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Abbreviation:
USP = U.S. Pharmacopeia

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Contrast Medium–induced Pulmonary Edema Is Aggravated by Silicone Contamination in Rats[1]

PURPOSE: To examine the effect of silicone contamination, which occurs in clinical settings during vial preparation with disposable syringes, on contrast medium–induced pulmonary edema in rats.

MATERIALS AND METHODS: Ioxaglate, ioversol, and iohexol, silicone-containing physiologic saline solutions, and three silicone-containing contrast media were separately, intravenously injected at 1.5 mL/min in rats. Pulmonary edema was evaluated as changes in the relative lung weight and in the water, sodium, and potassium contents of the lung.

RESULTS: Intravenous injection of ioxaglate induced marked pulmonary edema, even with a dose of only 4 g of iodine per kilogram of body weight. In contrast, ioversol and iohexol induced significant pulmonary edema only after the injection of large doses (6 g of iodine per kilogram; $P < .05$). The injection of 4 μL/mL silicone-containing physiologic saline at a dose of 18.75 mL/kg also produced marked pulmonary edema, whereas doses of 6.25 and 12.5 mL/kg showed no significant influence. The addition of an ineffective dose (12.5 mL of physiologic saline per kilogram of body weight) of silicone in contrast medium substantially aggravated the pulmonary edema induced by the contrast medium alone; this phenomenon was also confirmed with morphologic observation.

CONCLUSION: Ionic contrast media are more toxic to the endothelial cells than are nonionic contrast media. Silicone contamination might be one of the causes of pulmonary edema after intravenous injection. However, caution must be exercised in extrapolating these results to humans.

Parenteral solutions for intravenous injection are often contaminated with extrinsic foreign particles (1). Findings of animal studies have demonstrated that particles in parenteral solutions produce undesirable effects, such as particle-induced coronary vasoconstriction (2), embolization of arterioles in the kidney (3), and granulomas (4). Findings of some investigations (3,5,6) have also revealed the involvement of glass particles from the opening of the package and cotton fibers and other particles from the ambient air that enter the contrast medium.

In the case of vial preparations, contrast medium is transferred into disposable plastic syringes for injection. We (7) recently found a marked increase in the particle contamination of contrast media during the loading of disposable syringes due to silicone released from the inner surface and the rubber plunger. However, little is known about the harmful effects of the injection of contrast medium contaminated with silicone.

Pulmonary edema is a severe adverse reaction that sometimes occurs after the intravascular injection of a contrast medium and, although this is rare, might be the main cause of death related to contrast media (8). In the present study, therefore, we investigated the influence of silicone contamination in pulmonary edema induced by contrast media in rats.

MATERIALS AND METHODS

Animals

Specific pathogen–free male Sprague-Dawley rats weighing 200–250 g were obtained from the Laboratory of Animal Experiments, Faculty of Medicine, Kyushu University, Fukuoka, Japan. Animals were given free access to food and water before the experiments.

This study was reviewed by the ethics committee regarding animal experiments at the Faculty of Medicine, Kyushu University, and was performed according to the Guidelines for Animal Experiments in the Faculty of Medicine, Kyushu University, and the law (no. 105) and guidelines for notification (no. 6) from the Japanese government.

Administration of Contrast Media in Study Rats or Physiologic Saline in Control Rats

Each nonanesthetized rat was placed in a plastic restrainer (model KN-328; Natsume, Tokyo, Japan); ioxaglate (Hexabrix 320, lot no. 3100, ionic dimer containing 320 mg of iodine per milliliter; Mallinckrodt Medical, St Louis, Mo), ioversol (Optiray 320, lot no. 305465J, nonionic monomer containing 320 mg of iodine per milliliter; Mallinckrodt Medical), or iohexol (Omnipaque 300, lot no. FQ41, nonionic monomer containing 300 mg of iodine per milliliter; Daiichi Pharmaceutical, Tokyo, Japan) was injected into the tail vein with a 25-gauge butterfly needle connected to an injection pump (Terumo, Tokyo, Japan) at a rate of 1.5 mL/min. Silicone-free plastic syringes (20-mL capacity; Top, Tokyo, Japan) were used for injection.

Control animals received injections of physiologic saline. In the study animals, the dose of the contrast medium was adjusted with the injection volume. Contrast medium at a dose of 2, 4, or 6 g of iodine per kilogram of body weight or a volume of physiologic saline equal to the volume of a dose of contrast medium at 6 g of iodine per kilogram was injected. Volume-related effects between the control group and the contrast media groups can therefore be excluded.

Preparation of Silicone-containing Contrast Media

Silicone-containing contrast media were prepared from commercially available contrast media by adding medical-grade silicone (silicone oil SH-200; Nacalai Tesque, Tokyo, Japan). Each silicone-containing solution was made on the basis of the number of contaminated particles in a previous report (7). Also, silicone (4 μL/mL) was added to the contrast media and physiologic saline. The solutions were filtered through a 5-μm membrane filter (Millex-SV; Millipore, Tokyo, Japan).

The degree of silicone contamination was evaluated by counting the particles derived from the interaction of the contrast media with silicone. Particle counting was performed with an automated light extinction method by using an automatic parenteral sampling system (Particle Measuring Systems, Boulder, Colo), as in a previous study (7). The prepared silicone-containing solutions of ioxaglate or ioversol were at 164% or 112%, respectively, of the U.S. Pharmacopeia (USP) acceptable limit of 6,000 pieces of 10 μm or larger per container; the solution of iohexol was at 76% of the USP limit. These differences among the three contrast media were based on the partition coefficient of their physicochemical properties (7).

To summarize, in the first experiment, we injected pure physiologic saline and pure contrast medium (ioxaglate, ioversol, or iohexol). In the second experiment, we injected pure physiologic saline and silicone-containing physiologic saline. In the third experiment, we injected pure contrast medium (4 g of iodine per kilogram) and silicone-containing contrast medium (4 g of iodine per kilogram).

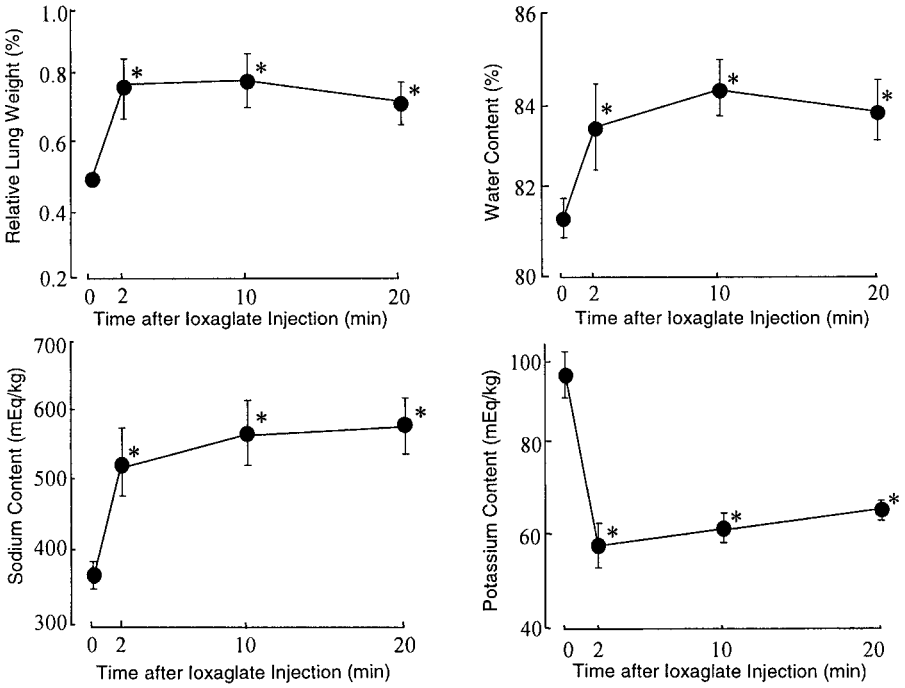


Figure 1. Graphs show the course of pulmonary edema development in rats after intravenous injection of ioxaglate. The maximum changes in the lung weight and potassium content were observed at 2 minutes after the injection, the maximum change in the water content was observed at 10 minutes, and the maximum change in the sodium content was observed at 20 minutes. Ioxaglate was intravenously injected at a dose of 6 g of iodine per kilogram and a rate of 1.5 mL/min. Each point with a vertical bar indicates the mean ± SEM for three to eight animals. Error bars are not shown when they are smaller than the symbols. $* = P < .05$ in a comparison with the value at 0 minute.

Water Content of Lung

The rats were lightly anesthetized with ether and killed by means of cervical vertebra dislocation at an appropriate time after injection. The chest was opened, and the lungs were removed rapidly. The lungs were then placed on absorbent paper, and nonpulmonary tissue was carefully trimmed off. The lobes of each lung were separated, and all extralobar vessels were removed. Compression was avoided to prevent passive bleeding and fluid discharge from the lung. The wet weight was recorded after any visible blood stains were removed. The lobes were then placed in a drying oven at 100°C for 24 hours to measure the dry weight. The percentage

TABLE 1
Effect of Contrast Medium Dose on Development of Pulmonary Edema

Contrast Medium	Relative Lung Weight (%)	Water Content (%)	Sodium Content (mEq/kg Tissue)	Potassium Content (mEq/kg Tissue)
Ioxaglate				
Saline solution*	0.45 ± 0.02	81.6 ± 0.7	429.0 ± 3.3	85.7 ± 9.0
2 g I/kg	0.48 ± 0.02	81.8 ± 0.5	408.7 ± 19.5	74.4 ± 2.0
4 g I/kg	0.63 ± 0.09	84.0 ± 1.0†	642.1 ± 85.0†	66.0 ± 8.5†
6 g I/kg	0.81 ± 0.08†	85.0 ± 0.7†	597.3 ± 48.5†	62.2 ± 3.5†
Ioversol				
Saline solution‡	0.50 ± 0.02	82.0 ± 0.3	442.1 ± 14.9	76.6 ± 4.5
2 g I/kg	0.44 ± 0.01	81.1 ± 0.1	389.0 ± 12.0	68.9 ± 5.9
4 g I/kg	0.55 ± 0.05	81.6 ± 0.7	448.0 ± 62.3	63.1 ± 8.3†
6 g I/kg	0.60 ± 0.01†	83.3 ± 0.4†	488.7 ± 7.4	62.3 ± 4.1†
Iohexol				
Saline solution§	0.47 ± 0.02	80.8 ± 0.8	422.2 ± 43.7	73.5 ± 5.2
2 g I/kg	0.46 ± 0.01	81.2 ± 0.4	388.0 ± 12.4	76.5 ± 5.7
4 g I/kg	0.53 ± 0.04	82.3 ± 0.7	441.8 ± 31.9	63.0 ± 2.9
6 g I/kg	0.83 ± 0.07†	85.2 ± 0.7†	604.4 ± 34.9†	57.0 ± 5.2†

Note.—Each measurement was obtained at 10 minutes after injection. Each value represents the mean ± SEM for six animals.

* Volume of saline solution equal to the volume of ioxaglate at a dose of 6 g of iodine per kilogram of body weight.

† $P < .05$ in a comparison with respective saline solution–injected groups.

‡ Volume of saline solution equal to the volume of ioversol at a dose of 6 g of iodine per kilogram of body weight.

§ Volume of saline solution equal to the volume of iohexol at a dose of 6 g of iodine per kilogram of body weight.

of water content was calculated as [(wet weight − dry weight)100]/(wet weight).

Measurement of Sodium and Potassium Contents

The dry lung lobes were subjected to wet ashing with a mixture of nitric acid and perchloric acid (2:1, vol/vol). After centrifugation at 1,000 *g* for 10 minutes, the supernatant was diluted with distilled and deionized water. After this dilution, the sodium and potassium contents were measured by means of atomic absorption spectrophotometry (model AA-6400F; Shimadzu, Kyoto, Japan) by using diluted standard solutions (sodium standard solution, 997 mg of sodium per liter, and potassium standard solution, 1,000 mg of potassium per liter; Wako Pure Chemical Industries, Osaka, Japan). Results were obtained from triplicate assays and are expressed in milliequivalents per kilogram of dried lung.

Statistical Analysis

At least six rats were studied in each experimental group. All data are expressed as the mean ± SEM. Analysis of variance and then the Fisher protected least significant difference test were performed. Significance was indicated with a *P* value of less than .05.

RESULTS

Time Course of Pulmonary Edema Formation

At 0 minute after ioxaglate injection, the mean relative lung weights and water, sodium, and potassium contents in untreated rats were 0.50% ± 0.01, 81.7% ± 0.5, 381.8 mEq ± 8.1, and 97.1 mEq ± 5.2 per kilogram of tissue, respectively (Fig 1). The relative lung weights and water and sodium contents increased significantly, and the potassium content decreased significantly at 2, 10, and 20 minutes after the injection of ioxaglate (6 grams of iodine per kilogram). Although no significant differences in these parameters were noted among these three time points, the maximum changes in the lung weights and potassium contents were observed at 2 minutes after the injection, the maximum changes in the water content were observed at 10 minutes, and the maximum changes in the sodium content were observed at 20 minutes. No significant effects on these parameters were observed at 2, 10, or 20 minutes following the injection of a volume of physiologic saline equal to the volume of a dose of contrast material at 6 g of iodine per kilogram. In the subsequent experiments, therefore, the evaluation at the 10-minute observation point was assumed to be representative of the degree of pulmonary edema.

Contrast Medium-induced Pulmonary Edema

Table 1 summarizes the dose-dependent effects of the three contrast media on the relative lung weights and on the water, sodium, and potassium contents. The data obtained at 10 minutes after injection were chosen as a reference. The relative lung weights and water contents increased with increases in the doses of the three contrast media. The dose-dependent elevation in the relative lung weights became significant at the dose of 6 g of iodine per kilogram for all three contrast media.

In parallel with these changes, the water, sodium, and potassium contents also showed significant changes at the dose of 6 g of iodine per kilogram for iohexol. For ioxaglate, however, these parameters showed significant changes even at a dose of 4 g of iodine per kilogram. For ioversol, the potassium contents showed significant decreases at doses of 4 and 6 g of iodine per kilogram, but the sodium contents showed no significant changes.

Silicone-induced Pulmonary Edema

Table 2 summarizes the effects of the intravenous injection of silicone (4 μL/mL) in physiologic saline on the relative lung weights and on the water, sodium, and potassium contents in rats. Those values did not change significantly after the injection of 6.25 or 12.5 mL of silicone-containing solution (4 μL/mL) per kilogram. However, injection of 18.75 mL of solution per kilogram significantly increased the relative lung weights and water and sodium contents.

Pulmonary Edema Induced by Silicone-containing Contrast Media

Table 3 shows the effect of silicone on the pulmonary edema induced with contrast medium (4 g of iodine per kilogram). The dose of the silicone-containing contrast medium (silicone concentration, 4 μL/mL) was 12.5 mL/kg; at this dose, silicone showed little influence on the parameters of pulmonary edema (Table 2). In this experiment (Table 3), each contrast medium also showed pulmonary edema to an extent similar to that observed in the earlier experiments (Table 1). Silicone-containing contrast medium significantly increased the lung weights.

Silicone-containing iohexol induced maximum edema and also caused significant changes in all other indexes.

The aggravation of contrast medium–induced pulmonary edema by silicone was also clearly observed morphologically (Fig 2). A left lung 10 minutes after the injection of silicone at a dose of 12.5 mL/kg (Fig 2c) was morphologically similar to that in the control rat (Fig 2a). A lung was slightly but apparently enlarged with the injection of iohexol at a dose of 4 g of iodine per kilogram (Fig 2b). This phenomenon became more marked after the injection of silicone-containing iohexol (Fig 2d).

TABLE 2
Silicone-induced Pulmonary Edema

Injection Volume (mL/kg)	No. of Rats	Relative Lung Weight (%)	Water Content (%)	Sodium Content (mEq/kg Tissue)	Potassium Content (mEq/kg Tissue)
Saline solution: 18.75	16	0.49 ± 0.02	81.8 ± 0.4	414.5 ± 15.8	80.7 ± 3.0
Silicone-containing saline solution					
6.25	6	0.46 ± 0.02	81.1 ± 0.6	391.2 ± 12.0	78.6 ± 1.2
12.5	6	0.48 ± 0.02	80.9 ± 0.2	381.3 ± 3.8	79.2 ± 3.2
18.75	6	0.59 ± 0.02*	83.3 ± 0.4*	510.8 ± 27.0*	71.0 ± 3.0

Note.—Each measurement was obtained at 10 minutes after injection. Each value represents the mean ± SEM.
* $P < .05$ in a comparison with the group with pure saline solution injected.

TABLE 3
Effect of Silicone Contamination on the Pulmonary Edema Induced with Contrast Media

Substance Injected	Relative Lung Weight (%)	Water Content (%)	Sodium Content (mEq/kg Tissue)	Potassium Content (mEq/kg Tissue)
Ioxaglate	0.64 ± 0.07	84.4 ± 0.8	661.9 ± 63.3	64.3 ± 6.2
Silicone-containing ioxaglate	0.82 ± 0.06*	85.1 ± 0.6	693.1 ± 47.0	63.2 ± 2.8
Ioversol	0.55 ± 0.04	81.8 ± 0.6	447.6 ± 48.3	60.1 ± 7.1
Silicone-containing ioversol	0.70 ± 0.06*	84.5 ± 0.8*	532.1 ± 56.9	60.1 ± 3.9
Iohexol	0.54 ± 0.03	81.9 ± 0.9	434.9 ± 33.9	63.4 ± 2.4
Silicone-containing iohexol	0.90 ± 0.05*	85.9 ± 0.3*	667.4 ± 39.2*	54.8 ± 1.9*

Note.—The dose of all contrast media was 4 g of iodine per kilogram of body weight. The silicone concentration was 4 μL/mL. The dose of all silicone-containing contrast media was 12.5 mL/kg. Each measurement was obtained at 10 minutes after injection. Each value represents the mean ± SEM for six animals.
* $P < .05$ in a comparison with the respective pure contrast medium–injected groups.

DISCUSSION

These results clearly demonstrate that the intravenous injection of currently used contrast media produces pulmonary edema in rats and that the edema is markedly aggravated by the contamination of contrast medium with silicone. An increase in lung weight is caused mainly by the increase in extravascular lung water (9,10). Hayashi et al (11) presented histologic evidence, together with the evaluation of lung weights, that the increase in the relative lung weights closely correlates with perivascular edema. However, a change in the lung weight following an injection of contrast medium may not be distinguishable from the vascular engorgement or presence of contrast medium in the lung. Thus, we also determined the water, sodium, and potassium contents in the lung as better indications of pulmonary edema (12).

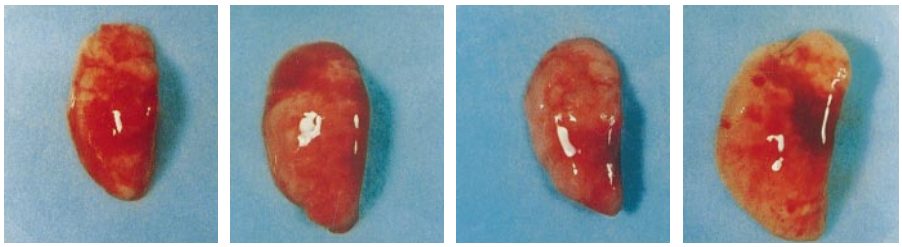
Time- and dose-dependency studies of pulmonary edema induced by contrast medium were also performed to decide the optimal time and dose for the evaluation of the effect of silicone contamination. The time course of the increase in the lung weight observed in the present study is in agreement with that reported by Mare and Violante (9). In addition, findings of the present investigation confirm that the substantial increases in lung weight are due to extravascular (interstitial or alveolar) fluid accumulation accompanied by disturbances of the ionic equilibrium, that is, sodium and water influx and potassium efflux. The water, sodium, and potassium contents are more sensitive than the lung weight in the detection of pulmonary edema induced by the ionic contrast medium ioxaglate.

Differences in the chemotoxicity and osmotoxicity of contrast media are considered to be responsible for the degree of pulmonary edema (13,14). In a Japanese prospective study of adverse reactions to intravenous contrast media (15), the incidences of severe reactions to ionic and nonionic contrast media were 0.22% and 0.04%, respectively, and the incidence of fatal reactions to ionic contrast media was 0.04%, while the incidence of fatal reactions to nonionic contrast media was 0%.

Beynon et al (16) reported that ioxaglate caused marked endothelial damage as an indication of chemotoxicity, while iohexol did not elicit substantial endothelial damage. In the present study, however, the large dose of iohexol of 6 g of iodine per kilogram produced the same degree of pulmonary edema as did ioxaglate. Therefore, it is suggested that large doses of the nonionic contrast media iohexol and ioversol can induce chemotoxic reactions. The very large doses of contrast media in the present study are well above clinically relevant doses, and results of this study are not immediately applicable to clinical conditions. However, since the larger doses of contrast media are clinically recommended for computed tomography and digital angiography (17), close attention should be paid to the risk of serious or fatal adverse reactions, including pulmonary edema.

Silicone, because of its inert biologic property (18), is supplied for manufacturing a variety of medical devices, such as intravenous tubing; pacemaker leads; joint prostheses; lens replacements; and mandibular, breast, and nasal implants. It has been reported that silicone elicits foreign body reactions such as granulomatous inflammation, fibrosis (19), and embolism (20–22).

We showed in this study that large amounts of silicone (18.75 mL/kg) produce pulmonary edema. Silicone alone, at the doses of 6.25–12.5 mL/kg set according to the injection volume, did not produce pulmonary edema. It is interesting that the addition of an ineffective dose (12.5 mL/kg) of silicone to all of the contrast media significantly aggravated the pulmonary edema induced by the contrast media alone. Significant changes in all indexes after the injection of silicone-containing iohexol were observed, even though the particle amounts were below the acceptable limit. These changes were also strongly supported by the morphologic findings of the swollen lungs.



a. **b.** **c.** **d.**

Figure 2. Photographs of left lungs demonstrate morphology at 10 minutes after the injection of **(a)** physiologic saline at 18.75 mL/kg, **(b)** iohexol at 4 g of iodine per kilogram, **(c)** silicone at 12.5 mL/kg, and **(d)** iohexol at 4 g of iodine per kilogram with silicone-containing solution at 12.5 mL/kg. The preparation of silicone-containing solutions is described in the text. The lung in **a** was morphologically similar to a nontreated lung. The lungs in **b** and **c** were slightly enlarged after the injection of **(b)** iohexol and **(c)** silicone. The aggravation of iohexol-induced pulmonary edema by silicone was clearly shown by the morphologic finding of a swollen lung in **d**.

Ioxaglate did not show a notable effect of silicone contamination in a comparison with the nonionic contrast media. This might be because the inherent chemotoxicity of ionic contrast media is enough to induce the pulmonary changes (23).

The observed aggravation of pulmonary edema following the injection of silicone-containing contrast medium may be due to several mechanisms. In general, the foreign particles in the parenteral solution cause the vascular endothelial injury (24) and lodge in the vessels and disturb the pulmonary circulation, which leads to elevated pulmonary venous pressure (20–22,25). However, silicone has no effect on the capillary filtration coefficient, which is used as an index of alterations in microvascular permeability in the lungs (26).

Immiscible particles are derived from the interaction of the contrast medium with silicone. These particles may produce pulmonary edema due to vascular endothelial injury and/or disturbance of pulmonary circulation. Consequently, the aggravating effect of silicone on the pulmonary edema induced with contrast medium may result from the synergistic effect of the contrast medium and silicone. For further exploration of the actual mechanism of the pulmonary edema formation, histologic examinations are necessary.

Findings of our previous study (27) showed that an electronic counting method based on light extinction could be used to determine the number of silicone droplets present as particles in a contrast medium. The USP acceptable limit is based on counts of particles with a diameter of 10 µm or larger and of 25 µm or larger. Since pulmonary capillaries vary between 8 and 12 µm, any particles larger than 12 µm are likely to be trapped and retained in the pulmonary vascular bed (28). Findings of an animal experiment (29) in which microspheres have been intravenously injected indicate that small particles enter the system circulation and end up in organs. However, the clinical importance of silicone droplets that are too small to be retained in the lungs is uncertain. Abnormal liver function in some patients undergoing hemodialysis was speculated to be a result of silicone particles in the liver derived from siliconized peristaltic blood pumps (30). However, the count of particles in the circulating solution was not determined in that study.

Practical application: Silicone contamination aggravated pulmonary edema that occurred after the intravenous injection of contrast medium in rats. Although in this experiment it was not possible to match conditions such as the dose and rate of injection of contrast medium, the results obtained raise the possibility that the incidence of pulmonary edema could be increased in patients who are examined by using contrast medium contaminated with silicone.

References

1. Borchert SJ, Abe A, Aldrich DS, et al. Particulate matter in parenteral products: a review. J Parenter Sci Technol 1986; 40:212–224.
2. David JH, Cetin E, Lary AR, et al. Particle-induced coronary vasoconstriction during cardioplegic infusion. J Thorac Cardiovasc Surg 1985; 89:428–438.
3. Brekkan A, Lexow PE, Woxholt G. Glass fragments and other particles contaminating contrast media. Acta Radiol Diagn 1975; 16:600–608.
4. Garvan JM, Gunner BW. Particulate contamination of intravenous fluid. Br J Clin Pract 1971; 25:119–121.
5. Winding O. Foreign bodies in contrast media for angiography. Am J Hosp Pharm 1977; 34:705–708.
6. Markus K, Loh A, Israel D. Microscopic air embolism during cerebral angiography and strategies for its avoidance. Lancet 1993; 341:784–787.
7. Sendo T, Otsubo K, Hisazumi A, et al. Particle contamination in contrast media induced by disposable syringes. J Pharm Sci 1995; 84:1490–1491.
8. Lalli AF. Contrast media reactions: data analysis and hypothesis. Radiology 1980; 134:1–12.
9. Mare K, Violante M. Pulmonary edema induced by high intravenous doses of diatrizoate in the rat. Acta Radiol Diagn 1983; 24:419–424.
10. Mare K, Violante M, Fischer HW. Pulmonary edema following high intravenous doses of ionic contrast media: effect of the anion composition and concentration. Invest Radiol 1984; 19:188–191.
11. Hayashi H, Kumazaki T, Asano G. Pulmonary edema induced by intravenous administration of contrast media: experimental study in rats. Radiat Med 1994; 12:47–52.
12. Pearce M, Yamashita J, Beazell B. Measurement of pulmonary edema. Circ Res 1965; 16:482–485.
13. Wood BP, Smith WL. Pulmonary edema in infants following injection of contrast media for urography. Radiology 1981; 130: 377–379.
14. Borish L, Martloff SM, Findlay SR. Radiographic contrast media-induced noncardiogenic pulmonary edema: case report and review of the literature. J Allergy Clin Immunol 1984; 74:104–107.
15. Yamaguchi K, Katayama H, Takashima T, et al. Prediction of severe adverse reactions to ionic and nonionic contrast media in Japan: evaluation of pretesting—a report from the Japanese Committee on the Safety of Contrast Media. Radiology 1991; 178:363–367.
16. Beynon HLC, Walport MJ, Dawson P. Vascular endothelial injury by intravascular contrast agents. Invest Radiol 1994; 29(suppl):195–197.
17. Shehadi W, Toniolo G. Adverse reactions to contrast media. Radiology 1980; 137: 299–302.
18. Branley S. Chemistry and properties of medical grade silicones. J Macromol Sci Chem A 1970; 4:529–544.
19. Busch H. Silicone toxicology. Arthritis Rheum 1994; 24:11–17.
20. Williams MA, Stephens JF, Brunckhorst LF. Identification of silicone in retinal vessels by electron probe x-ray microanalysis. J Histochem Cytochem 1975; 24:149–151.
21. Orenstein JM, Aaron B, Buchholz B, et al. Microemboli observed in deaths following cardiopulmonary bypass surgery. Hum Pathol 1982; 13:1082–1090.
22. Rodriguez MA, Martinez MC, Lopez-Artiguez M, et al. Lung embolism with liquid silicone. J Forensic Sci 1989; 34:504–510.
23. Dawson P. Chemotoxicity of contrast media and clinical adverse effects: a review. Invest Radiol 1985; 20:52–59.
24. Dorris GG, Bivins BA, Rapp RP, et al. Inflammatory potential of foreign particu-

lates in parenteral drugs. Anesth Analg 1977; 56:422–428.
25. Morisette M, Gagnon R, Lamoureux J, et al. Effect of angiographic contrast media on colloid oncotic pressure. Am Heart J 1980; 100:319–324.
26. Townsley MI, Taylor GE, Korthuis RJ, et al. Promethazine or DPPD pretreatment attenuates oleic acid-induced injury in isolated canine lungs. J Appl Physiol 1985; 59:39–46.
27. Sendo T, Hirakawa M, Yaginuma M, et al. Quality evaluation of radiographic contrast media in large volume prefilled syringes and vials. Acad Radiol 1998; 5:444–447.
28. Kanke M, Simmons GH, Weiss DL, et al. Clearance of ^{141}Ce-labeled microspheres from blood and distribution in specific organs following intravenous and intraarterial administration in beagle dogs. J Pharm Sci 1980; 69:755–762.
29. Lyon TC, Beasley JD, Cutright DE. Particle contamination of dextran for intravenous use: an in vitro and in vivo study. Military Med 1974; 141:466–469.
30. Hunt J, Farthing MJG, Baker LRI. Silicone in the liver: possible late effects. Gut 1989; 30:239–242.