Guess

AN-1240

Tissue Reactions to Organotin-Stabilized Polyvinyl Chloride (PVC) Catheters

Wallace L. Guess, PhD, and John B. Stetson, MD

There has been an increasing incidence of glottic inflammatory reactions. A search of the literature for a cause disclosed that leachable substances in polyvinyl chloride (PVC) could cause tissue injury. A study revealed that PVC slivers cut from some catheters intended for endotracheal use caused toxic reactions when implanted in rabbit muscle. Cell culture studies were corroborative. The toxic substance was identified as an organotin compound. The investigators concluded that plastic devices for use in human patients should not contain organotin stabilizers or any other leachable toxic agent, and that standards for plastic devices used in medical practice should be established.

Although small tubes were used for resuscitation during the 18th century, the first detailed account of the use of an endotracheal tube for maintenance of the airway was that of Macewen in 1880.[1] In his article, Macewen noted priority in placing tubes in the trachea rather than in performing tracheostomy. He wrote:

> The writer introduced cylindrical tubes by the mouth into the trachea, and retained them *in situ* for thirty-six hours, removing them when required for ablution (say every twelve hours); two such cases having been treated with perfect success.

At the end of the article, Macewen deduced, "the tubes, in these cases at least, were harmless."

There have been various attempts to use endotracheal tubes as airways at various times.[2,3] During the late 1880's many articles appeared concerning the use of endotracheal tubes and devices in patients with diphtheria. The patients who underwent plastic surgery as a result of injuries received during World War I afforded an opportunity for the placement of endotracheal and nasotracheal tubes for anesthesia and maintenance of the airway. The introduction of plastic tubes for prolonged endotracheal use dates from about 1949 when Dwyer et al[4] reported shaping tubes to avoid damaging the tracheal mucosa. They formed a mandrel of copper tubing and shaped the tube over the mandrel with boiling water. After cooling, the tube assumed the shape of the mandrel. The mandrel had a posterior curve at its lower end to form the tube so it would not press against the anterior wall of the trachea.

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Following the lead of Dwyer, Briggs[5] published his report of the use of a plastic endotracheal tube for a period of 42 days. He noted that the tube assumed anatomical shape in the body. In 1951, Urry[6] published a report dealing with this subject.

During the 1960's, there has been renewed interest in the prolonged use of endotracheal tubes.[7-13] In many cases, intubation has been by the nasotracheal route. It has proved to be especially useful in infants and children. As popularity of the technique increased, various discussions arose as to when an endotracheal tube should be employed and when tracheostomy should be performed. At the present time, consideration for prolonged therapy with tubes seems to follow these five general rules: (1) Prolonged use of tubes is employed rather than tracheostomy when "the end of the case is in view." By this rule, a patient with severe cerebral damage

From the Drug-Plastic Research and Toxicology Laboratories, College of Pharmacy, University of Texas, Austin (Dr. Guess), and the Division of Anesthesiology, Ohio State University Medical College, Columbus (Dr. Stetson).

Reprint requests to 410 W Tenth Ave, Columbus, Ohio 43210 (Dr. Stetson).

would probably undergo tracheostomy at an early date for ease of prolonged ventilation or bronchial toilet or both. On the other hand, a patient who is expected to "be on his own" within five or six days would be treated with a tube maintained in place for a prolonged period of time. Because of the high incidence of complications with tracheostomy in infants and small children, they often are treated via nasotracheal intubation rather than by tracheostomy. (2) An endotracheal tube, when used, is not a "tight fit"; the tube need only to be big enough for the patient to breathe through or breathe through and around spontaneously, or for therapy with a ventilator. If such therapy is used, a volume ventilator is employed, often with a controlled leak. (3) In infants and children, nasal intubation is almost always used for prolonged therapy; in adults the oral route must be used at times. The size of the nares in the adult does not allow the passage of as large a tube (by relative size) as it does in an infant. (4) If a patient is awake, he can eat and drink while a nasal tube is in place. (5) Adequate humidification must be used to compensate for bypassing the nose.

Although one of us (J.B.S.) had been impressed by the lack of reactions to the use of polyvinyl chloride (PVC) endotracheal and nasotracheal tubes,[14] during the past year or two he has seen an increased incidence of white plaque-like tissue reactions at the glottis. This he attributed to iatrogenic infection. During review of the literature on PVC products, the photographs seen in the article by Guess and Autian[15] were striking in that the tissue reactions shown looked like those seen in the glottic area of patients treated by prolonged therapy with tubes. A joint study seemed to be indicated. This communication is the outgrowth of collaboration of a clinician and a basic investigator. It is not meant to incriminate or endorse any particular manufacturer. All strive to have ideal products. As there can be a variation from lot to lot of PVC, it is imperative that there be tissue testing to assure that each lot is not injurious.

It is readily apparent from rabbit tissue reactions to the endotracheal tubes that some present testing programs for revealing potential toxicity may not be totally adequate. We do not imply that all, or even most complications occurring after intubation are due to tissue reactions. Rough instrumentation, tubes that are too large, infection due to unsterile equipment, rigid tubes, and even residual ethylene oxide from sterilization procedures may induce more morbidity than substances which are toxic to tissue. We do wish to focus attention on an overlooked and preventable cause of tissue damage. The testing techniques used by one of us (W.L.G.) are able to detect the toxic nature of the tubes intended for endotracheal use. A critical comparison of why one technique of evaluation failed while another succeeded reveals one simple, yet significant difference. One commercial technique dealt with a highly diluted extract from the plastic, while our technique used the plastic itself. The commercial technique is a highly desirable method of evaluation for plastics that may be used for packaging food or pharmaceutical products, but it does not adequately test for the safety of medical applications of plastic devices. Although probably not adequate for testing food or pharmaceutical-packaging plastics, our data are an indication of how our techniques revealed the toxicity (or lack of it) for products of three manufacturers or distributors of tubes intended for nasotracheal and endotracheal use.

What is surprising is that nearly five years have elapsed since the publication by Little and Parkhouse,[16] of their paper entitled "Tissue Reactions to Polymers." Although the emphasis in their paper was directed toward particle size in polymers, they noted that inflammatory reactions of tissue to chemical additives do occur. As far as is known, no action has been taken on the last sentence in their paper:

> Reactions to chemical additives are less easy to characterise [sic], and the introduction of a British Standards specification, or the equivalent, to cover polymers and plastics used medically is suggested.

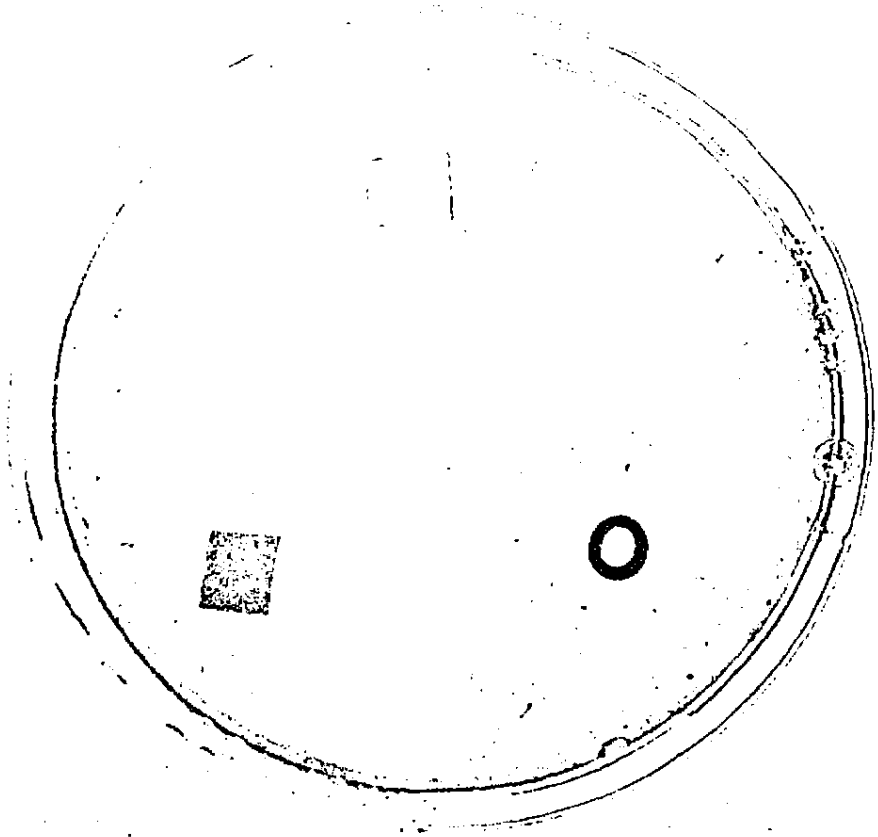
Methods and Results

Experimental Procedure.—Three groups of plastic devices used as nasotracheal, endotracheal, or tracheostomy tubes were received and labeled according to source. Sections were cut from each device from a portion that would have intimate tissue contact when the device was in location in a human patient. These sections were then evaluated for toxic potential. Control materials included a known toxic PVC formulation, a known nontoxic polyethylene formulation, and some widely used suture material, including surgical gut, plastic, and silk.

Cell Culture Evaluation.—The technique of cell culture evaluation of plastics has been reported in detail,[17] but the essentials will be given here for ease of following the test procedure.

Mouse fibroblasts (strain L-929) and ten-day chick embryo cells were allowed to grow into a monolayer in Petri dishes. The growth medium was removed and replaced with a thin layer of nutrient agar for support of the plastic test material. The cultures were stained with vital dye (neutral red) and the plastics were implanted on the surface of the agar. After 24 hours of incubation at 95 F (35 C), the plates were removed and examined for evidence of toxicity as denoted by a clear, colorless zone of dead cells around the plastic sample. The area around the periphery unaffected by the toxic material remained a uniform pink color. Figure 1 depicts a typical plate from this experiment and illustrates the toxicity of the PVC plastic tube intended for endotracheal insertion to the cells by the clear zone surrounding the plastic ring.

The results of this test on all three groups of plastics and controls are summarized in Table 1. Although reasonable doubt can be raised concerning



1. Typical toxic response of chick embryo cells to tube for endotracheal use. Note dead cells around circular tube sample. Positive control plastic (clear polyvinyl chloride square) has fewer surrounding dead cells. Negative control (darker square, polyethylene) shows normal cell growth under and around sample.

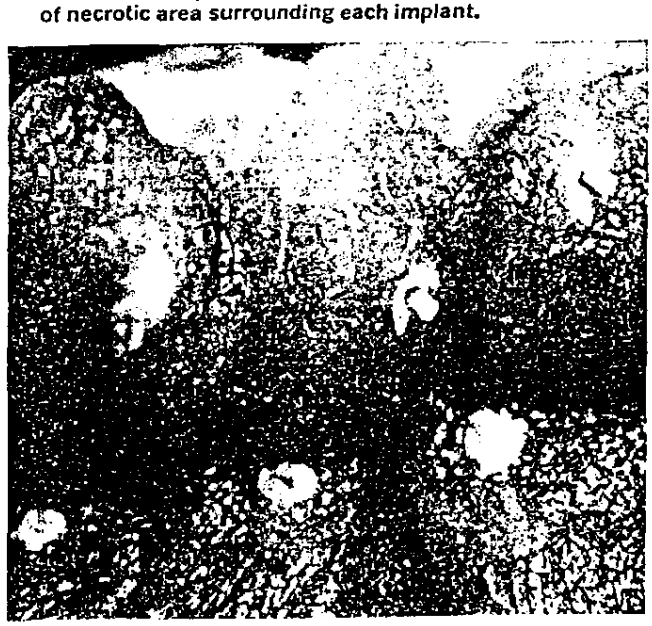
the equating of tissue cultures to laryngeal mucosa other than muscle implantation, the authors know of no other reproducible "simple" technique for testing plastic medical products.

Rabbit Muscle Implantation.—The test plastics were cut into slivers approximately 1 mm wide and 1 cm long. These were inserted into a 15-gauge needle and implanted into the paravertebral muscle of anesthetized, cleanly shaven New Zealand rabbits. The animals were killed and the implantation site was examined grossly for evidence of a tissue reaction to the plastics. Figure 2 illustrates a typical negative response to a nonplastic implant control. Figure 3 illustrates a typical toxic response characterized by a zone of necrosis surrounding the shaft of the implanted plastic. It should be emphasized that microscopic examination of all implant sites is essential to a full evaluation. Tissue reactions not grossly visible may exhibit microscopic toxic manifestations. In this study, the greatest reaction noted was one of necrosis surrounding the implant site of some of the evaluated plastics.

Analytical Examination.—In

2. Negative control plastic (polyethylene) implant in paravertebral muscle of rabbit. There is no visible damage to surrounding tissue from plastic implants.

3. Necrotic reaction surrounding sliver of one of toxic samples of tubes for endotracheal use implanted for one week into paravertebral muscle of rabbit. Note size of necrotic area surrounding each implant.



order to determine the exact nature of the toxic material in the plastic tubes evaluated by cell culture and muscle implantation, a section of one of the PVC tubes (X-427) was cut into small pieces, placed in an extractor, and extracted for 24 hours with 95% ethanol. The ethanol was removed by gentle heat under a nitrogen flush, and the residue was saved for evaluation. Thin layer chromatographic (TLC) examination of the residue revealed the presence of several additives, and these were separated by column chromatography with silica gel and infusorial earth (50:50) in the column, and eluting with benzene and ether (varying ratio). The primary plasticizer was examined by infrared analysis and was found to be identical with tributyl acetyl citrate.

Tributyl acetyl citrate is not in general use in this country even though it is generally of a fairly low order of toxicity. In addition to the plasticizer, there was found an organotin compound. This stabilizer has been identified as a mercapto ester of an organotin. In the United States, it is believed that only one organotin compound (stannous stearate, a poor stabilizer and an organic-tin compound not in general use) has been approved by the Food and Drug Administration for packaging material. For this reason, it was surprising to find organotin in these plastics used for medical applications. A series of organotin esters have been evaluated, and all in the series showed a corrosive action when in direct contact with tissue.[18]

Table 1.—Biological Evaluation of Plastic Tubes

Source	Code No.	Device and Application	Color	Plastic Type	Reaction: Cell Culture L*	Reaction: Cell Culture CE†	Reaction: Rabbit Intramuscular
A	X-423	Tube, endotracheal, nasal	Pale blue-green	PVC‡	P§	P	P
	X-424	Tube with inflatable cuff, endotracheal	Pale blue-green	PVC	P	P	P
	X-425	Tube, Jackson-Rees, endotracheal	Pale blue-green	PVC	P	P	P
	X-426	Tube, tracheostomy	Amber, clear	PVC	P	P	P
	X-427	Tube with inflatable cuff, tracheostomy	Amber, clear	PVC	P	P	P
	X-432 A	Tube, Jackson-Rees, endotracheal	Pale blue-green	PVC	P	P	P
	X-432 B	Tube with inflatable cuff, endotracheal	Pale blue-green	PVC	P	P	P
	X-432 C	Tube, endotracheal, nasal-oral	Amber, clear	PVC	N§	N	N
	X-432 D	Tube with inflatable cuff, tracheostomy	Amber, clear	PVC	P	P	P
	X-432 E	Tube, endotracheal, nasal	Pale blue-green	PVC	P	P	P
	X-432 F	Tube, tracheostomy	Pale green, clear	PVC	P	P	P
B	X-433 A	Tube with inflatable cuff, tracheostomy	Amber, clear	PVC	N	N	N
	X-433 B	Tube with inflatable cuff, tracheostomy	Amber, clear	PVC	N	N	N
	X-433 C	Airway	White, opaque	PE‡	N	N	N
	X-433 D	Tube, endotracheal	Clear	PVC	N	N	N
	X-433 E	Tube, endotracheal	Amber, opaque	PVC	P	P	P
	X-433 F	Tube, endotracheal	White	PVC	N	N	N
	X-433 G	Cole tube	Orange	PVC	P	P	P
C	X-433 H	Cole tube	White, opaque	PVC	P	P	P
	X-433 I	Tube, endotracheal	White, opaque	PVC	P	P	P
	X-433 J	Tube with inflatable cuff, endotracheal	White, opaque	PVC	P	P	P
		Controls					
	X-438	Surgical gut chromic suture			N	N	N
	X-439	Synthetic suture			N	N	N
	X-440	Surgical gut, plain 00			N	N	N
	X-441	Polyester fiber, suture			N	N	N
	X-442	Braided silk suture			N	N	N

*Mouse fibroblasts (strain L-929).
†Chick embryo.
‡PVC signifies polyvinyl chloride; PE, polyethylene.
§P signifies positive; N, negative.

Table 2.—Analysis of Endotracheal Tubes

Source	Code No.	Device and Application	Stabilizer	Primary Plasticizer	No. of Spots on TLC*
A	X-427	Tube with inflatable cuff, tracheostomy	Mercapto ester of organotin	Tributyl acetyl citrate	6
B	X-433 E	Tube, endotracheal	Organotin	Dialkyl phthalate	3
C	X-433 J	Tube, endotracheal	Organotin	Mixed phthalate and sebacate	6

*Thin layer chromatography.

Table 1 shows that tubes intended for endotracheal use from two other sources, X-433 E and X-433 I, were toxic to cells in monolayer culture and to rabbit tissue. Attempts were made to assay the nature of the toxicant in each of these tubes, and it was found that these tubes contained an organotin stabilizer. Table 2 summarizes the analytical data from representative plastic tubes which showed toxicity from each source. It was found that the organotin stabilizers and not the primary plasticizers were the primary cause of toxicity. From the number of spots observed in TLC, there were obviously other components, but the available quantity of these prevented absolute analysis. Preliminary observations indicated these spots to be epoxidized soya bean oil and perhaps a sebacate secondary plasticizer, though the presence of these could not be confirmed. It is a credible supposition that the tissue reactions observed in human patients were possibly due to the organotin stabilizer, which leached from the plastic to the tissue, where it caused a corrosive, necrotic reaction. Analytic examination revealed that organotin was not present in tubes that gave negative cell culture and negative results of rabbit muscle implantation tests.

Comment

It was found that certain devices for intubation demonstrated toxicity to cells in culture and to rabbit muscle tissue. Analysis of a single toxic de-

vice from each source showed the presence of an organotin compound and specific plasticizers of a generally nontoxic nature. Devices that were not shown to be toxic by these tests did not contain organotin. It has been demonstrated in prior research that organotin compounds are highly toxic to rabbit tissue and generally cause necrosis when they come in direct contact with such tissue.

Due to the bell-shaped curve of incidence of human reactions, it may be impossible to ever fabricate a medical device or drug that will not cause an unwanted reaction. As it is the aim of all companies manufacturing plastic devices for use in human patients to make a nontoxic product, it is suggested that controlled experiments be performed to compare the reactions of primate tracheal mucosa to those of rabbit paravertebral muscle and cell cultures. If comparison of results show statistical validity, it is suggested that organotin stabilizers (or any other leachable toxic agent) not be used in plastics that will be in prolonged contact with human body fluids. It is further suggested that standards for testing plastic devices used in medical practice should be established for the utmost safety in patients. As some plastics can migrate, adsorb, or change structure, this testing should probably be of the sterile, packaged, printed unit as it will be used in the patient.

References

1. Macewen, W.: *Introduction of Tracheal Tubes by the Mouth Instead of Performing Tracheotomy or Laryngotomy*, *Brit Med J* 2:122-124 (July 24) 1880; 2:163-165 (July 31) 1880.
2. Gillespie, N.A.: Prolonged Use of an Endotracheal Tube: Report of Case, *Anesthesiology* 3:217-218 (March) 1942.
3. Foregger, R.: Use of Endotracheal Tube in Therapy of Post-Traumatic Pulmonary Secretions, *Anesthesiology* 7:285-290 (May) 1946.
4. Dwyer, C.S.; Kronenberg, S.; and Saklad, M.: The Endotracheal Tube: A Consideration of Its Traumatic Effects With a Suggestion for the Modification Thereof, *Anesthesiology* 10: 714-728 (Nov) 1949.
5. Briggs, B.D.: Prolonged Endotracheal Intubation, *Anesthesiology* 11:129-131 (Jan) 1950.
6. Urry, A.G.: The Prolonged Use of Endotracheal Tubes: Case Reports, *Anesthesiology* 12:662-664 (Sept) 1951.
7. Davenport, H.: Management of Respiratory Obstruction Following Removal of a Tracheostomy Tube, *Canad Med Assoc J* 91:1074-1075 (Nov) 1964.
8. McDonald, I.H., and Stocks, J.G.: Prolonged Nasotracheal Intubation, *Brit J Anaesth* 37:161-173 (March) 1965.
9. Reid, D.H., and Tunstall, M.E.: Treatment of Respiratory-Distress Syndrome of Newborn With Nasotracheal Intubation and Intermittent Positive-Pressure Respiration, *Lancet* 1:1196-1197 (June 5) 1965.
10. Thomas, D.V., et al: Prolonged Respirator Use in Pulmonary Insufficiency of Newborn, *JAMA* 193:183-190 (July 19) 1965.
11. Steven, I.M., and Allen, T.H.: Prolonged Endotracheal Intubation in Infants and Children, *Brit J Anaesth* 37:566-573 (Aug) 1965.
12. Stetson, J.B.: Tracheostomy or Prolonged Intubation, *Anaesthesia* 20:508 (Oct) 1965.
13. Rees, G.J., and Owen-Thomas, J.B.: A Technique of Pulmonary Ventilation With a Nasotracheal Tube, *Brit J Anaesth* 38:901-906 (Nov) 1966.
14. Stetson, J.B.: Discussion of "Hypoventilation in Patients" by H. C. A. Lassen, *Ann NY Acad Sci* 121:897 (March 24) 1965.
15. Guess, W.L., and Autian, J.: Biological Testing of Plastics: To be Used in Medical Practice, *Amer J Hosp Pharm* 21:260-267 (June) 1964.
16. Little, K., and Parkhouse, J.: Tissue Reactions to Polymers, *Lancet* 2:857-861 (Oct 27) 1962.
17. Guess, W.L., et al: Agar Diffusion Method for Toxicity Screening of Plastics on Cultured Cell Monolayers, *J Pharm Sci* 54:1545-1547 (Oct) 1965.
18. Guess, W.L., et al: Parenteral Toxicity of a Series of Dioctyl and Dibutyl Tin Stabilizers Used in PVC Formulations, *Tech Papers Soc Plastic Engineers* 12:XXV-4, 1966.

SOVIET PHYSICIAN "PATHFINDER" IN SPACE MEDICINE.—Boris Yegorov (1937-), Soviet physician, became a "pathfinder" in space medicine in 1964 when he accompanied two cosmonauts in the first three-man flight in the spaceship *Voskhod*

The crew consisted of Col Vladimir Komarov, pilot; Konstantin Feoktistov, engineer with a master's degree in the technical sciences; and Yegorov. While the pilot and engineer were busy with their duties, the physician collected data for an array of medical, biological, and psychological studies.

The exploit was commemorated in postage stamps by the USSR and several satellite countries. In the two large Soviet stamps illustrated, Yegorov is the third figure. He also is shown alone on a 4-kopeck issue.—Mirt, J.A., "Medical Pathfinders on Postage Stamps."

Komarov (at left on large stamps) was killed April 24, 1967, on reentry after solo space flight.