

Allergy to Formaldehyde and Ethylene-Oxide

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INTRODUCTION

Formaldehyde (F) and ethylene oxide (ETO) are volatile small chemicals widely used in the industry, and are used as sterilizing agents in medicine. At high concentrations, they are toxic and can induce irritative side effects, but they act as reactive haptens and can become allergenic leading mostly either to IgE-mediated reactions or contact dermatitis.

These compounds are used to sterilize medical materials, particularly kidney dialyzers. Owing to the repetitive exposure of patients to these chemicals, most IgE-mediated reactions occur in hemodialysis patients (1).

FORMALDEHYDE

Formaldehyde (Fig. 1) is a sterilizing agent having adverse health effects recently reviewed by the Council on Scientific Affairs of the American Medical Association (2). Formaldehyde acts on humans principally as an irritant to the eyes and respiratory system, impairing the mucociliary clearance, and can produce allergic reactions in the form of contact dermatitis when aqueous F comes into contact with the skin or IgE-mediated hypersensitivity. Finally,

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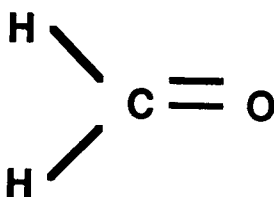


Fig. 1. Chemical formula of formaldehyde.

F was shown to be carcinogenic in rodents, and certain regulatory agencies regard it as a possible carcinogen in humans.

Use

Preservatives

Formaldehyde is an ubiquitous and potent sensitizer, both in industry and in medicine because of antimicrobial properties. Shampoos, soaps, lotions, water-soluble creams, powders, and dentifrices may contain F as a preservative. Cream constituents, such as polyethylene glycols (carbowaxes, macrogols), BNPD (2-bromo-2-nitropropane-1,3-diol), Germall (imidazolidinyl urea), Quaternium-15, *N*-(3-chloroallyl)-hexamini-um chloride, and trioxymethylene (paraformaldehyde), can form F as well as hexaethylenetriamine used in antiperspirants (3,4).

Sterilizing Agents

Formaldehyde is a sterilizing gas used in medicine. It can cause occupational asthma in nurses (5), doctors (6), anatomists, dentists (7), pathologists (8), pharmacists, or morticians.

Formaldehyde was one of the earliest substances used for sterilizing kidney dialyzer membranes, especially for the reuse dialyzers. It has been associated with significant savings in the total cost of providing hemodialysis services and may increase the biocompatibility of devices. Formaldehyde is still the primary disinfectant of reused hollow-fiber dialyzers and with stringent recommendations, F concentrations in the final rinse solution range from 2–10 ppm. Adverse effects are generally related to the residual levels and the cumulative dose of F received by the patients (9).

Biologic Preparations

Formaldehyde has limited use in biologic preparations, but it is used to prepare the Merck Sharp and Dohme hepatitis B vaccine (10) and F-polymerized allergoids. However, in these preparations, F is present in extremely low quantities that cannot sensitize an individual and that are acceptable by Pharmacopeas.

Construction Materials

Formaldehyde can be released from urea-formaldehyde foam insulation (UFFI) and a number of formaldehyde-resin containing products, such as particleboard, plywood, and permanent press fabrics used in the construction of wood products, adhesives, and carpeting. It is also widely used in the production of textiles, paint, glues, and plastics. It was found to induce irritative side effects at the workplace (11) and the home (12,13).

MECHANISMS OF REACTIONS

Although F is a very simple chemical, allergy to F is well documented. However, except for contact dermatitis, these reactions are far less frequent than irritative ones.

Allergy

Type I Hypersensitivity Reactions

Apparent type I hypersensitivity reactions have been observed in patients after instillation of a root canal paste containing F-releasing compounds (7). However, these reactions were not confirmed by the titration of F-specific IgE. Immediate-type allergic reactions were demonstrated in patients undergoing long-term hemodialysis (14–16) by means of RAST. One of these patients presented anaphylactic shock occurring 26 h after skin application of an F patch test (14). The specificity of IgE antibodies is not completely elucidated. As for other reactive haptens, F was coupled to the solid phase by means of human serum albumin (HSA), and it appears that the specificity of the antibodies was directed toward the F–HSA complex (14,15). However, since F can degrade proteins (17), it

is not known whether the antibodies are not specific to the degraded epitopes on the proteins that are not regarded anymore as self by the immune system. Thus, F might induce a pseudo-autoimmune disease. Formaldehyde-specific IgE is more prevalent in patients heavily exposed to F by iv route, such as dialysis patients, than in subjects exposed by inhaled route. The clinical relevance of F-HSA-IgE antibodies is not completely established, since it was correlated with anaphylactic symptoms in some (14,16), but not all studies (15).

Type III Hypersensitivity Reactions

Formaldehyde-HSA-specific IgG has been found in many individuals exposed to F by inhaled or parenteral routes (18-20). They are most prevalent in subjects who received F by iv route, but the clinical relevance of these antibodies remains to be determined since they are not related to symptoms.

Type IV Hypersensitivity Reactions

Allergic contact dermatitis to F has been documented for many years (3,4), and was found to be the result of both F and F-releasing agents. The diagnosis of contact dermatitis to F is based on patch tests, but care must be taken not to use high concentrations because it has irritant properties and many false-positive tests have been observed (21).

Autoimmune Disease

Formaldehyde reacts strongly with self proteins, and it has been suggested that it might be responsible for a pseudo-autoimmune disease. One study showed that these antibodies could be specifically directed to the N blood group antigen of F-treated red blood cells, but the clinical relevance of these antibodies has never been established (22,23).

Nonspecific Mechanisms

Formaldehyde causes an irritation of the eyes and mucous membranes of the respiratory tract in a dose-dependent manner. It induces also a dose-dependent decrease in mucociliary activity (24). In patients undergoing long-term hemodialysis, pseudo-anaphylac-

tic reactions have been observed (25). Formaldehyde is extremely irritating on the skin, and irritant reactions may be observed and differentiated from allergic contact dermatitis.

Anatomical Sites of Reactions

Dermatologic Symptoms

Formaldehyde was found to cause *contact dermatitis* in nurses and doctors handling devices sterilized with F. It also sensitizes many subjects in whom F or F-releasing compounds, such as creams, dentifrices, or antiperspirants, are applied onto their skin (3,26,27). Local exacerbation of contact hand eczema occurred in response to F contained in hepatitis vaccine B (10). Formaldehyde is among the top ten sensitizers and is incorporated in patch test standard series recommended by the International Contact Dermatitis Research Group, but the exact prevalence of F contact sensitivity remains to be determined because most studies used irritant patch test concentrations.

Diffuse maculopapular rash has been described in patients with a positive patch test to F after exposure to this chemical (4). *Erythema multiforme* with liver involvement has been described in two patients after occupational exposure to F (28). *Facial and intraoral anioedema* have also been observed, especially in dentistry (7,29), but these symptoms may likely be related to anaphylaxis.

Ocular and Respiratory Symptoms

The acute inhalation of F primarily affects the eyes and airways causing irritative nasal, ocular, and bronchial symptoms. Although some of these reactions are IgE-mediated (30), most of them are toxic and are therefore dose-dependent (2,20,31). Usually, F does not elicit severe reactions, since its unpleasant and irritating odor prevents one from breathing high concentrations. Short-term airborne exposure levels of approx 30 ppm cause irritation of the eyes and the mucous membranes of the respiratory tract, whereas long-term exposure may lead to similar effects at lower concentrations (1–6 ppm) (32,33). At concentrations typical of industrial, commercial, or domestic exposure (3 ppm), F challenge was shown to induce unpleasant ocular and nasal reactions, but there was

no increase in nasal airways resistance and no altered pulmonary function; also, bronchial reactivity to methacholine was unchanged (34). Asthmatic subjects are hyperreactive to F, and relatively low concentrations have provoked or exacerbated asthma (35), but such reactions are inconstantly reproduced during inhalation challenge tests (36–38). It was recently observed that the inhalation of F increased the nonspecific bronchial reactivity to methacholine in asthmatics (36). The long-term intermittent exposure of F does not appear to induce a higher incidence of chronic bronchitis or pulmonary function deficit (39,40).

Anaphylactic Shock

Anaphylactic shock is a very rare event in patients exposed to F. It was described only in hemodialysis patients receiving iv F (14–16) (Fig. 2) and in those who had an instillation of a root canal paste containing F-releasing compounds (7,29). The demonstration of an IgE-mediated immune mechanism was not always confirmed. In a study performed in 110 hemodialysis patients receiving F-sterilized reused dialyzers, Bousquet et al. (16) observed six patients presenting with severe anaphylactic shock and F–HSA–IgE antibodies (Fig. 3). Symptoms subsided when F-sterilized dialyzers were replaced by ETO-sterilized devices. Most patients with F-anaphylaxis had increased numbers of peripheral blood eosinophils. In two other studies, the relationship between a positive F–HSA–RAST and symptoms was not so clear (15,41).

Pseudo-Allergic Reactions

Pseudo-allergic reactions to F have only been described in patients undergoing long-term hemodialysis (25). Ten patients who reported symptoms (pruritus, eye irritation, and/or minor anaphylactic shock) during dialysis were studied. None of them had a positive F–HSA–RAST, but five had a positive skin prick test. During six consecutive double-blind placebo-controlled challenges with dialyzers sterilized with F or ETO, five patients presented the previously reported symptoms when dialysis was done with F-sterilized devices. When F-sterilized dialyzers were replaced by ETO-sterilized devices, symptoms disappeared.

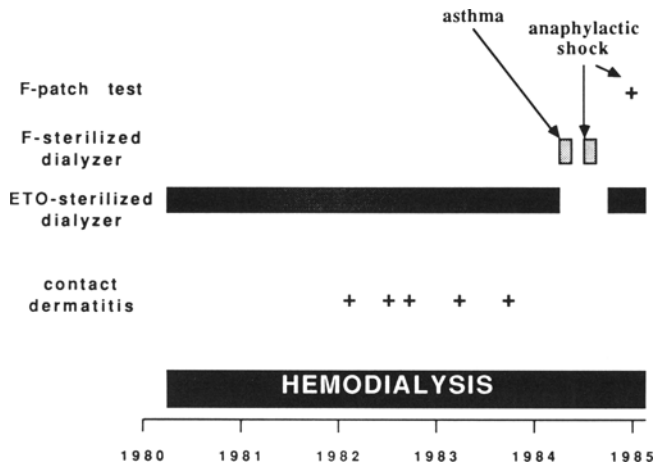


Fig. 2. Anaphylactic shock to formaldehyde in a patient sensitized by cutaneous contact with formaldehyde who developed asthma on first exposure to formaldehyde-sterilized dialyzer and two anaphylactic shocks (one after the second session of formaldehyde-sterilized dialyzer and a second after a patch test). F-HSA-IgE was positive. From Maurice et al. (14).

BRONCHOSPASM	●●●					●	
ANAPHYLAXIS		●	○○	○○○	○	●	○
PRURITUS	●●●●○○		●●●				●●
FIRST USE SYNDROME	●●●○○○ ●●●●●●						
NO SYMPTOM	●●●○○○ ●●●●●● ●●●●●● ●●●●●● ●●●●●● ●●●●●● ●●●●●● ●●●●●● ●●●●●● ●●●●●●						
FORMALDEHYDE IgE	-	+	-	-	-	-	-
FORMALDEHYDE DBIVC			+				
ETHYLENE OXIDE IgE	-	-	-	+	+	-	-
PHTHALIC ANHYDRIDE IgE	-	-	-	-	+	+	-
EFFLUENT PRICK TEST	-	-	-	-	-	-	+

Fig. 3. Incidence of allergic and pseudo-allergic symptoms in a population of patients undergoing long-term hemodialysis with ETO-sterilized dialyzers. O: atopic patient, ●: nonatopic patient, DBIVC: double-blind iv challenge. From Bousquet et al. (25,50). ETO, F, and phthalic anhydride were tested by RAST (Pharmacia Diagnostics).

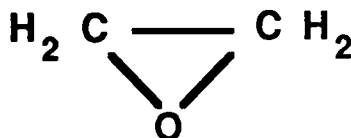


Fig. 4. Chemical formula of ethylene oxide.

ETHYLENE OXIDE

Ethylene oxide, 1,2-epoxy-ethane (Fig. 4) is a gas widely used in the industry as a starting material for various derivatives, and in the USA, ETO ranks within the list of the top 25 chemicals. Only <0.05% of the total production is consumed for medical use. Ethylene oxide is commonly used to sterilize plastic medical materials that cannot withstand heat sterilization (47). It is capable of alkylating amino, carboxyl, hydroxyl, and sulfhydryl groups and, therefore, can react with various protein moieties making it a strong sensitizing hapten (43). Ethylene oxide can be adsorbed by plastics and medical equipment, such as dialyzers, and residual ETO is released slowly so that trace amounts of ETO may persist for long periods of time in porous plastics (44).

Mechanisms of Reactions

Toxic Reactions

At high concentrations, ETO may cause chemical burns of the skin, gastrointestinal, and respiratory systems as well as various CNS effects. Safety standards require reduction of exposure to 1 ppm and medical surveillance for exposed workers, since the odor threshold is over 100 ppm (44). Long-term exposure might lead to cancer, and ETO is considered to be potentially carcinogenic. However, these toxic reactions concern mostly subjects involved in ETO production or those handling it during sterilization procedure. On the other hand, residual ETO in sterilized materials may cause hemolysis (45).

Allergic Reactions

Type I Hypersensitivity Reaction. The initial report of ETO-anaphylactic reactions in patients undergoing long-term hemodialysis (46) was confirmed by many other investigators in hemodialysis (47–51), peritoneal dialysis (51,52), plasma, and plateletpheresis (53,54).

It was shown that ETO was able to react with HSA, and IgE antibodies were directed to the complex formed by ETO and HSA (47,48). The diagnosis of ETO allergy can be done by skin tests with ETO-HSA conjugates, ETO-HSA-RAST, and/or histamine release (47,55). In hemodialysis patients, skin tests are not very sensitive owing to the decreased skin reactivity of these patients (50,51). Only a fraction of patients with ETO-HSA positive RAST experience anaphylactic reactions (Fig. 5).

Type III Hypersensitivity Reactions. IgG antibodies specific for ETO have been demonstrated (48,52). They are present often in hemodialysis patients, but are not associated with symptoms.

Type IV Hypersensitivity Reactions. Type IV reactions of the contact dermatitis type are relatively frequent. The diagnosis is based on patch tests that are difficult to perform, since ETO has irritative properties when used at high concentrations and ETO is a volatile compound, which should be mixed in petrolatum at a proper concentration (<1000 ppm) (56). Ethylene oxide can be polymerized in several compounds, including polyethylene glycol, and patch tests to this latter chemical have been found to be positive (57).

Pseudo-Allergic Reactions. Ethylene oxide gas can be extremely irritating, and irritant reactions should be differentiated from allergic contact dermatitis.

Anatomic Sites of Reaction

Dermatologic Symptoms

The most common dermatologic symptom is *contact dermatitis*, which has been reported after occupational exposure in patients manufacturing ETO (58-60) or ETO-sterilized devices, and after exposure to face masks, gauze, and prepacked nitrofurazone dressings sterilized by ETO gas (60). Many patients with ETO-HSA-IgE present a chronic and severe *pruritus*, which subsides when the sterilizing agent is replaced. Other dermatologic symptoms are those of anaphylactic shock and associate generalized urticaria and/or and angioedema.

Eye Symptoms

In industrial settings, ETO solutions act as vesicant and may cause conjunctivitis if splashed in the eye (4). Intraocular lenses

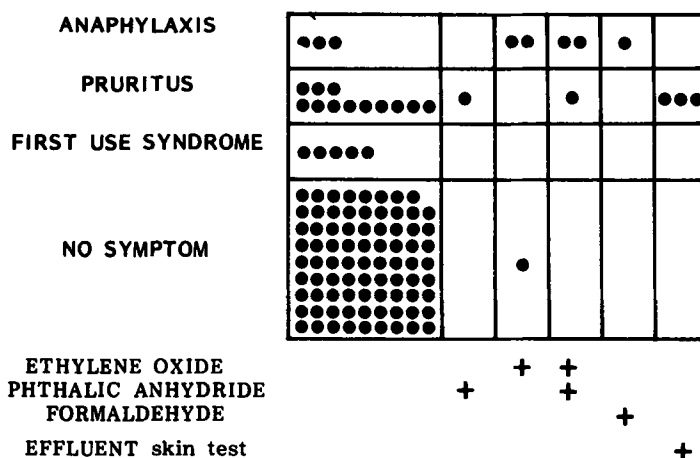


Fig. 5. Incidence of allergic and pseudo-allergic symptoms in a population of patients undergoing long-term hemodialysis with F-sterilized dialyzers. From Bousquet et al. (16). ETO, F, and phthalic anhydride were tested by RAST (Pharmacia Diagnostics).

may be sterilized with ETO, and inflammatory reactions have been observed and attributed to ETO hypersensitivity (61).

Respiratory Symptoms

Asthma and rhinitis are common features of ETO IgE-mediated allergy. They may be observed alone or in combination with other symptoms of anaphylaxis. Patients often develop respiratory symptoms after the onset of dialysis, but patients who had asthma prior to dialysis may have an aggravation of their symptoms (49).

Anaphylactic Shock

The majority of ETO IgE-mediated allergic reactions are in the form of anaphylactic shock of variable severity ranging from minor symptoms to life-threatening reactions requiring immediate therapy with adrenaline. In addition to usual anaphylactic symptoms, patients often describe a sensation of burning or heat throughout the body or at the vascular access site before systemic symptoms are manifest. Systemic anaphylaxis may be preceded for some days or weeks by local urticaria at the site of the injection. These reactions usually start within 30 min after the onset of dialysis. Eosinophilia is common among ETO-allergic patients. Many patients

developing ETO-allergic reactions are atopic (50,62). The prevalence rate of immediate systemic IgE-mediated reactions among patients undergoing long-term hemodialysis ranges from 12–42% (4). These reactions are much less frequent among peritoneal dialysis populations, repeat plasmapheresis donors (0.0002%), and plateletpheresis donors (51–54).

In hemodialysis, the majority of anaphylactic reactions are related to ETO allergy (62,63), especially when new dialyzers are used. On the other hand, F allergy is important with reused dialyzers.

Anecdotal reports have incriminated ETO in anaphylactic shocks with other devices, but confirmation is still lacking. Stanley et al. (64) reported several deaths of children who died after open-heart surgery from shock. When ETO-sterilized tubes were replaced, such deaths disappeared. Other reports of anaphylactic shocks possibly resulting from ETO hypersensitivity include exposure to ETO-sterilized catheters or ETO-sterilized suture materials (65,66).

PREVENTIVE MEASURES

In order to avoid the sensitization of patients and the occurrence of symptoms in allergic individuals, the kinetics of release of ETO from hollow-fiber dialyzers was examined (67). The deaeration and washing of dialyzers show that the ETO content of membranes decreases rapidly at first and then is followed by a second slower decrease. Even after prolonged storage time, ETO residual is still detectable. These residuals need special rinsing to be eliminated (68). After an initial rinsing with 500 mL of saline at 37°C, Ansorge et al. (68) proposed the performance of an additional rinsing with 1500 mL and the avoidance of the administration of the rinsing fluid. Using this technique, Bousquet et al. (50) showed that most of the ETO-allergic patients could tolerate dialyses without symptoms.

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REFERENCES

1. Ing, T. S., Ivanovich, P. T., and Daugirdas, J. T. (1987), *Artif. Organs* **11**, 79–81.
2. Council on Scientific Affairs (1989), Formaldehyde: Council Report. *JAMA* **261**, 1183–1187.
3. Andersen, K. E. and Maibach, H. I. (1983), De Weck, A. L. and Bundgaard, H. (eds.), *Handbook of Experimental Pharmacology*, vol. 63, *Allergic Reactions to Drugs*, Springer Verlag, Berlin, pp. 313–378.
4. Weiner, M. and Bernstein, I. L. (1989), *Clinical Pharmacology*, vol. 14.
5. Hendrick, D. J. and Lane, D. J. (1977), *Br. J. Ind. Med.* **34**, 11–18.
6. Sakula, A. (1975), *Lancet* **ii**, 816.
7. Molina, C., Passemard, N., and Godefroid, J. M. (1971), *Rev. Franç. Allergol.* **11**, 11–18.
8. Kwong, F., Kraske, G., Nelson, A. M., and Klaustermeyer, W. B. (1983), *Ann. Allergy* **50**, 326–328.
9. Hakim, R. M., Friedrich, R. A., Lowrie, E. G., Mantilla, J. M., and Lee, C. (1985), *Kidney Int.* **28**, 936–943.
10. Heyderman, E. and Brown, B. M. E. (1986), *Lancet* **522**, 523.
11. Cockcroft, D. W., Hoepfner, V. H., and Dolovich, J. (1982), *Chest* **82**, 49–53.
12. Bandana, E. J. (1980), *Immunol. Allergy Pract.* **11**, 11–23.
13. Godish, T. (1981), *J. Environ. Health* **44**, 116–121.
14. Maurice, F., Rivory, J. P., Larsson, P. H., Johansson, S. G. O., and Bousquet, J. (1986), *J. Allergy Clin. Immunol.* **77**, 594–597.
15. Patterson, R., Pateras, V., Grammer, L. C., and Harris, K. E. (1986), *Int. Archs. Allergy Appl. Immunol.* **79**, 53–59.
16. Bousquet, J., Mourad, C., Canaud, B. et al. *Ann. Allergy*, in press.
17. Horsfall, F. L., Jr. (1934), *J. Immunol.* **27**, 553–567.
18. Thrasher, J. D., Wojdani, A., Cheung, G., and Heuser, G. (1987), *Arch. Environ. Health* **42**, 347–350.
19. Broughton, A., Thrasher, D., and Gard, Z. (1988), *Am. J. Ind. Med.* **13**, 463–472.
20. Patterson, R., Dykewicz, M. S., Evans, R. III. et al. (1989), *J. Allergy Clin. Immunol.* **84**, 359–366.
21. Marcussen, P. V. (1959), *Acta Derm. Venereol. (Stockh.)* **39**, 348–359.
22. Crosson, J. T., Moulds, J., Comty, C. M., and Polesky, H. F. (1976), *Kidney Int.* **10**, 463–470.
23. Kaehny, W. D., Miller, G. E., and White, W. L. (1977), *Kidney Int.* **12**, 59–65.
24. Morgan, K. T., Patterson, D. L., and Gross, E. A. (1986), *Toxicol. Appl. Pharmacol.* **82**, 1–13.
25. Bousquet, J., Rivory, J. P., Maurice, F. et al. (1987), *Clin. Allergy* **17**, 499–507.
26. Camarasa, J. G. (1986), *Contact Derm.* **14**, 191, 192.
27. Rudner, E. J. (1981), *Contact Derm.* **3**, 208, 209.
28. Nethercott, J. R., Alberts, J., Guirguis, S. et al. (1982), *Contact Derm.* **3**, 314.
29. Forman, G. and Ord, R. A. (1986), *Br. J. Dent. J.* **160**, 348–350.
30. Wilhelmsson, B. and Holmstrom, M. (1987), *Lancet* **ii**, 164.

31. Kramps, J. A., Lucy, T. C., Peltenburg, P. R. M. et al. (1989), *Clin. Exp. Allergy* **19**, 509–514.
32. Assembly of Life Science Committee on Aldehydes, Formaldehyde and Other Aldehydes. National Research Council. Washington DC, National Academy Press, 1981.
33. Imbus, H. R. (1985), *J. Allergy Clin. Immunol.* **76**, 831–840.
34. Kulle, T. J., Sauder, L. R., Hebel, J. R. et al. (1987), *J. Air Pollt. Control Assoc.* **37**, 919–924.
35. Nordman, H., Keskinen, H., and Tuppurainen, M. (1985), *J. Allergy Clin. Immunol.* **75**, 91–99.
36. Witek, T. J., Jr., Schacter, E. N., Tosun, T. et al. (1987), *Arch. Environ. Health* **42**, 230–237.
37. Burge, P. S., Harries, M. G., Lam, W. K., O'Brien, I. M., and Patchett, P. A. (1985), *Thorax* **40**, 255–260.
38. Frigas, E., Filley, W. V., and Reed, C. E. (1984), *Mayo Clin. Proc.* **39**, 295–299.
39. Dal Corso, R. D. and Blunden, P. B. (1984), *J. Occup. Med.* **26**, 91–97.
40. Horvath, E. P., Jr., Anderson, H., Jr., Pierce, W. E. et al. (1988), *JAMA* **259**, 701–707.
41. Dolovich, J., Evans, S., Baurmeister, U., Schultze, H., Ali, M., and Shimizu, A. (1987), *Artif. Organs* **11**, 93–96.
42. Bruch, C. W. (1972), Phillips, G. B. and Miller, W. S. (eds.), *Industrial Sterilization*, Duke University Press, Durham, NC, pp. 49–62.
43. Grammer, L. C. and Patterson, R. (1987), *Artif. Organs* **11**, 97–99.
44. Glazer, Z. R. (1979), *J. Environ. Pathol. Toxicol.* **2**, 173–208.
45. O'Leary, R. K. and Guess, W. L. (1968), *J. Pharm. Sci.* **57**, 12–17.
46. Poothullil, J., Shimizu, A., Day, R. P., and Dolovich, J. (1975), *Ann. Intern. Med.* **82**, 58–60.
47. Bommer, J., Barth, H. P., Wilhems, O. H. et al. (1985), *Lancet* **ii**, 1382–1384.
48. Grammer, L. C., Shaugnessy, M. A., Paterson, B. F. et al. (1985), *J. Allergy Clin. Immunol.* **76**, 670–675.
49. Rumpf, K. W., Seubert, A., Valentin, R. et al. (1985), *Lancet* **ii**, 1385–1387.
50. Bousquet, J., Maurice, F., Rivory, J. P. et al. (1988), *J. Allergy Clin. Immunol.* **81**, 605–610.
51. Marshall, U. C., Shimizu, A., Srnith, E. K. M. et al. (1984), *Clin. Nephrol.* **21**, 346–349.
52. Patterson, R., Lerner, C., Roberts, M. et al. (1986), *Am. J. Kidney Dis.* **8**, 64–66.
53. Leitman, S. F., Boltansky, H., Alter, H. J. et al. (1986), *N. Engl. J. Med.* **315**, 1192–1196.
54. Dolovich, J., Sagona, M., Pearson, F. et al. (1987), *Transfusion* **27**, 90–93.
55. Pearson, F., Bruszer, G., Lee, W. et al. (1987), *Artif. Organs* **11**, 100–103.
56. Shupack, J. L., Andersen, S. R., and Romano, J. S. (1981), *J. Lab. Clin. Med.* **98**, 723–728.
57. Broonk, W. J. and Van Ketel, W. G. (1981), *Clin. Exp. Dermatol.* **6**, 385–390.
58. Hanifin, J. M. (1971), *JAMA* **217**, 213.
59. Taylor, J. S. (1977), *Cutis* **19**, 189–192.

60. Fisher, A. A. (1984), *Cutis* **34**, 20–24.
61. Stark, W. J. and Rosembaum, P. (1980), *Ophthalmology* **87**, 385–390.
62. Villarroel, F. and Clarkowski, A. A. (1985), *J. Artif. Organs* **9**, 231–238.
63. Nicholls, A. (1986), *Br. Med. J.* **292**, 1221, 1222.
64. Stanley, P., Bertranou, E., Forest, F., and Langevin, L. (1971), *J. Thorac. Cardiovasc. Surg.* **61**, 309–314.
65. Lebrech, D., Masquet, C., and Rueff, B. (1977), *N. Presse Méd.* **33**, 2991.
66. Bommer, J. and Titz, E. (1987), *Artif. Organs* **11**, 111–117.
67. Henne, W., Dietrich, W., Pelger, M., and Von Sengbusch, G. (1987), *Artif. Organs* **8**, 306–309.
68. Ansorge, W., Pelger, M., Dietrich, W., and Baurmeister, U. (1987), *Artif. Organs* **11**, 118–122.