.0; E2, 72.0 ± 17.9; E4, 97.3 ± 20.0; E5, 131.7 ± 10.3; P < 0.003), angiogenesis (no. of vessels/mm of peritoneum: CON, 10.7 ± 9.4; E1, 15.4 ± 15.6; E2, 27.0 ± 14.0; E4, 39.8 ± 15.7; E5, 90.1 ± 8.1; P < 0.0003), MTCM (6.5 ± 1.5 × 10⁻⁵ cm/min, mean CON: 18.0 ± 1.1 × 10⁻⁵ cm/min, mean E1–E5, P < 0.0001), Josm (0.0013 ± 0.0001 cm/min, mean CON: 0.0017 ± 0.0001 cm/min, mean E1–E5, P < 0.01). No significant differences were found for MTCA. IHC demonstrated strong staining for all treated animals and correlated with the ACL. This mouse model demonstrates that ip silicone catheters result in progressive FBR, altering the submesothelial anatomy and transperitoneal transport, and will form the basis for mechanistic studies in genetically-altered animals.

While research concerned with preservation of the peritoneal barrier has focused on biocompatibility of the dialysate solution, there is a growing awareness that the catheter represents a foreign body that produces local inflammatory changes without apparent infection (6, 8). An inflammatory response develops within 18 h on the surface of plastic disks placed in the cavity of mice, but this was not linked to changes in the peritoneum or transperitoneal transport (26). Human (24) and animal (13) studies have demonstrated chronic peritoneal inflammation with no culture-positive signs of infection by the catheter. However, there has been little work concerned with the cellular mechanisms related to the foreign body reaction in the peritoneum or the potential for changes in transport after foreign body exposure.

Our hypothesis is that the presence of sterile catheters inside the peritoneal cavity causes a foreign body reaction without solution injection and results in local inflammatory changes in the peritoneum and transport alterations across the peritoneum. In addition, we hypothesize that the degree of inflammation is dependent upon the duration of catheter implantation. To address these hypotheses, we developed a unique mouse model of sterile inflammation. We placed silicone ring catheters in the abdomens of C57BL mice and observed them for 1–5 wk with no further intervention. Upon removal of the catheters, we performed experiments to characterize the histological and functional changes to the peritoneum and the inflammatory response of the cells adherent to the catheter. Cytokine and electron microscopy of the abdomen and the catheter adherent cell layer (ACL) demonstrate that the animals were free of bacteria. Our results showed significant differences between the control animals and those exposed to sterile silicone catheters and a variation of response with weeks of exposure within the experimental group.

MATERIALS AND METHODS

Materials. [¹⁴C]mannitol was purchased from Moravek Biochemicals (Brea, CA) and detected by liquid scintillation counting (Packard Tricarb 2500 TR, Ramsey, MN). FITC-labeled BSA (FITC-BSA) was purchased from Sigma (St. Louis, MO) and was used as delivered. Fluorescence was detected with a Turner TD 700 spectrophotometer (Turner Biosystems, Sunnyvale, CA). The following were used in the immunohistochemical studies and purchased from Santa Cruz Biotechnology, Santa Cruz, CA; cytokertatin (sc-32328); monoclonal broad-spectrum anti-cytokeratin to demonstrate mesothelial cells; CD8 (sc-7970); monoclonal antibodies for lymphocytes; vimentin (sc-32327); monoclonal antibody that reacts with myofibroblasts in a proliferating and motile stage but not fixed fibroblasts; basic fibroblast growth factor (bFGF; sc-79); rabbit polyclonal IgG anti-FGF-2; transforming growth factor β1 (TGF-β1; sc-146): rabbit polyclonal IgG anti-TGF-β1; vascular endothelial growth factor (VEGF; sc-7269): rabbit polyclonal IgG anti-VEGF. F4/80 (MCA497G, AbDserotec, Oxford, UK); monoclonal antibodies used to discriminate macrophages from myofibroblasts and fibroblasts; and α-smooth muscle actin (α-SMA; MAB-1420, R&D Systems, Minneapolis, MN). Immunoperoxidase staining kits were used to visualize positive staining. They were Elite ABC kits (pk-6101 and pk-6102, from Vector Labs), and ABC staining kits (sc-2017, sc-2023 and sc-2019 from Santa Cruz Biotechnology). To reduce nonspecific staining, an avidin/biotin blocking system (X0590, Dako) was applied.

Experimental overview. 40 C57Bl/6F female mice were obtained from Harlan Laboratories and divided into eight groups. Our laboratory has traditionally used female rodents for experiments because males tend to grow more rapidly and to have more intra-abdominal fat that may interfere with transport measurements. However, the effect of rodent gender on the foreign body reaction in the peritoneum is unknown. Four groups of mice (n = 28) were surgically implanted with five silicone catheters intraperitoneally (ip) and monitored for 1–5 wk. Four additional groups (n = 12) underwent sham operations without catheter implantation and were observed concurrently with the catheter groups. After 1–5 wk, the animals were anesthetized and catheters were carefully removed from the abdomen.
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and ACL, after separation from the catheter, were cultured to ensure sterility. Scanning electron microscopy (SEM) and transmission electron microscopy (results not shown) were also performed on the ACL to confirm the absence of bacteria. Transport experiments to determine the mass transfer coefficients of mannitol (MTCM) and albumin (MTCAL), and the osmotic flux (Josm), were carried out with chambers affixed to the abdominal wall. At the time of death, the weights (g) of the animals were approximately the same: 1 wk, 22.7 ± 0.7; 2 wk, 23.8 ± 0.7; 4 wk, 23.9 ± 0.6; 5 wk, 22.3 ± 0.5 (1-way ANOVA, \( P > 0.15 \)). After animal death, samples of abdominal wall were studied with immunohistochemistry for cytokines, and immunocytochemistry was used to determine cell markers in the ACL.

The experimental protocols for this study were approved by the Institutional Animal Care and Use Committee of the University of Mississippi Medical Center and were carried out in accordance with the Guide for the Care and Use of Laboratory Animals from the National Institutes of Health and the guidelines of the Animal Welfare Act.

**Catheter preparation and implantation.** Medical grade silicone catheter material (5 Fr, OD 1.7 mm) was purchased from Access Technologies (Skokie, IL) and cut into 3-cm lengths and formed into 1-cm-diameter rings. The catheters were sterilized in 100% ethyl alcohol for 96 h to remove dust and foreign material. The catheters were rinsed twice in sterile, pyrogen-free Krebs solution for 1 h and then gas-autoclaved.

All mice were anesthetized with isoflurane gas via the Euthanex Small Animal Anesthesia System (1–4%, Euthanex model 2500, Palmer, PA). Using aseptic techniques, an 8-mm midline incision was made in the abdomen, and five catheter rings were placed into the abdomen. Antibiotics (0.5 mg cefazolin and 1 mg gentamicin) were injected intraperitoneally just before closure. The muscle was closed with absorbable sutures (Vicryl 4.0, Ethicon, Somerville, NJ), and the overlying skin was closed with wound clips. The animal was returned to its cage and closely monitored until ambulatory (typically <5 min). The animals were subsequently checked three times/week, and catheters were recovered at 1, 2, 4, or 5 wk. Animal groups were designated “E” for catheter-bearing mice (E1, E2, E4, E5, with the number corresponding to the number of weeks) or “C” for control animals (C1, C2, C4, C5).

**Recovery of catheter and ACL.** After 1, 2, 4, and 5 wk, each animal was anesthetized with isoflurane gas (1–4%). The abdomen was opened using aseptic techniques, and abdominal swabs were taken for culture and cell count. The catheter loops were carefully removed using sterile techniques. Approximately 90% of the catheters were easily removed from the abdomen and were free of adhesions; the other 10% were adhered to the omentum, and only a few (<2%) were completely encased within omentum. When tissue was found adhered to the catheters, it was typically at the joint where the two ends of the catheter met to make the loop and appeared tan-yellow with focal areas of hemorrhage. Except for the adherent tissue, the gross appearance of the peritoneum was normal. From one of the loops, a 0.5-cm piece was cut and placed into a culture dish. The remainder of the loop was cut into small pieces and placed in a sterile centrifuge tube with Krebs solution on ice. It was then treated with a Sonic Dismembrator (model 100, Fisher Scientific, Pittsburgh, PA) for three 30-s bursts at ~50–70% power to separate cells from the catheter. A small amount of material from the fluid in the centrifuge tube was cultured for 5 days to check for bacterial growth. The other four loops were placed in 5 ml of 2.5% glutaraldehyde solution (pH 7.1) in a sterile metal container for 10 min to fix the cells; the container with the loops was then placed on ice, and ultrasound was used as above to separate the adherent cells from the catheters. (23)

**Analysis of ACL.** To determine the density of white cells in the ACL (23), 0.5 ml of the solution was transferred to black polycarbonate 25-mm membrane filters (0.1 μm, GE Water and Process Technology), and a vacuum was applied to remove the fluid. For 2 min, 0.5 ml of 0.01 mg/ml Acidine Orange (Sigma) in 100 mM phosphate buffer (pH = 7.2) was added. Minimum vacuum was applied to remove the stain, and the membrane was set to dry for 2 min. The dried membrane was placed on a clean glass microscope slide, covered with immersion oil and coverslip to examine with Epifluorescence. The cell density was measured by three independent observers and averaged to calculate the ACL number of white cells per unit area of catheter. The remaining material was centrifuged for 60 min to obtain a pellet of material. The supernatant was removed, replaced with 1 ml of 2.5% glutaraldehyde, and resuspended and transferred to a 1.5-ml Eppendorf tube for molecular/EM studies.

**Transport studies.** Transport studies were carried out as previously described (9). After catheter loop recovery, each mouse was maintained at surgical anesthesia with 1–3% isoflurane, and rectal temperature was maintained at 35–38°C with overhead heating lamps and the Euthanex water-jacketed warming system. Mean arterial blood pressure (BP) was kept >75 mmHg with infusion of isotonic solution during the experiment. A carotid arterial catheter was inserted for sampling and BP monitoring. A jugular venous catheter was placed for infusion. A plastic chamber (1.5 cm in height and ~0.9 cm in diameter, manufactured from polystyrene) was affixed to the serosa of the left, mid-abdominal wall with cyanoacrylate glue. To measure osmotic filtration flux (Josm) and small-solute mannitol transport from the chamber into the tissue, a hypertonic solution (4% mannitol in Krebs-Ringer bicarbonate) containing [14C]mannitol (3 μCi in 3 ml) was placed in the chamber to a level <1 cm height for 120 min, during which the chamber volume was measured every 30 min and 20-microliter samples of chamber fluid were taken at 0, 30, 60, 90, and 120 min for 14C determination. Simultaneously, 0.1 ml of FITC-BSA (20 mg in 0.5 ml Krebs-Ringer bicarbonate) was injected intravenously as a bolus, and its appearance into the small chamber was measured to calculate MTCAL (7). Fifty-microliter blood samples were taken at 0, 10, and 120 min to satisfy the calculation. The osmolality was checked at 0-, 60-, and 120-min intervals by withdrawing 10-μl samples from the chamber.

**Calculations.** Statistical calculations were carried out using NCSS 97 (Number Crunching Statistical System, Kaysville, UT). All results are presented as mean ± SEM.

**Fig. 1.** Scanning electron microscopy (SEM) of in situ inflammatory cells on silicone catheters at 1 wk.

SEM

750x

Silicone Catheter-Mouse 1 wk

SEM

5000x
are presented as means ± SE. One way- and two-way-ANOVA were utilized to compare different data sets. Probability of a type I error was set at \( P \leq 0.05 \) for significance.

As in our previous publication (7), the following equation is fitted to the mass transfer data for mannitol using the program Scientist (Micromath, Salt Lake City, UT)

\[
\frac{d(V_{\text{chamber}} C_{\text{chamber}})}{dt} = -MTC_{M} \cdot A_{\text{chamber}} (C_{\text{chamber}} - C_{\text{plasma}}) \] (1)

where \( V_{\text{chamber}} \) = volume in the chamber, \( C_{\text{chamber}} \) = tracer concentration in chamber, \( t \) = time, \( MTC \) = mass transfer coefficient for the abdominal wall, \( A_{\text{chamber}} \) = area of the base of the chamber, and \( C_{\text{plasma}} \) = plasma tracer concentration.

The osmotically induced fluid from the tissue to the chamber \( (J_{\text{osm}}) \) was calculated as follows:

\[
J_{\text{osm}} = \frac{\Delta V_{\text{chamber}}}{\Delta t \cdot A_{\text{chamber}}} \] (2)

where \( \Delta V_{\text{chamber}} \) = change in chamber volume and \( \Delta t \) = change in time.

The mass transfer coefficient for albumin \( (MTC_{A}) \) was calculated in a similar fashion:

![Duration of Catheter Implantation](image)

Fig. 2. Cellular makeup of sterile adherent cell layer on the silicone catheter includes macrophages (F4/80), NK and CD8-T cells (CD8), mesothelial-like (cytokeratin and vimentin) and fibroblastic-like cells (vimentin), and T lymphocytes and dendritic cells (CD3). Brown staining indicates positive cells.
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\[
\text{MTC}_A = \frac{\Delta I_{\text{chamber}} V_{\text{chamber}}}{I_{\text{plasma}} \cdot \Delta t \cdot A_{\text{chamber}}}
\]

where \( I \) = fluorescence (FITC) measured in the chamber or in the plasma, and \( I_{\text{plasma}} \) represents the mean plasma concentration over \( \Delta t \).

**Tissue recovery.** At the end of the transport studies, the mouse was euthanized with isoflurane gas and tissue samples were obtained. The abdominal wall, adjacent to and untouched by the chamber, was collected and frozen. Portions of the contralateral abdominal wall corresponding to the position of the chamber were collected and placed in 10% formalin for histological analysis.

**EM.** For SEM, a portion of the catheter with intact ACL was fixed in 2.5% glutaraldehyde, with postfixation in phosphate-buffered 2% osmium tetroxide for 1 h, dehydrated, dried, and sputter-coated with gold for SEM and examined with a JSM T-300 scanning electron microscope (Jeol USA, Plano, TX).

**Histological analysis.** Histological studies and image analysis were carried out as before (5, 6). Trichrome staining was used for determinations of the submesothelial compact zone thickness, and CD31 immunohistochemistry was used to determine angiogenesis. Three investigators examined each slide, and the average measurements by the three investigators for thickness of the submesothelium and CD31 counts were examined. The immunohistochemical stains, \( \alpha \)-SMA, FGF2, TGF-\( \beta \), and VEGF, were rated as 1–4, with 4 being intense staining, 3 being moderate staining, 2 being light staining, and 1 being no staining. Five sections of each control and treated group were examined by three independent observers and averaged to obtain a single score. Immunocytochemical analysis of the ACL was carried out as before (8) with the reagents listed above to identify the inflammatory cell type in the ACL.

**RESULTS**

**Culture results.** All bacterial cultures of the peritoneal swab, the catheter with intact ACL, and the separated ACL were negative, demonstrating sterility.

**Catheter cell response.** Figure 1 is a SEM of the intact ACL after 1 wk in the mouse. Average estimated total white cell counts of the ACL (number of cells \( \times 10^6/cm^2 \) of catheter) for weeks 1–5 are as follows: E1, 3.43 \( \pm \) 0.27; E2, 2.50 \( \pm \) 0.22; E4, 2.65 \( \pm \) 0.23; and E5, 2.52 \( \pm \) 0.21. The decline in total white cell density from the first week was significant (\( P < 0.05 \) 1-way ANOVA).

Figure 2 demonstrates the immunocytochemistry analysis of the sterile ACL: macrophages (F4/80), dendritic cells and T lymphocytes (CD3), NK and T lymphocytes (CD8), mesothelial cells (cytokeratin), and fibroblastic-like cells (vimentin). Vimentin has been shown to lightly stain mesothelial cells (19); however, the stain is more intense in cells that have undergone epithelial-to-mesenchymal transformation induced by immunological stress (1), as shown in Fig. 2. Each of these stains and therefore the corresponding cell types are present during all durations of the catheter implantation.

**Structural changes in peritoneum.** Figure 3 demonstrates the structural alterations after 1, 2, 4, and 5 wk of exposure. Marked trends in submesothelial thickness vs. time of implantation were noted (\( \mu m \)): CON, 18.8 \pm 12.3; E1, 46.1 \pm 20.0; E2, 72.0 \pm 17.9; E4, 97.3 \pm 20.0; E5, 131.7 \pm 10.3; \( P < 0.003 \)) and angiogenesis in the peritoneum (no. of vessels/mm of peritoneum: CON, 10.7 \pm 9.4; E1, 15.4 \pm 15.6; E2, 27.0 \pm 14.0; E4, 39.8 \pm 15.7; E5, 90.1 \pm 8.1; \( P < 0.0003 \)). As an additional method of determining angiogenesis, we estimated the vessel density (vessels/mm\(^2\), means \( \pm \) SE) to be: CON 65 \pm 55;

![Fig. 3. Structural alterations after 1-, 2-, 4-, and 5-wk exposure to silicone catheters. The progression of both submesothelial thickening and angiogenesis vs. untreated controls is significant (1-way ANOVA, \( P < 0.003 \)).](http://ajprenal.physiology.org/)

**DISCUSSION**

**Uniqueness of animal model.** While most mouse models are designed to test effects of dialysate on the peritoneum (12, 30) or to investigate peritoneal physiology (18), our animal model focuses on the effects of catheter polymeric material on the inflammatory response of the peritoneum, including: the cells that adhere to plastic material, the local changes to tissue histology, and alterations in transport phenomena. The model utilizes ring-shaped catheters for several reasons. The rings of tubing minimize trauma to the peritoneum and to the gut, can be made from any relevant material, and allow for easy retrieval from the peritoneal cavity. Other researchers (25) have used plastic discs to determine the nature of the ACL but have not studied the associated tissue response. In addition, the edges of this disk shape may abrade the peritoneum and do not mimic the PD catheter. The uniform size of tubing presents a defined surface of interaction so that adherent cells can be studied after separation from the catheter via sonication. After many attempts to study the in situ ACL, we found that the ACL...
structure was rarely intact after sectioning it together with the silicone catheter. The closed abdomen ensures sterility and still permits intraperitoneal injections via a needle if desired (8), thus essentially eliminating the complication and often confounding factor of infection. In a preliminary study (21), CD-1 mice without catheters received 10 ml of hypertonic dialysis solution daily for 60 days via needle and syringe. There was a variable response in the peritoneum of these mice, with some areas appearing completely normal and others demonstrating hypercellularity in the submesothelial compact zone (between the mesothelial cells and the muscle of the abdominal wall). The degree of inflammation was not as severe as that reported here, nor was it as uniform, demonstrating further differences between animals with catheters and those without. Percutane-

Fig. 4. Inflammatory markers in tissue and the cells adhering to the catheter. Top left, 1 wk; top right, 2 wk; bottom left, 4 wk; bottom right 5 wk. α-SMA, α-smooth muscle actin; TGF-β, transforming growth factor-β. Brown staining indicates positive cells. In all weeks, staining is significantly different from the controls. Changes in tissue staining are also observed from weeks 1-5 in the treated animals. Bar = 100 μm in each micrograph.
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Table 1. Immunohistochemical scores vs. treatment (catheter vs. control) and treatment duration

<table>
<thead>
<tr>
<th>Stain</th>
<th>CON**</th>
<th>1 wk</th>
<th>2 wk</th>
<th>4 wk</th>
<th>5 wk</th>
<th>Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-SMA</td>
<td>1.17 ± 0.10</td>
<td>2.46 ± 0.18</td>
<td>2.93 ± 0.16</td>
<td>2.62 ± 0.18</td>
<td>3.26 ± 0.09</td>
<td>P &lt; 0.04</td>
</tr>
<tr>
<td>FGF-2</td>
<td>1.06 ± 0.12</td>
<td>2.50 ± 0.21</td>
<td>2.96 ± 0.18</td>
<td>2.42 ± 0.21</td>
<td>2.82 ± 0.11</td>
<td>P &gt; 0.04</td>
</tr>
<tr>
<td>TGF-β</td>
<td>1.11 ± 0.12</td>
<td>2.58 ± 0.21</td>
<td>2.60 ± 0.19</td>
<td>2.29 ± 0.21</td>
<td>2.92 ± 0.11</td>
<td>P &gt; 0.04</td>
</tr>
<tr>
<td>VEGF</td>
<td>1.10 ± 0.08</td>
<td>2.79 ± 0.13</td>
<td>4.00 ± 0.12</td>
<td>3.25 ± 0.13</td>
<td>3.83 ± 0.07</td>
<td>P &lt; 0.04</td>
</tr>
</tbody>
</table>

Values are means ± SE. α-SMA, α-smooth muscle actin; TGF-β, transforming growth factor-β. +Significance of 2-way ANOVA for weeks 1–5. **Averaged control values for all weeks are provided. Control values were significantly different from catheter animals at each week in 2-way ANOVA (P < 10^-4).

Bacterial catheters often require use of daily antibiotics because they are prone to bacterial infection (28). Other models (11) have used infected implants to study bacterial biofilm formation but have not examined the resulting tissue or transport phenomena.

In this model, we couple the ACL analysis with peritoneal immunohistochemistry (8) and our validated techniques of transperitoneal solute and water transport (7) to study the progression of sterile inflammation from the foreign body. One limitation to our data set is the exclusive use of female mice that might alter the immune response of this strain of mice. While physiological responses of murine models are known to depend on gender (16), there is controversy with regard to the immune system (14, 17). A second limitation is precise correlation with human histology, which is essentially nonexistent for the weeks immediately following catheter implantation. Published observations of peritoneal effluent in the first 2 wk after catheter placement have demonstrated marked increases in ip white blood cells, particularly neutrophils, without evidence of infection (3). In preliminary work, we have confirmed this, but a peritoneal biopsy is contraindicated in this postoperative period. Despite these limitations, animal models are especially valuable because they can longitudinally define steps in an immune reaction, and tissue is readily available for study.

ACL. Previous work with various polymer disks has identified the ACL as being made up of macrophages, mast cells, and neutrophils (2, 27). We have found that the ACL contains no bacteria but includes the typical inflammatory cells of the peritoneal cavity: macrophages, T cells, dendritic cells, mesothelial cells, and fibroblastic cells. The finding of α-SMA and vimentin staining in the ACL suggests the presence of myofibroblasts that are likely derived from the abnormal submesothelium of treated animals (1, 29). While we did not investigate the mechanisms of adherence of the cells to the polymer tubing, other workers have implicated the deposition of fibrinogen on the polymer surface and irreversible protein denaturation that lead to cellular binding (15).

Foreign body reaction: structural changes in tissue. Our results in Fig. 3 clearly demonstrate progressive increases in submesothelial thickening and ongoing angiogenesis over the 5 wk of exposure to the silicone catheters. Because of the uniqueness of the model, there are no data for precise comparison. However, a rubber intraperitoneal implant in rats was completely encapsulated by 3 wk, with subsequent resolution of the foreign body response by 4 wk (13). In contrast, our previous observation in rats showed that there was no resolution of the inflammatory changes over 4 wk and significantly greater inflammation in animals injected via catheters up to 5 mo than those without a catheter (8). However, there may indeed be resolution of the inflammatory changes in mice beyond 5 wk, if there are no injections of solution (13). Further experiments will have to be carried out to answer this question.

Foreign body reaction: transport changes. Exposure of the peritoneum to silicone catheter material results in alterations of albumin and water transport from plasma to the peritoneal cavity (see Fig. 5). There were minor changes in the transport of the small molecule mannitol (molecular size equal to glucose) that were significantly different from control animals by 5 wk. The significant rises in the osmotically driven water flow and the albumin transport in the treated animals correlate with the increased angiogenesis of Fig. 3. However, to form a direct correlation of transport with angiogenesis, all of the vessels counted in Fig. 3 need to be perfused with blood. The percentage of new vessels containing blood was not determined, and therefore we do not know how many of the newly formed vessels are perfused.

Because of our method of measurement using a transport chamber (4, 9), there are only rat data in the literature for direct comparison. Compared with measurements in the rat (8), our determinations of the MTCm in mice are on the same order of magnitude. Clearance of 125I-albumin from plasma to the 2.5-ml solution in the peritoneal cavity has been determined in C57Bl/6J mice to be 0.08–0.10 μl/min in whole-cavity experiments while the clearance of glucose was 52 μl/min (20). By using a scaling factor of (body weight)^0.67, we can estimate the anatomic peritoneal area of a 30-g mouse (4) from a 70-kg

![Fig. 5. Transport alterations due to peritoneal exposure to silicone catheters. The mass transfer coefficient of albumin (MTCalb) treated vs. control animals was significant (P < 0.001, 2-way ANOVA), while osmotic water flux (Josm) for treated animals was significantly different from untreated controls (CON) and demonstrated significant differences in weeks of exposure (**P < 0.01, 2-way ANOVA). No significant differences were noted for the mass transfer coefficient for mannitol (MTCmannitol) between controls and treated animals.](http://ajprenal.physiology.org/DownloadedFrom/10.2203/33.5.2017)
human with an area of 1.1 m² (22) to be 1.1 × (0.03/70)^{0.67} ≈ 0.006 m² or 60 cm². From our previous work (10), we estimate that the volume used in the experiments would be in contact with ~16% of this area or 9.6 cm². By dividing each rate by the area, we obtain estimated \( \text{MTC}_{\text{glucose}} \sim 5 \mu l\text{-min}^{-1}\text{-cm}^{-2} \) and \( \text{MTC}_{\alpha} \sim 0.01 \mu l\text{-min}^{-1}\text{-cm}^{-2} \). The estimated parameter for glucose is very close to our mannitol values in Fig. 5, but the estimate for albumin was an order of magnitude lower than our results. The discrepancy may be due to possible loss of 125I label in vivo that can substantially lower the calculated rates when the free isotope is subtracted from the total transporting to the cavity, and the authors acknowledge the low rate of transfer for radioactive iodinated serum albumin. (20)

In summary, we have developed a unique animal model to study sterile, progressive foreign body reactions in the peritoneal cavity. Exposure of a polymer with a defined surface area, ease of insertion and retrieval, is analyzed with immunochemical techniques applied to the cells adhered to the polymer and the tissue from the peritoneum. When combined with the transperitoneal transport studies, structural and functional effects of the inflammatory process are thereby studied. It is hoped that this model will provide a basis for studying the mechanism of foreign body reactions with genetically altered mice.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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