Causes of Damage to Tissues by Polymers and Elastomers Used in the Fabrication of Tracheal Devices

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Prolonged exposure of body tissues to tracheal devices has demonstrated that some devices injure tissues. Techniques for safety-testing of polymers (plastic) and elastomers (rubber) by implantation in rabbit muscle and by cell culture are described. Use of these tests should prevent distribution of toxic devices. Products safety-tested by the manufacturers are marked "IT" or "Z-79." Sterilization of a tracheal device may change it from nontoxic to toxic. The compositions of polymeric and elastomeric devices and problems of sterilization are described.

CANNULATION of the trachea via tracheostomy or by the nasal or oral route is not a new operation. The Philosophical Transactions of the Royal Society, 1730,[1] contained Dr. Martin's account of the use of a "common *cannula* for dropsy" as a tracheostomy tube. The patient, a young man, had upper airway obstruction. The cannula which served as an airway for four days, was removed when the cause of the obstruction (probably inflammation and edema) had disappeared. Kite[2] was awarded the Silver Medal of the Royal Humane Society in 1788 for his "Essay on Reanimation." An illustration of a curved metal tube "to pass beyond the glottis" accompanies the text. Kite acknowledged that he did not originate the use of such a device.

T. Spencer Wells provided instructions for nasotracheal intubation in 1841.[3] In 1880, Macewen[4] published his observations on the use of a flexible orotracheal tube in four cases. The tubes were retained by two of the patients ". . . *in situ* for thirty-six hours . . . ." Noel Gillespie's case report,[5] published in this Journal, cited the observations of Macewen. Gillespie's patient remained intubated for 51 hours. Bernard Briggs' patient was intubated for 42 days,[6] inaugurating the use of prolonged endotracheal intubation, a development which has created new demands on those who fabricate, clean, and sterilize endotracheal devices.

Nilsson's 1951 thesis[7] presented a critical examination of the virtues and complications of prolonged tracheal intubation of adult patients recovering from drug overdoses. Nine years later, Colgan *et al.*[8] maintained an oral endotracheal tube in place for four days (except for a two-hour trial without the tube on the beginning of the third day). Their patient was a 2,480-g male infant who had respiratory distress syndrome. The tracheal tube was used to administer IPPV, and the infant survived. Brandstater[9] recommended prolonged endotracheal intubation as an alternative to tracheostomy in infants. During the early 1960's, following a lecture tour by Brandstater,[9a] our Australian colleagues[10-15] tried prolonged endotracheal intubation and reported its virtues and hazards.

Lindholm[16] has described the results of a prospective study of prolonged endotracheal intubation at Uppsala University Hospital in an excellent review which has a worthy bibliography. A review edited by Stetson[17] contains information about tracheal devices as well as discussion of tracheostomy and prolonged endotracheal intubation.

The shapes of tracheal devices and degrees

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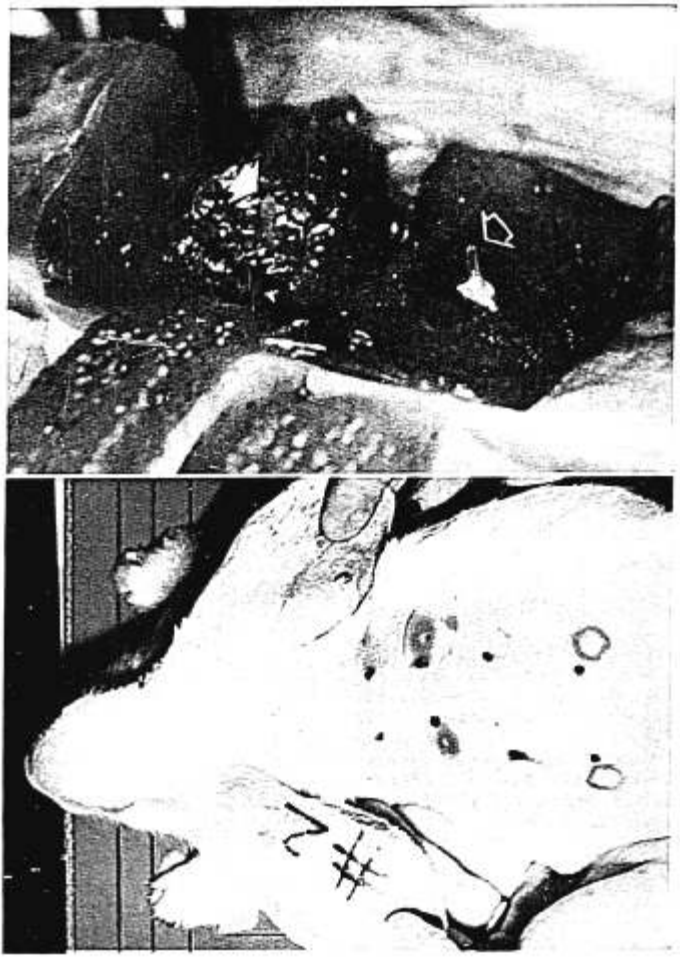


FIG. 1 (top). The rabbit-muscle-implantation test. A sliver of a polymeric endotracheal tube and a sliver of a known nontoxic polymer were implanted in the paravertebral muscles of a New Zealand rabbit. The sliver of endotracheal tube (in this case, a clear polymer) is indicated by an arrow silhouette. It is surrounded by an area of necrosis and fibrosis, indicating a leachable toxic substance in the formulation. The sliver of blue-white nontoxic polymer is indicated by a white arrow. The rabbit was sacrificed seven days after the slivers were implanted. The photograph was taken when the muscles were sectioned. The color of a polymer is not related to toxicity (see text). Not all "toxic" reactions are apparent to the unaided eye. Microscopic examination of the area of implantation is done by a pathologist after fixation and staining of the tissues.

of inflation of tracheal cuffs are not discussed in this paper. Recommendations regarding shapes of tracheal devices are contained in the publications of Dwyer *et al.*,[18] Lindholm,[19] Aberdeen,[20] and Kerr *et al.*[21] Too large an endotracheal tube can injure tracheal mucosa.[22] Ischemia, especially at the cricoid ring, can occur in infants if the tube is too large.[23, 24] The pressure of a tensely inflated cuff can also cause mucosal ischemia.

The need for the present review was suggested by "Endotracheal Tube Warning!" published in the *Newsletter* of the American Society of Anesthesiologists,[25] an editorial in the Journal of the American Medical Association,[26] and a leading article in The British Medical Journal.[27] The review consists of four sections. The first reviews safety-testing of polymeric and elastomeric tracheal devices. In this paper, "polymer" refers to man-made molecules and may be read as "plastic." "Elastomer" refers to naturally-occurring molecules and may be read as "rubber." The second World War and the Japanese occupation of southeast Asia necessitated the development of molecules with properties similar to those of elastomers. These synthetic "rubbers" are defined in the section on elastomers. The second and third sections of the review deal with polymers and elastomers, respectively. The fourth reviews problems of cleaning and sterilization, with emphasis on ethylene oxide sterilization. The discussion at the conclusion of the paper contains the authors' recommendations.

Safety-testing of Polymeric and Elastomeric Tracheal Devices

Tracheal devices (oral tubes, nasal tubes, and tracheostomy tubes) are used in immediate contact with body tissues and are bathed by body fluids as well as by irrigating and mucolytic fluids (and vapors) introduced through them. Plastic (polymeric) and rubber (elastomeric) devices contain additives to give specific properties to the tubes. Certain additives, if released from the devices, will elicit biological responses when they come in contact with tissues.

Tracheal devices fabricated from polymers and elastomers may act or react in the following ways:

Leaching. One or more ingredients migrate from the device into fluids and tissues.

Sorption (adsorption and absorption). Constituents of the body, gases or vapors passing through the tube, or STERILIZING FLUIDS OR GASES remain in the device.

Chemical reactivity. A constituent of the body, gas vapor, or STERILIZING MATERIAL reacts by covalent bonding with the polymer or elastomer or one of the additive materials.

Permeation. Gases, vapors, or sterilizing gases or vapors permeate the device. The material permeating the device, if not compatible with the polymer or elastomer, may cause degradation of the polymer or elastomer.

Alterations in the physical properties of the device. Depending upon one or more of the above, or resulting from "environmental effects" such as the heat of autoclaving, the device may undergo sufficient change or degradation to prevent its functioning as intended. Bosomworth and Hamelberg[28] have studied the effects of sterilization techniques on the physical properties of endotracheal tubes and cuffs.

Tracheal devices, in the same conditions as when used, should be safety-tested. For this reason, we strongly favor use of sterile, one-use devices. Such a unit should be sold in a protective package and guaranteed to be sterile, nonpyrogenic, and compatible with long contact with tissues. If sterilization or

FIG. 2 (bottom). Trypan blue visualization of rabbit intracutaneous irritation. Black spots are markers for injection area. *Key:* Nape injection sites were saline solution negative controls. The next two were extracts from the toxic endotracheal tube. The next two were extracts from a nontoxic endotracheal tube. The rear two were 20 per cent ethanol positive controls. The method is so sensitive that a needle track at the third injection site (right side) may be seen.

Expenses for inclusion of this color plate have been met by equal grants from: The Foregger Company, Inc., Ohio Medical Products, Portex Division of Smiths Industries, Inc., and Sherwood Medical Industries, Inc.

other preparation is done in the hospital, sterility, pyrogenicity, and tissue-implantation testing should be performed according to a predetermined schedule to assure patient safety. Tissue-implantation testing can be contracted to a laboratory that routinely performs these tests. Cell-culture techniques are more sensitive than muscle implantation and can be substituted for implantation testing. It might also be of value to test devices after clinical use. Some anesthetic vapors may permeate, be sorbed by, or react with some devices.

Safety testing can be divided into biological tests and physical-chemical tests. The following outline is offered as a guide.

Biological Tests

Direct Tests of the Device

1) Sterility and pyrogen testing.

2) Acute intramuscular tissue toxicity. Slivers 1 mm wide and 1 cm long are cut from the device. A sliver is inserted into a 15-gauge needle and implanted in the paravertebral muscle of an anesthetized, cleanly shaven New Zealand rabbit. Toxic and nontoxic control slivers are implanted at other dermatomes, as controls. A week later the rabbit is sacrificed. The muscle is removed *en bloc* and the tissue divided so the incision opens the muscle near the midpoint of the implanted sliver. The implantation site is examined with a hand lens for evidence of tissue reaction. Figure 1 shows the results of such testing. There is some variation in the duration of implantation, depending upon the laboratory. Some laboratories sacrifice the rabbit at 72 hours, believing that it might adjust to a minor irritation in seven days, but that irritation will produce a response evident on microscopic examination at 72 hours. Seven-day implantation yields more conspicuous changes with a very toxic implant, and allows time for a reaction if there is any degradation or transformation of the device while in contact with tissues. Obviously, microscopic examination of the tissues by a pathologist is essential for a complete evaluation.

3) Cell-culture testing. Cell-culture testing [29, 30] is faster than muscle implantation (24 hours rather than seven days) and more sensitive. Unfortunately, the technique is more demanding, and few laboratories are equipped to perform the test. Mouse fibroblasts (strain L-929) and ten-day chick embryo cells are allowed to grow into a monolayer in separate Petri dishes. The growth medium is removed and replaced with a thin layer of nutrient agar. Cultures are stained with a vital dye (neutral red) and samples of the device to be tested and toxic and nontoxic control samples are implanted on the surface of the agar. The cultures are incubated at 95 F (35 C) for 24 hours. They are then examined for evidence of toxicity. If the material tested is toxic, there is a clear, colorless zone of dead cells surrounding the sample. Nontoxic samples do not affect the cell culture, and the culture adjacent to the sample is a uniform pink color (fig. 3).

4) Long-term implantation in several species of mammals at several sites to detect latent toxicity or carcinogenic activity.

Tests of Solvent Systems

Solvents employed are physiologic saline solution, 95 per cent ethyl alcohol, and cottonseed, or sesame oil. Weighed samples of the device are autoclaved for an hour with the saline solvent and the oil solvent systems. Because the ethanol system cannot be autoclaved, extraction with gentle heat is employed. The eluate is separated out. If the material being tested is destroyed by autoclave treatment, the plastic-solvent system is stored for a week at 50 C. The alcohol solvent is evaporated to remove most of the alcohol and reconstituted with physiologic saline solution or the residue is suspended in a vehicle suitable for injection. The eluates of saline

solution and oil are used as obtained. In all tests, samples of the solvents are also tested as controls.

1) Cell-culture testing as described in 3, above.
2) Intradermal tests in rabbits [(intravenous trypan blue is often employed to aid in estimations of response (fig. 2)].
3) Acute toxicity tests. Five mice each receive either the control or 1 ml of the saline eluate or the reconstituted alcohol eluate by intravenous injection. The mice are then observed for 168 hours. Similar groups of mice receive the same injections by the intraperitoneal route and are observed for 168 hours.
4) Rats or rabbits are prepared so that blood pressure and respiratory rate can be recorded. After control observations they are injected with the saline or reconstituted eluate (both tested). Any changes are noted.
5) Tests of hemolysis.
6) Subacute toxicity tests. Nonlethal doses of each of the eluates are administered to animals by the intraperitoneal route each day for two to six weeks. Weights are recorded daily. Peripheral blood is examined weekly. The animals are sacrificed at the end of the test and body organs, including bone marrow, are examined.
7) Antigenicity tests.

Physical-Chemical Tests

Direct Tests of the Device

1) Differential thermal analysis.
2) Analysis of attenuated total reflectance.
3) Determination of tensile strength.
4) Pyrolysis and gas chromatography.
5) Metal analysis (often includes ashing).
6) Separation of the polymer or elastomer from the other constituents and identification of the components (if possible).

Tests of Solvent Systems

Samples of the device are treated as in the biological tests of solvent systems, except that distilled water is substituted for saline solution.

1) Tests of the water eluate.
   a. *p*H determination.
   b. Determination of acid content.
   c. Identification of reducing agents.
   d. Metal analyses.
   e. Determination of chloride content.
   f. Thin-layer chromatographic analysis.
   g. Gas chromatographic analysis.
   h. Phosphorescence tests.
2) Tests of alcohol and oil elucates: thin-layer and gas chromatographic techniques are used in an attempt to separate and identify extracted constituents.

Even more sophisticated studies may be necessary. To identify the toxic substance or substances in one endotracheal tube, it was sectioned into small pieces and extracted for 24 hours in 95 per cent ethanol in a Soxhlet extractor. The ethanol was then evaporated with gentle heat and a nitrogen flush, the residue examined by thin-layer chromatography, and the additives separated by column chromatography. The column was silica gel HF-Celite 545 (50:50), and elution with benzene and ether in various ratios.

The primary plasticizer was then identified by infrared analysis. An example of a thin-layer chromatographic plate is shown in figure 4.

When purchasing tracheal devices, the anesthesiologist should examine them to make sure they are marked "I.T." or "Z-79." "I.T." stands for "implantation tested"; "Z-79" for Committee Z-79 (Anesthesia Equipment) of the U.S.A. Standards Institute. *The presence of these letters indicate that the manufacturer has tested a device from each lot manufactured either by implantation in rabbit muscle or by a cell culture technique and warrants the device to be free of any toxicity that can be shown by these tests.*

Plastics

The word "plastic" defines a property, not the content, of the material. Within each type of "plastic" there are wide variations in physical properties as well as composition. For example, polyethylene, commonly used in the fabrication of medical devices, can be low-density, medium-density, or a high-density polyethylene. The properties of polyethylene materials of the different densities differ considerably. High-density polyethylene can be used for a hip prosthesis; low- and medium-density polyethylenes cannot.

From a chemical viewpoint, most plastics are synthetic in origin; only a few are of plant origin (rubber and some high-molecular-weight gums). Plastics are synthesized from short-chain compounds known as monomers, which are composed primarily of carbon, hydrogen, and oxygen. By a series of reactions ("polymerization reactions"), the monomers are joined together to form polymers. Polymers are the basic material for fabrication of "plastics." We will use the term "polymer" to refer to man-made plastics, "elastomer" for naturally-occurring plastics.

In addition to the carbon, hydrogen, and oxygen which comprise the basic polymeric unit, occasionally other chemical moieties are attached to the long-chain compound. Primarily these are chlorides, fluorides, acetates, and a few others. An example is the polymer polyvinylchloride, made from vinyl chloride monomers polymerized together.

Neither polyethylene nor polyvinylchloride is a "pure" chemical. Chemical agents are added to the basic polymer to give the finished product desired properties not inherent in the molecule itself. For example, plasticizers may be added to control flexibility; stabilizers, to improve heat stability; antioxidants, to prevent deterioration on exposure to oxygen or ozone; pigments, for coloration. The concentrations of additives may vary from traces to about 60 per cent of the total weight. The additive materials generally are the primary sources of tissue irritation from soft, flexible, loose-fitting, endotracheal tubes. Plastics used to form tracheal tubes are polyvinylchloride nylon (un-

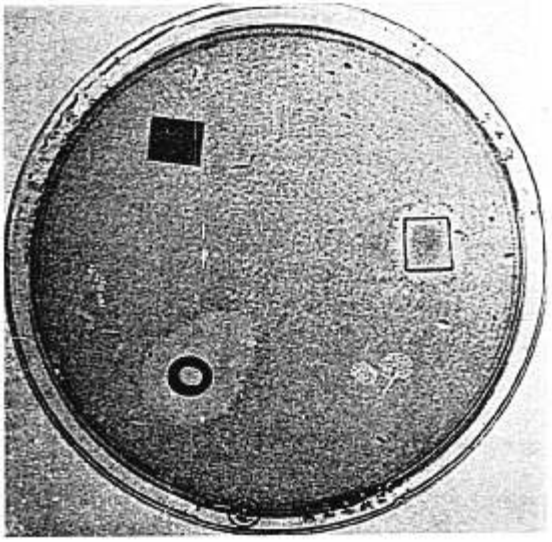


FIG. 3. A 24-hour tissue culture. The dark square is a piece of polymer of known nontoxic composition (negative control). The white square is a piece of polymer of known tissue-toxic composition (positive control). The black ring is a cross-section of a red rubber endotracheal tube. Clear areas indicate dead cells. Note relative sizes of the clear areas around the endotracheal tube tested and the known toxic polymer–control.

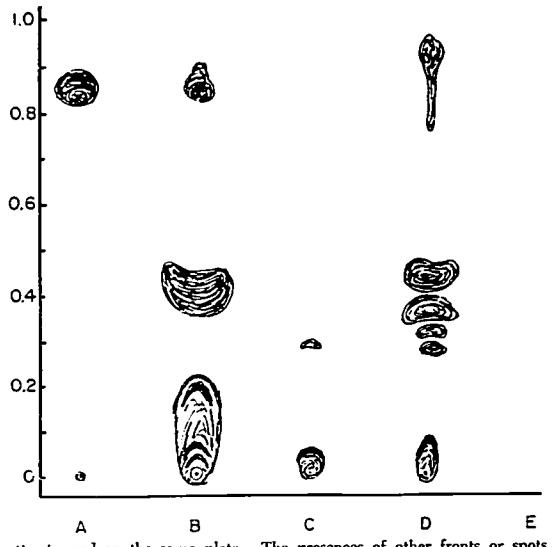


FIG. 4. Thin-layer chromatograph (TLC) plate. *A*, dibutyltin di-iso-octyl thioglycolate; *B*, x-618 endotracheal tube; *C*, dibutyltin dilaurate; *D*, x-889 endotracheal tube; *E*, dioctyl phthalate. The spots have been outlined with a marker. Tube x-618 was "toxic" on implantation in rabbit muscle and cell-culture testing. Tube x-889 was nontoxic when similarly tested. The TLC was made of extracts from the tubes, two organotin stabilizers, and DOP (a plasticizer). Tube x-618 has the same RF fronts as dibutyltin di-iso-octyl thioglycollate. Further chemical tests confirmed the presence of an organotin in x-618. No organotin was found in x-889. TLC procedures identify only the number of materials in an extract. Therefore, the individual spots found in an extract are identifiable only when a known reference material, such as the toxic organotin, is used on the same plate. The presences of other fronts or spots are not significant unless identified.

defined type), polyethylene (density not specified), and Teflon, the two most popular being polyvinylchloride and polyethylene. These polymers offer the anesthesiologist a variety of degrees of rigidity, smoothness, and flexibility; low resistances to gas flow; ease of connection to respirators; ease in cleaning; and economy. Brief definitions of the polymers and some of their specific advantages and disadvantages follow.

TEFLON

Teflon is DuPont's trade name for a fluorocarbon. As a group, plastics with fluorocarbons are noted for their resistance to chemical attack and low surface energy, which makes the surfaces slippery and nonadhesive. Teflon, when prepared for use in tracheal tubes, is generally a pure polymer, that is, the plastic is composed almost entirely of the polymer itself, with no significant amount of additive. This plastic may be sterilized by boiling, autoclaving, or soaking in antiseptic without harm to the physical properties of the tracheal tube. It is essentially nonwettable, and evokes minimay tissue reactions in patients when used in tracheostomy tubes. In our laboratory, we have never seen a toxic reaction to a fluorocarbon designed for medical application. However, Teflon endotracheal tubes are rigid and tend to irritate tissue by rubbing. Teflon is expensive and seems to offer little advantage over metallic tracheostomy tubes.

NYLON

Nylon is a generic name for a family of materials known as polyamide resins. Nylon is also a DuPont product. DuPont has defined nylon as "a generic term for any long-chained synthetic polymeric amide which has recurring amide groups as an integral part of the main chain and which is capable of being formed into a filament in which the structural elements are oriented in the direction of the axis." The chemical composition of nylon can be as varied as the ingenuity of a producer allows.

The most commonly used nylon is nylon 6-6 (hexamethylene diamine adipic acid). Most nylons are tough, resistant materials unaffected by many chemicals, solvents, and lipid materials. However, nylons are destroyed by mineral acids and are easily stained by food. Some nylons can be sterilized by autoclaving. Unfortunately, nylon is a relatively unstable polymer, degraded to some degree by moist heat, and we have found that repeated or prolonged heating will convert a nylon formerly nontoxic (to cells in culture) to one toxic to the same cells. To enhance the stability of nylon, antioxidants or other stabilizers or additives may be added to the basic resin.

Tissue reactions to nylon are both physical and chemical. Tracheal tubes made of nylon are relatively rigid and have the disadvantages of metallic tubes. In addition, the surface of nylon is not as smooth as that of Teflon or polyethylene, and friction between the tube and contacting tissues is a source of physical irritation. Chemical irritation to tissues may arise from traces of monomer or reactants left in the material.

Polyethylene

Polyethylenes belong to a class of compounds known as polyolefins, currently among the most widely used thermoplastic materials in the medical field. As a type of plastic, they are noted for their resistance to chemicals and low moisture absorption. Most devices made of polyethylene and used in or on the human body are of the low-density type. In general, as the density of polyethylene increases, hardness, heat deformation, stiffness, tensile strength, and resistance to permeability increase.

Low-density polyethylene is comparatively flexible and has good impact strength and relatively good heat resistance. It is more transparent than the high-density type, and its surface feels "waxy." Polyethylenes, in general, are resistant to acids and bases, but are attacked to some degree by oxidizing agents. Polyethylenes have good moisture resistance and permeability to oxygen and carbon dioxide; the resistance and permeability are a function of density. Volatile materials such as anesthetics penetrate the polyethylenes rapidly.

Most polyethylenes are tissue-compatible and essentially nontoxic, but we have evaluated low-density polyethylenes in which the low-molecular-weight fractions (monomers, dimers, trimers, etc.) are of such proportions that some diffuse out of the tubes and come into contact with tissues, causing localized reactions. It is relatively easy to formulate a polyethylene that has low percentages of low-molecular-weight fractions that would be essentially nontoxic.

Polyvinylchloride

Polyvinylchloride (PVC) resin in its pure state may be formed into a rigid device, a form offering no advantage over metallic tubes and, indeed, never used in making tracheal tubes. However, PVC resins can be compounded to produce various degrees of flexibility through the use of additives such as plasticizers, stabilizers colorants, lubricants, and other filler materials.

We have found that the problems with polyvinylchloride are twofold: 1) the basic resin material itself, and 2) the additives. First, vinyl chloride, the monomeric structural unit, is an unsaturated, chlorinated hydrocarbon having the structure $CH_2=CHCl$. When vinyl chloride is heated with a catalyst such as benzoyl peroxide, the double bond of the monomer opens and polymerization occurs. As the vinyl chloride polymerizes, forming the polyvinylchloride resin, it precepitates from the mixture and may be separated from the reactants in a variety of ways, a process generally called the "bulk" process. In an alternative process, the "emulsion" process, the vinyl chloride monomer is emulsified in water, using soap or some other ionic emulsifier. Polymerization occurs as described above, the emulsion is broken, and the polymer is separated out. A third method, the "suspension" method, utilizes nonionic dispersing agents to suspend the vinyl chloride in water where, with peroxides, the polymerization takes place. These descriptions of the three methods for obtaining PVC resin are included here to emphasize that all the polymerization reactions depend to a degree on formation of an insoluble polymer which is separated out by physical methods. The possibility remains that reaction materials, partially-polymerized materials, and contaminants can be trapped in the polymer

particles. On several occasions we have been able to demonstrate that the resin itself will induce necrosis in muscle; in addition, strong eosinophilic reactions have occurred when this material has been implanted in muscle tissue. Such resins also have shown toxicity to cells in culture, but after the same basic resins were washed with 95 per cent ethanol, toxic reactions could not be elicited, indicating that the contaminating material can be removed from the basic PVC resin. It is unfortunate that most of the PVC resin available for use in medical applications is a commercial grade, not a specially purified, medical grade.

The second problem, that of additives, is perhaps even more serious than the problem of the resins. Plasticizers added to polyvinylchloride resins produce plastics with various degrees of flexibility and smoothness. A variety of plasticizers (usually alcoholic esters of phthalic, adipic, sebacic and citric acids) may be used in concentrations as high as 60 per cent of the entire formulation. In addition to plasticizers, other additives may go into a PVC formulation. The exact combination of additives is largely determined by the intended use. In almost all PVC devices a second ingredient, a stabilizer, has been added. Polyvinylchloride resin is unstable; it becomes discolored, brittle, and more acidic as degradation proceeds. Stabilizers retard degradation and provide a high degree of clarity to the final device. Some stabilizers serve a dual purpose, both plasticizing and stabilizing. Most PVC endotracheal tubes found in the past to be toxic have been toxic because of the stabilizers.

Among the more desirable stabilizers for polyvinylchloride plastics are the compounds in the large group known as "organotin" compounds. Without going into detail about the many organotins used in polyvinylchloride formulations, it can be said that at the time of the toxicity warning printed in the A.S.A. Newsletter, toxic formulations were being made using toxic organotin stabilizers. The stabilizers were incorporated into polyvinylchloride in concentrations of approximately 1 per cent of the total formulations. Generally speaking, organotins migrate to the surfaces of the tubes by way of the plasticizer, which acts as the carrier (in general, the softer and more flexible a polymer, the less strongly the component parts are bound; parts are therefore more free to migrate and be leached). Organotin compounds, when used in PVC plastics, are highly necrotizing. Figure 1 shows a piece of rabbit muscle in which has been implanted a sliver of polyvinylchloride plastic containing an organotin stabilizer; an area of necrosis surrounds the implant. Since the warning issued by the A.S.A., most manufacturers have deleted organotin stabilizers from their formulations and are using relatively nontoxic calcium or zinc soaps as stabilizers. Although most manufacturers employ nontoxic stabilizers in the fabrication of tracheal devices, unfortunately we still find toxic responses following implantation of PVC slivers from endotracheal tubes and other medical devices. The physician must insist that before it be sold, a polymeric or elastomeric device be tested under conditions of use for tissue compatibility. As proof of such testing, the device should bear the letters "IT" or "Z-79."

Most plasticizers used in medical devices today are relatively nontoxic both to contiguous tissues and to distant organs (if a stabilizer enters the systemic circulation). Probably the most commonly used are dioctyl phthalate (di-2-ethylhexyl phthalate) and the esters of sebacic acid. In general, these compounds are fairly stable and do not cause toxic responses (by implantation test or cell culture testing) when included in the formulation of a PVC.

One group of plasticizer–stabilizers that has toxic potential includes the epoxidized soya oils. We have examined different lots of epoxidized soya oil from the same manufacturer which have the same identification number. Some of the liquids were crystal clear, some cloudy, some contained flaky material; still others contained insoluble residues in rather large amounts. When so little control is exerted over a compound that is to be placed in a medical device, problems arise. We have demonstrated that some epoxidized soya oils are toxic to cells in culture, to rabbits on intracutaneous injection, and to mice after intraperitoneal injection. All of these tests tend to reflect upon the irritative nature of some of these epoxidized soya oils. Therefore, it should be a matter of caution to observe tissues sur-

rounding endotracheal tubes for signs of inflammation which may not be caused by infection, but may result from materials leached from the PVC.

PVC polymeric devices are the most widely used, and offer the greatest opportunity for hazard. Only implantation or cell-culture safety-tested devices should be used for long-term tracheal, urethral, biliary, or other intubations.

Elastomeric Tracheal Devices

Caoutchouc, a milk-like fluid, is obtained by tapping certain tropical shrubs or trees. The fluid is subjected to additives and treatments, both at the plantation and by the fabricator of rubber devices. The final product is said to be made from "natural rubber," although elastomers can be formed by chemical synthesis also.

The Oxford group called attention to imperfections of tracheal tube materials a decade ago.[31, 32] Cooperation between suppliers and clinicians corrected many of these imperfections, so that they later were able to report: "We have been unable to find a patient with a tracheal stenosis who had his tracheostomy in Oxford, and who was then fitted immediately with a Radcliffe tracheostomy tube. For this reason we continue to use modern red rubber tracheostomy tubes in preference to any of the currently available plastic tubes."[33] Their excellent clinical results, in addition to offering testimonial of surgical and clinical care, reflect on the value of using nontoxic tracheal devices. We have tissue-tested several Radcliffe tracheostomy tubes: they have been nontoxic on almost all occasions employing all tests, including sensitive cell-culture techniques. We hope that the manufacturers of the Oxford tubes will test their products by implantation in rabbit muscle or cell culture techniques, marking the tubes "IT" or "Z-79" as an indication of nontoxic response.

Not all rubber tracheal tubes are nontoxic, as can be seen in figure 3. A clear zone of dead cells surrounds the section of rubber endotracheal tube laid on the agar support medium. We recently reported a toxicity evaluation of nine cuffs and seven tracheal tubes. The cuffs and tubes were made of red rubber or latex in the United States, West Germany, or the United Kingdom. Results are listed in table 1. The need for a tissue-testing program is obvious. It is also obvious that the cell-culture technique is more sensitive than implantation in rabbit muscle. Because cell culture is more rapid, manufacturers could use it for screening.

Most caoutchouc is obtained from the tree, *Hevea braziliensis*. The natural latex, collected in cups, is subject to contamination with indigenous particulate matter such as insects, bark, dust, etc. Much of this matter is removed by straining before the latex is coagulated with acetic or formic acid, sodium silicofluoride, or ammonia. The coagulated latex is washed, then dried in pans or by smoking over a fire. The next step in processing is vulcanization, with sulfur and benzoylperoxide the most commonly used vulcanizing agents. Other vulcanizing agents are tetramethylthiuram, disulfide, selenium, tellurium, aromatic compounds, dioximes, diisocyanates, and dinitroso compounds. Some vulcanizing materials are trapped in free form in the final rubber product, but the vulcanizing material constitutes only a small percentage of the finished rubber device.

During vulcanization, accelerators increase the speed of the reaction and allow it to be carried out at a lower temperature. Organic accelerators such as the thiurams, dithiocarbamates, diphenylguanidine, or the mercaptobenzothiazoles may be employed; besides the accelerators, activators of the accelerators are used. The most frequently used activator is magnesium oxide; others being lead monoxide, zinc oxide, and red and white lead. ACCELERATORS OFTEN CAN BE LEACHED FROM RUBBER DEVICES.

Fillers are added to produce desired physical properties such as hardness or resistance to chemicals or heat. The most common fillers are asbestos powder, clays, talc, carbon black, zinc oxide, magnesium carbonate, and silicon dioxide. Although the fillers are not chemical toxicants, they can be sources of physical irritation.

Because oxygen has a degrading effect on rubber, antioxidants such as phenyl-beta-naphthylamine are added to the mix. The antioxidant is often found in solution after exposure of the device to a solvent system. To

TABLE 1. Toxicity Evaluation of Rubber Endotracheal Tubes

Code	Type of Rubber	Part Used	Mfg. Source	Biological Evaluation Results				
				Untreated Rubber		Autoclaved Saline Extracts		
				Cell Culture	Implant	Cell Culture	Intradermal*	Mouse IP
X-610	Latex	Cuff	U.S.	Positive	Negative	Positive	2+	N.D.†
X-611	Latex	Cuff	U.S.	Positive	Negative	Positive	2+	N. D.
X-612	Latex	Cuff	England	Positive	Positive	Positive	3+	N.D.
X-613	Red rubber	Tube	W. Germany	Positive	Negative	Negative	0	Normal
X-614a	Latex	Cuff	U.S.	Positive	Positive	N.D.†	1+	N.D.
X-614b	Red rubber	Tube	U.S.	Positive	Positive	Positive	0	Normal
X-615a	Red rubber	Cuff	England	Negative	Negative	N.D.	1+	N.D.
X-615b	Red rubber	Tube	England	Negative	Negative	Negative	0	Normal
X-616a	Latex	Cuff	Unknown	Positive	Negative	Positive	1+	N.D.
X-616b	Red rubber	Tube	W. Germany	Positive	Negative	Negative	0	Normal
X-617a	Latex	Cuff	W. Germany	Positive	Negative	N.D.	0	N.D.
X-617b	Red rubber	Tube	W. Germany	Positive	Positive	Negative	0	Normal
X-635a	Latex	Cuff	England	Negative	Negative	Negative	0	N.D.
X-635b	Latex	Tube	England	Positive	Positive	Negative	2+	Normal
X-636a	Red rubber	Cuff	England	Positive	Negative	Positive	0	Normal
X-636b	Red rubber	Tube	England	Positive	Negative	Positive	0	Normal

* 1+ = perceptible erythema; 2+ = readily visible erythema; 3+ = very red, often swollen.
† N.D. = not done, insufficient material.
Reproduced with permission from: Guess W L, Stetson J B: Tissue toxicity from rubber endotracheal tubes. Int. Anesth Clin (in press).

soften the rubber devices, and to facilitate processing, plasticizers in various combinations are often added. Plasticizers are vegetable and mineral oils, fatty acids, waxes, tars, and/or resins. As can be expected, most plasticizers are lipid-soluble, and they may be extractable by fatty tissue touching the devices.

While some elastomeric devices are allowed to remain their natural color, others are colored. Titanium dioxide is currently the best white pigment in common use. Other coloring agents used include pure iron oxides, zinc oxide, zinc sulfide, and some of the stronger organic dyes.

These same additives used in fabricating devices from natural elastomers are used in devices made from synthetic rubber. Synthetic rubbers are produced by chemically rearranging the molecular structures of certain unsaturated hydrocarbons and their derivatives. The monomers formed are then polymerized. The five types of synthetic rubber are:

1) Buna-S, a copolymer of butadiene and styrene.
2) Buna-N, a copolymer of butadiene and acrylonitrile.
3) "Butyl," a copolymer of isobutylene and isoprene.
4) "Neoprene," a polymer of chloroprene.
5) "Thiopol," a group of polysulfide rubbers.

Natural rubber, a polymer of isoprene (C_5H_8), has a molecular weight of about 300,000. The nature of the end groups of the polymer is not known, but polymerization is not complete. There are usually small amounts of nonpolymerized monomers and some partially polymerized short chains left in the mix. IF THERE IS AN EXCESS OF MONOMERS AND SHORT CHAINS, THE FINISHED DEVICE MAY PRODUCE TISSUE TOXICITY. Little and Parkhouse[32] warned of this danger.

Fabrication of safe elastomeric devices for medical use is a complex process. The manufacturer must be diligent, knowledgeable in the field of elastomers, and of unquestioned integrity. If the company that sells the devices is not their manufacturer, a hiatus in communication or responsibility may develop. For this reason, the purchaser and the seller of the device must insist that it (or the pack-

age) is marked "IT" or "Z-79" as assurance that the manufacturer has safety-tested a device from each lot fabricated.

Silicone Rubber

The past few years have seen the introduction of an exciting new material for medical application. Silastic is the trade name of a group of silicone rubbers known as polysiloxanes. "Medical grade silicone" describes a specific silicone rubber manufactured under rigidly controlled conditions and reserved for pharmaceutical and medical applications. Braley[64] has outlined the chemistry of the silicones. Smelted silicone is treated with methyl chloride to produce dimethyl dichlorosilane:

$$Si + 2\ CH_3Cl \rightarrow Cl{-}Si(CH_3)_2{-}Cl$$

This in turn is treated with water, which causes the probable formation of dimethylsilanediol:

$$Cl{-}Si(CH_3)_2{-}Cl + 2\ HOH \rightarrow OH{-}Si(CH_3)_2{-}OH + 2\ HCl$$

This compound is extremely unstable and immediately condenses with other molecules to form long chains of silicon–oxygen atoms with two methyl groups on each silicon:

$$-Si(CH_3)_2-O-Si(CH_3)_2-O-\left[Si(CH_3)_2-O\right]_x-Si(CH_3)_2-O-$$

The condensate is a clear, water-like fluid. The length of the polymer chain determines the viscosity of the fluid. Medical-grade silicone rubber is made from a high-viscosity polydimethyl siloxane to which has been added pure silica (for strengthening purposes) and a vulcanizing agent. The vulcanizing agent most commonly used is dichlorobenzoyl peroxide. The vulcanizing process changes the liquid silicone rubber into a solid form. After vulcanization, the product is cured. Curing "drives" off the vulcanizing agent, leaving a pure medical-grade silicone rubber with silica added to strengthen the basic product.

The attributes of silicones are:

1) They can be autoclaved.
2) They do not deteriorate with time.
3) Tissues do not stick to them, and fluids do not "wet" silicone tubes.
4) When properly prepared, medical-grade silicone rubbers cause little tissue reaction.
5) The body does not attack them to any great extent and alter their properties.

Silicone rubbers have been used in the fabrication of prosthetic devices for draining cerebrospinal fluid, to replace vitreous fluid in the eye, as materials for rebuilding ears, noses, cheeks, etc., and for prosthetic heart valves. In thousands of medical applications there have been few reports of adverse reactions to MEDICAL-GRADE SILICONE RUBBERS.

We have tested only one silicone rubber device, an Aberdeen type infant treacheostomy tube sent us by colleagues at the Buffalo Children's Hospital. It was not toxic when tested by implantation in rabbit paravertebral muscle.

Sterilization of Tracheal Devices

> It is now generally accepted that any article which has to pass beyond the glottis ought to be treated as a sterile article, . . .
> *P. J. Helliwell*[34]

Helliwell's recent statement was a furtherance of the 1962 pronouncement of Stark, Green, and Pask.[35] In 1962, Stark and Pask advocated a central sterile supply of rubber endotracheal tubes,[36] the tubes to be discarded after six autoclave treatments. Their report attests to the deleterious effects of heat upon rubber. In 1964, Stratford, Clark, and Dixon[37] found that a ten-minute soaking in 5 per cent chlorhexidine followed by two minutes of boiling would disinfect anesthesia apparatus. The procedure was time-consuming because of the two separate steps.

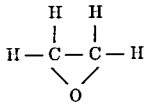
Cold sterilizing procedures may not be effective owing to the possibility of contamination of the disinfectant solution.[38] Some phenol-containing solutions may cause loss of pigment[39] in the skin of persons using them. A depigmentation injury from use of an anesthesia face mask soaked in a germicide[40] has been reported. Use of benzalkonium chloride to sterilize a plastic suction catheter has caused contact dermatitis of the trachea.[41]

"Problems in Sterilization of Medical Equipment" have been summarized in an exhibit prepared by Rendell-Baker, Roberts and Watson.[42]

Attempts were made to find simpler means of sterilizing anesthetic equipment. In 1958, Hallowell *et al.* suggested ethylene oxide (ETO) for sterilization of ampules and in 1962, Snow[43] advocated ETO for sterilization of anesthesia equipment. Jenkins and Edgar thought ETO would be good for sterilizing small items such as the Ruben valve.[45] Five years ago, the Guy's Hospital group published their program for "The Cleaning, Disinfecting and Sterilising of Anaesthetic Equipment,"[46] strongly favoring the use of an ETO–carbon dioxide mix. Because ETO is a flammable vapor, it is generally mixed with carbon dioxide or a Freon gas as a damping and diluting agent. Because it is diluted, it is important to know the concentration of the gas that reaches the object to be sterilized. The Guy's group pointed out that the color change seen on the 3M Indox gas sterilizer tape they use indicates only exposure to ETO, not the concentration of the vapor. For information about the concentration of ETO surrounding the device to be sterilized, an object such as the Royce sachet should be placed inside the "pack." Bishop, Robertson, and Williams[47] have provided a description of the Royce sachet.

For ETO sterilization to be effective, there must be humidification. The Whiston group added liquid water to the ETO delivery pipes of their assembly for sterilizing ventilators.[48] After the development of systems for sterilizing ventilators with ETO, it became necessary to learn how to clear ETO from the machines,[49] and anesthesiologists are still investigating ETO dissipation.[50] The published "Safe Standard of Aeration for Ethylene Oxide Sterilized Supplies"[51] cannot be accepted as final or safe. The suggestions of White[52] can be followed, but it must be noted that a "properly designed aerator" is not defined in item 2 ("A properly designed aerator heated to 50 C may be used to reduce safe aeration time to 12–18 hours"). Injury to patients from ETO-sterilized anesthesia equipment has been reported from Cleveland[53] and New York.[54] ETO can also harm anesthesia equipment[28]

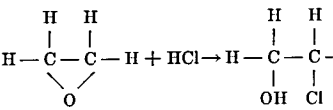
Because of its importance as a possible cause of morbidity following use of a tracheal device, some discussion of ETO is warranted. ETO is a cyclic ether:



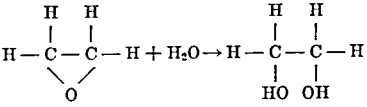
It freezes at −111.3 C, boils at 10.7 C, is completely soluble in water at 10 C; autoignition temperature is 1,060 F, and it is flammable in air at 3.0–100 per cent by volume. Gaseous ethylene oxide sterilization is an extremely complex procedure.[55–58]

If ETO in proper concentration (with proper humidity) reaches the object to be sterilized, it acts by alkylation, *i.e.*, replacement of an available hydrogen ion with a hydroxyethyl group. This causes inactivation of many sulfhydryl, amino, or carboxyl groups of protein molecules. Human protein molecules are just as vulnerable to this action as bacterial (and viral) molecules. Porous objects made of polymers and elastomers sorb ETO. The problems of clearing ETO from medical devices are as complex as the problems of ETO sterilization, dissipation varying with the object sterilized, heat, air changes, over-wrap material, etc. Toxic effects of long exposure to small amounts of ETO left as residuals are not known. Gingrich's work is a step in this direction; we hope he will continue his trials.[59]

In addition to residual ETO, residual ETO reaction products may remain in the object sterilized. Free chloride ions (said to be especially prevalent in gamma-sterilized polyvinylchloride devices) can combine with ETO to form 2-chloroethanol:



2-Chloroethanol is toxic to tissues.[60–62] ETO may react with water to form ethylene glycol:



Any acidic material, even water with a high carbon dioxide content, will act as a catalyst for this reaction. The Cleveland Clinic group felt that the cause of tissue damage in their patients was a film of detergent and ethylene glycol left on the surfaces of endotracheal tubes.

As previously noted, if in-hospital sterilization of tracheal devices is done, there must be a program of sterility, pyrogenicity, and tissue safety-testing. O'Leary and Guess[63] demonstrated that residual ETO in certain medical-grade plastics can cause extensive hemolysis and death of cells in tissue-culture plates.

If residual ETO is measured, measurement must be done directly by chromatographic or similar techniques, not indirectly by weight of the device. When residual ETO in devices is measured, a scale can be constructed correlating residual ETO with toxic responses elicited in the rabbit (muscle implantation) or cell death using culture techniques. The scale can be used to facilitate in-hospital safety programs or manufacturer on-line quality control.

Discussion and Recommendations

Following the excellent example set by Bernard Briggs, one of us (J. B. S.) became an enthusiastic supporter of prolonged tracheal intubation.[65-67] About five years ago, unexplained glottic inflammation appeared in some infants following prolonged tracheal intubation. Ethylene oxide-sterilized tubes were discarded and only new gamma-irradiated tubes were used, but the inflammation continued to appear. Perusal of publications devoted to polymer technology revealed a woeful ignorance of the structures of materials used by anesthesiologists. It was apparent that many of the purveyors of polymeric and elastomeric devices were not much better informed. Many of the articles which one of us (J. B. S.) found concerning safety-testing of polymers were written by the other (W. L. G.). Contact with him was established and a fruitful collaboration has continued since. We have called attention to tissue reactions to organotin-stabilized polyvinylchloride catheters.[68, 69] Physicians engaged in perfusion experiments became aware of the deleterious effects of using organotin-stabilized PVC tubing.[70-72] Investigations of elastomeric devices followed (see table 1 and fig. 3). It was assumed that all anesthesiologists were aware of the dangers of ethylene oxide sterilization. This assumption was probably in error, and we and other anesthesiologists[42, 59, 73-75] are correcting the deficiency.

Prolonged tracheal intubation can be of real therapeutic value. Therefore, safe tracheal devices, sterile and nonpyrogenic, must be available. If sterilization is done in the hospital, those performing the task must be aware that polyvinylchloride will sorb ETO and benzalkonium chloride or other "cold" sterilants in large amounts. Leaching times may be prolonged, with the danger of new molecule formation. "One-use" sterile devices eliminate this problem. The devices must be chemically and physically inert to all body tissues; there must be no "toxic" responses to them; cells must not die, there must be no migration of eosinophils to tracheal mucosa or other manifestations of allergic response; no unusual mitosis or other indication of carcinogenic potential should occur. The devices, directly or indirectly, must not cause hemolysis of erythrocytes or changes in blood clotting. There must be no change in the tissue compatibility of the device during prolonged contact with the trachea. The device must not change physically (except that thermolability that will allow the device to mold to body contour at body temperature is desirable) or degrade. The danger of degradation of tracheal devices may not be as great as the danger of degradation of devices used in other parts of the body, *i.e.*, biliary drains, gastric tubes removing acid stomach contents, Miller-Abbot tubes removing alkaline intestinal secretions, urinary bladder catheters, and so on. Table 2 lists degradation products that can form when different polymers are exposed to heat and/or acids, bases, oxidizing agents, enzymes, or microorganisms.

In addition to degradation owing to physical, chemical, or biologic causes, elastomers and polymers may undergo random degradation. The polymer chain may rupture or scission may occur at random points; the resulting fragments will be larger than the original monomeric units from which the polymer was formed. Polymers may also "unzip," releasing monomeric units from the polymer

chain; it is thought that unzipping reactions may be catalyzed by some degradation products.

The possibility of degradation emphasizes the necessity for adequate safety-testing. Perhaps we should test devices after use, especially if anesthetic gases or vapors have been employed, to determine if degradation has occurred. It may seem a remote possibility, but perhaps under certain conditions a fluorinated hydrocarbon could react with a tracheal device to produce an elutable substance that could cause reticuloendothelial, renal, or hepatic injury.

The symbols "IT" and "Z-79" have been deliberately reiterated in this paper, reminiscent of the repetition of "one sterilizer control" in an excellent textbook about regional block.[76] The reason for the repetition in both instances is to emphasize the importance of a visible safety indicator. The letters "IT" are an abbreviation for "implantation test," in particular, the test for plastic containers described on page 905 of the U. S. Pharmacopeia XVII. "Z-79" refers to Committee Z-79 of the U.S.A. Standards Institute, a group which has not formally outlined a safety-testing program; however, after our original report[68] was published a subcommittee was formed to investigate problems of plastic tracheal tubes. If the manufacturer uses the rabbit implantation test, either as described in the USP XVII or as modified by U. S. Government purchasing requirements, or uses cell-culture safety-testing (more sensitive than the implantation test), he marks the device "Z-79" as a warranty of safety. Although there is no law or declaration concerning the use of these symbols, usage and understanding have placed an implied warranty on their presence. Journals that accept advertisements for tracheal devices should insist that the devices be safety-tested, and information about the testing program should be included in the advertisement.

With rising labor costs, it appears that safe tracheal devices can best be obtained by fabrication of large lots (to facilitate safety testing) utilizing man-made polymers, automated machine fabrication and packaging, and sterilizing techniques that leave no residuals and do not alter the devices or basic materials. Such devices can be one-use–disposable. Resistance to introduction of disposable devices can be expected. Acceptance of disposable syringes and needles and factory-made fluids was a gradual process. It is hoped that in the near future we will remember the worn, "favorite," tracheal tube in the same way that we remember the silver urethral catheter. For those who fear that we will be buried under an avalanche of plastic wastes, it should be remembered that demand creates supply. Pyrolyzers have been built to return waste plastics to use as chemical intermediates. As plastic disposables become ubiquitous in the hospital, we can anticipate a pyrolysis unit in each medical center to convert polymer wastes to raw material.[77]

TABLE 2. Degradation Products of Selected Polymers

Polymer	Degradation Products
Polypropylene	Peroxides, formaldehyde, acetaldehyde, propyl alcohol, acetone, CO, H_2
Polyethylene	Peroxides, aldehydes, alcohols, acids, esters, polyenes, CO, H_2
Polyvinylchloride plasticized with dioctyl phthalate (di-2-ethylhexyl phthalate)	HCl, benzene, 26 aliphatic and aromatic hydrocarbons, dichloroethane, toluene and other alkyl sol solvents
Polyamides (nylon)	Caprolactams, cyclopentanone, alkanes, alkenes, NH_3
Polycarbonate	Methane, CO, phenol, CO_2
Polyvinylidene fluoride	HF, peroxides, aldehydes

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Pediatrics

PHLEBITIS IN INFANTS Infusion phlebitis occurs commonly in infants and children. The high incidence of phlebitis in infants with cutdowns appears to be the result of complete blocking of small peripheral veins, which prevents the dilution and buffering of the infusate by blood. Generally, peripheral cutdowns should be used only when needle puncture is not feasible. Glucose infusion solutions may cause chemical irritation of the endothelium, which is then followed by inflammation and thrombosis. Buffering of glucose infusions with sodium bicarbonate immediately prior to administration may reduce the incidence of phlebitis. (*Faukalsrud, A. W.: Postinfusion Phlebitis in Infants and Children; How to Avoid this Complication, Clin. Pediat. 8: 135 (March) 1969.*)

ANXIETY IN CHILDREN In a study of 144 pediatric patients ranging in age from one to eight years, the presence of parents immediately prior to elective surgery had no measurable beneficial effect on the emotional state of the children prior to induction of anesthesia. Children between one and five years of age exhibited more anxiety than children between five and eight years of age. (*Lee, J. S., and Greene, N.: Parental Presence and Emotional State of Children Prior to Surgery, Clin. Pediat. 8: 126 (March) 1969.*) ABSTRACTER'S COMMENT: "Rooming in" should not be eliminated because of the evidence in this paper. The crucial question to be answered remains the effect of "rooming in" (plus all other techniques designed to alleviate anxiety) on the posthospitalization behavior of the child. Conclusions based on an evaluation of the emotional state of a child at a single point in time may be misleading.