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September 19, 1972

TO: Occupational Health Committee

SUBJECT: Toxicology and Carcinogenesis of Plastics

Gentlemen:

I call to your attention the review article by Fritz Bischoff, "Organic Polymer Biocompatibility and Toxicology," appearing in the September issue of Clinical Chemistry (Vol. 18, No. 9, pages 869-894, 1972). In this publication, Dr. Bischoff discusses a wide range of safety and toxicity problems associated with the use of plastics, including those that have been of some concern to our Committee, such as vinyl chloride monomer and phthalate plasticizers.

Sincerely,

Kenneth D. Johnson

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Assistant Technical Director
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KDJ:mkb
Distribution "B"
cc : Vinyl Chloride Monomer Task Group
Phthalate Esters Task Group

review

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Organic Polymer Biocompatibility and Toxicology

Fritz Bischoff

Adverse effects of organic polymers used for plasma extenders, tissue adhesives, bone cements, contraceptive devices, prostheses, artificial organs, food packaging, cooking, and laboratory ware are appraised. Parenteral polymer disintegration involves hydrolytic, redox, and degradation reactions. Accumulative toxicity of plasticizers, antioxidants, and monomers liberated from plastic containers warrants investigation. Main problems with heart-assist devices are clotting and blood destruction; with plasma extenders, thesaurismotic reactions; with acrylic bone glues, transitory hypotension; with artificial kidneys, loss of metabolic essentials; with silicone heart valves, uptake of lipids; with silicone chin implants, bone resorption; and with liquid silicone mammary amplification, lumpy breasts and mastitis. A polymer fume fever is linked with pyrolysis of polytetrafluoroethylene. Human solid-state carcinogenesis constitutes a calculated risk with polymer implants. In rodents, all solid polymers tested produced cancer; chemical carcinogenesis was induced by a polyvinyl chloride copolymer, vinyl chloride, polycaprolactam, liquid silicone, and some brands of polytetrafluoroethylene.

Additional Keyphrases *prosthetic devices, artificial organs • clotting • polymerization • silicones • in vivo polymer degradation • carcinogenesis • evidence from experiments on animals • self-curing resins • contraceptive and erectile devices • acrylic polymers • safety testing procedures • tissue reactions • drug release from silicone depots • tumor induction • food contamination • use of polymers in clinical chemistry • polyvinylpyrrolidone • methylmethacrylate • Teflon • artificial kidney • heart valves*

The Age of Synthetic Plastics

During 1966 twenty billion pounds of synthetic polymers were involved in American consumer products (*1*). By 1971 the sales of low-density polyethylene alone totalled 4.4 billion pounds (*2*). Synthetic polymers are rapidly replacing time-tested natural polymers such as glass and cotton. The impact of synthetic polymers in the human environment, as in food packaging and surgical implantation, is unique because there has been no opportunity to apply the criteria of long-standing experience through the ages. In the history of man, the effects of materials used for new purposes have been insidious at times. Powdered cinnabar served extensively as a cosmetic in ancient Rome (*3*). Lead plumbing (*4*) and the sweetening of wine with lead compounds produced widespread lead poisoning during early Roman and Renaissance times (*5*). A false sense of security may arise from the implication that adverse effects of new products are predictable with the sophisticated tools of science.

This review evaluates the limitations as well as the applications of safety testing for synthetic organic polymers that affect the human scene. It is hoped that proper allocation of research funds for the study of polymer biocompatibility will be stimulated. Perhaps too much money is spent on the artificial heart and not enough on testing the safety of polymers used in food packaging and cooking. An aging cardiac official holding research purse strings may give the artificial heart high priority even though it can only briefly prolong the life of a man with generalized vascular deterioration. To the young family, the ubiquitous long-term association with polymers and the risk of insidious cumulative toxicity are of more subjective interest. In a sense then, the synthetic polymers may have elicited more ethical and moral problems than chemical ones.

Synthetic Organic Polymer Chemistry

The present review is limited to macromolecules created in recent times by the organic chemist and loosely referred to as polymers or plastics. Polymers are formed from small molecules by two types of chemical reactions. In the condensation process, the macromolecule is produced by the elimination of reaction products. With addition polymerization, which is achieved by the liberation of free radicals, no reaction products are eliminated; the empirical formula of the monomer and the polymer derived from it are the same. The proteins and starches are macromoles formed by con-

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densation reactions. The silicas exemplify inorganic addition polymerization.

The polymer chemist is not only confronted with initiating the process of polymerization but also controlling it. Peroxides, photosensitizers, and redox catalysts are used to initiate a type of free-radical chain-reaction polymerization. Cationic or anionic polymerisation is induced by compounds with strongly acid or basic potentials. Metallo-organic compounds are thought to be in this category. The free-radical and anionic systems give polymers of high molecular weight. Recently an organolithium catalyst was shown to orient stereoisomerism (*6*). Other substances are used to stop or slow down the process of polymerization or to direct alternate paths of polymerization *viz.*, straight chain vs. side chain. In describing a commercial polymer product it is important to know whether it contains plasticizers, inhibitors, catalysts, fillers, stabilizers, antioxidants, curing agents, and (or) unreacted monomer (*7, 8*).

Condensation Polymerization

The condensation polymers of commerce include three well-represented chemical categories. In the formation of the polyamides or polyesters, a dicarboxylic acid derivative reacts with a *diamine* or with a dihydroxy compound, respectively. In the formation of the polycarbonates a carbonic acid derivative reacts with a dihydroxy compound. The dicarboxy chains linking with the two hydroxy groups may be aromatic. Polyhexamethylene adipamide, one of the nylons, is an example of a polyamide condensation polymer. Dacron is a polyethylene terephthalate, *viz.*, an aromatic polyester. The chemistry of silicone formation is described in the section on *Silicones*.

Addition Polymerization

Ethylene and its substitution products are the monomers involved in the vinyl addition polymerizations of commerce: ethylene, propylene, vinyl chloride, vinylidene chloride, vinylpyrrolidone, vinyl benzene (styrene), vinyl cyanide, methyl methacrylate, methyl α-cyanoacrylate and its homologs, tetrafluoroethylene, chlorotrifluoroethylene, etc. Because vinyl alcohol does not exist, vinyl acetate is the starting material for the preparation of polyvinyl alcohol. In these polymerisations, a free-radical catalyst usually breaks the double ethylene bond, beginning propagation. However, spontaneous free-radical generation within the monomer itself, as at high temperatures or with radiation, initiates polymerization. Polymerization is terminated when two ensuing chains, each with a *free bond*, couple or rearrange.

Instead of the breaking of a double bond, addition polymerisation may be initiated by the breaking of a ring as in the amide linkage in 2-pyrrolidone (to form nylon 4) and in caprolactam (to form nylon 6). The breaking of the double bonds between nitrogen and carbon in the diisocyanates with addition of diols forms the polyurethanes. This is another type of addition polymerization, because no reaction products are lost.

Silicones

Silicones (*9, 10*) comprise a variety of organic silicon compounds that have in common —Si—O—Si— and —Si—C— linkages. They are structurally related to the silicas and silicates, which also have the —Si—O—Si linkage, but not to the orthoesters of silicic acid, which are monomers. The silicon atoms in a silicone may have one, two, or three oxygen linkages. Those with two oxygen linkages form chains or rings. A terminal silicon atom in a straight or side chain would have one oxygen linkage.

Hydride, hydroxyl, chloro, and other groups are linked to the silicon tetrahedron to make the silicone more reactive. A fluid silicone is represented by a straight chain in which methyl groups are the organic radicals. Silicone gums have much longer chains, comprising *thousands of silicon atoms per silicone molecule*. A rubber is formed from a gum by cross-linking methyl carbons by a free-radical vulcanization process. Long-chain silicones are for the most part formed by condensation reactions that would not produce free radicals.

Because silicon, like carbon, has a valence of four it is tempting to consider the silicones with alkyl or phenyl groups as analogous to unreactive long-chain hydrocarbons. The cross-linkage of the methyl groups in the formation of a silicone rubber demonstrates the molecule is vulnerable to chemical attack. Moreover, the silicon oxygen bond is ionic as well as covalent. It is therefore of great importance to establish by safety testing in experimental animals or by clinical observation whether there is any difference in physiologic response between the long-chain saturated hydrocarbons and the silicones.

Silicic acid is recognized as a normal human dietary constituent that penetrates the intestinal wall and is rapidly excreted in the urine (*11*). Recently, essential metabolic roles have been assigned to silicic acid in vertebrates (*12*). Silicon is present in bone in concentrations exceeding that in adjacent tissues during active periosteal and endochondral calcification (*13*). Possible analogous or blocking effects for silicones should be kept in mind.

Disintegration of the Polymer in Vivo

Physical disintegration at the implant site and appearance of urinary tagged carbon compounds after implantation of tagged polymers demonstrate that polymers are not immune from attack by body defense mechanisms (*14*). In general, a polymer has a greatly decreased toxicity over that of its monomer because of lessened solubility and transportability by body fluids. Moreover, in a polymer the vulnerable groups would be less open to attack because of protection by steric configurations. The polymer engenders the foreign body reaction and becomes surrounded by the fibrous capsule, which greatly reduces exchange with body fluids.

Chemical Mechanisms

The mechanisms of the chemical disintegration of polymers are speculative. Linkages vulnerable to hydrolysis by way of hydrogen ions, hydroxyl ions, or water would include those of the polyesters and polyurethanes. Polyhexamethylene adipamide and polycaprolactam are attacked hydrolytically, but polyethylene terephthalate to a much lesser extent, possibly because it is hydrophobic. Types of polyurethane, however, can be prepared that are hydrolyzed to a lesser extent than polyethylene terephthalate (*15*). The role of the hydrolytic enzymes in these hydrolyses is unknown. When dependent on hydrolysis breakdown, the hydrophilic nature of the polymer is of great importance in determining its stability (*16*). Even though a polymer may not be vulnerable to hydrolysis, a carbon to carbon linkage can be broken by a tissue free radical or attack by oxygen. Reduction–oxidation enzyme systems are probably not involved, because they occur in the mitochondria. The breakdown of polyethylene, which would appear to consist of very stable linkages, requires the presence of free radicals in tissue metabolism (*7*). An essentially hydrocarbon structure like polyethylene is subject to oxidation when pressed into a film in the presence of air at the melting point, forming carbonyl, carboxyl, and alcohol groups (*15*).

Oxidation–reduction reactions such as alcohols and aldehydes to carboxylic acids, degradation reactions such as decarboxylation and cleavage of double bonds, and addition reactions to double bonds are possible. Thus the ester, carboxyl, and amide groups of the polyurethanes are vulnerable when other properties are conducive to chemical reaction. The faster deterioration of polyurethane foam contrasted with rigid polyurethanes implanted in rats has been noted (*16*); a semicured Silastic rubber crumbled and disintegrated under similar conditions (*17*).

Tagged Polymers

When radioactive polystyrene, polyethylene, and polymethylmethacrylate films were implanted subcutaneously into rats, urinary radioactivity, which was small, did not appear for 21, 26, and 51 weeks, respectively, and then continued until the implants were removed. Radioactive *styrene injected subcutaneously* into rats lost most of the radioactivity in 35 h by urinary excretion (*18*). This indicated breakdown of the implanted polystyrene, because unreacted monomer would have been released immediately after implantation (*14*). The compound vulnerable to hydrolysis, polymethylmethacrylate, had the longer latent period, and the vulnerability of the carbon-to-carbon linkage for the two other compounds is indicated. Radioactive [^{14}C]- and [^{3}H]polymethylmethacrylate implants (6 × 6, 6 × 12, 12 × 12, and 15 × 15 mm) were compared subcutaneously with nontagged implants in female Swiss mice. Radioactivity, which did not influence tumor incidence, was noted in the urine for the first 8 weeks after implantation, indicating the presence of trapped monomers (*19*). The in vivo degradation of [^{14}C]methyl-2-cyanoacrylate, tagged at the number three carbon, has been studied in rats. Less than 10% of the radioactivity remained at the implant site after 150 days. The tagged degradation products appeared mostly in the urine and feces. Expiration of tagged carbon dioxide, while not measured, was indicated by failure to account for all the radioactivity (*20*).

Carcinogenic Mechanisms Related to Polymers

Since solid-state carcinogenesis is associated with polymer implants, the latest research in this field will be covered in some detail. The etiology of a polymer-induced cancer may relate to a chemical carcinogen, a solid-state surface, or a combination of both. Important steps in the determination of the solid-state carcinogenic mechanism are outlined in Table 1 (*1, 11, 21, 22*).

Limitations of Safety Testing

Disenchantment with the results and procedures used in safety testing (*1, 21*) is reflected in the reports of the Food Protection Committee of the National Academy of Sciences (*22*) and the World Health Organization (*23*). The phenomenon of solid-state carcinogenesis at the rodent subcutaneous test site was a major objection.

Statistical analysis. Statistical analysis of experimental data was strongly influenced in this country and England by two articles in *Physiological Reviews* (*24, 25*). During the period 1929–1961 the Yate's correction for discontinuity was generally not applied to the chi-square four-fold table. The use of the binomial distribution without correction for small numbers was widespread. With conventional experimental numbers of 20 to 50, the incidence of an experimental observation would have to be increased by 1 or 2 to establish a confidence level of 95% when the Yate's correction is applied. The erroneous assumption of significance is mitigated when the control incidence is 0, because only half the frequency curve should be used. There is, moreover, the theoretical challenge that statistics are not applicable when the control incidence is 0. With a spontaneous fibrosarcoma incidence of 1% or less in the colony, one local fibrosarcoma in an experimental series of 30 may have significance (*26*): the local area represents a small fraction of the total area subject to spontaneous fibrosarcoma development. Since it has been repeatedly demonstrated that many carcinogenic responses are sex- and strain-linked, the practice of constituting experimental groups comprised of both sexes and (or) multiple strains introduced factors that are not amenable to statistical analysis.

The injection vehicle. Natural vegetable oils such as sesame oil are commonly used as the oily vehicle for the test compound on subcutaneous injection. Among the objections for banning the use of natural oily vehicles (*21*) are:

- the normal variation from batch to batch, particularly for minor constituents that are often chemically reactive both with the test compound and endogenous metabolites

Table 1. Historical Landmarks of Solid State Carcin genesis

Experiments and/or deductions	Investigators	Year
Production of local adenocarcinomas by glass tubes inserted in guinea pig gall bladders.	Petrov and Krotkina	1933
Production of local sarcomas by bakelite disks implanted subcutaneously into rats. Mice failed to do so.	Turner	1941
Production of local sarcomas in rats by cellulose films wrapped around kidneys or implanted subcutaneously.	Oppenheimer, Oppenheimer, and Stout	1948
Recognition of foreign body carcinogenesis without the involvement of a chemical carcinogen.	Zollinger	1952
Recognition of the importance of the physical form of the implant in the etiology of foreign body tumors.	Alexander	1954
Smooth surface carcinogenesis. Recognition that the carcinogenic process was involved in the formation of the fibrous capsule which was conditioned by the smoothness and size of the implant.	Nothdurft	1955
Production of local sarcomas through encapsulation of intraperitoneally implanted gold leaves in rats.	Hecht as cited by Nothdurft	Before 1955
Production of local sarcomas through subcutaneous or intraperitoneal implantation of platinum foils in rats.	Nothdurft	1955
Recognition of cholesterol-crystal smooth surface carcinogenesis.	Bischoff and and Bryson	1960
Production of local sarcomas by subcutaneous implantation of rigid tin foil in rats.	Oppenheimer et al.	1961
Correlation of local cancer production with physical state of foreign substance—liquid, semi-liquid, solid.	Shubik et al.	1962
Introduction of 'solid-state carcinogenesis' to replace 'smooth surface carcinogenesis' because the smooth surfaces of liquids are not locally carcinogenic.	Bischoff and Bryson	1963
Production of local subcutaneous sarcomas by implanted *n*-dotriacontane disks in rats.	Bryson and Bischoff	1966
Production of local subcutaneous sarcomas by implanted disks of cholesteryl or glyceryl palmitate in rats.	Bischoff and Bryson	1969

- solubility factors leading to solid deposits (solid-state carcinogenesis)
- toxic components producing amyloidosis in the host

Multiple injections at the subcutaneous site. Multiple subcutaneous injections of the test compound on a weekly or biweekly basis extending over many months interfere with normal homeostatic control. Cancers so produced can lead to false labeling of compounds as carcinogens. The initial local reparative process to any subcutaneous injection is innocuous enough because mature fibrous tissue results. Repeated injection at the same site prevents the normal healing process (*96*). The production of local fibrosarcomas in rats that received 74 weekly injections of carboxymethylcellulose, polyvinylpyrrolidone, and polyoxyethylene sorbitan monostearate ("Tween 60") (*87*) would not appear to have much significance. When a single subcutaneous injection of a chemical leads to a local neoplasm, then the evidence for a chemical carcinogen is more conclusive. (See section on *Plasma Extenders* and *Water-Soluble Polymers* for complications arising with high tumor incidence in controls.)

Theoretical Considerations

Polymer free radicals. Free-radical formation during polymerization can be measured by paramagnetic resonance absorption spectroscopy (*28*). At its inception a dimer has one free radical per original monomer. For macromole polymers ranging in molecular weight from thousands to millions, the ratio of free radical to number of parent monomers becomes vanishingly low. If the polymer products used in everyday life

consisted solely of stable high-molecular-weight polymers, there would be little rationale for postulating a role for free radicals in polymer toxicology. However, a wide variance in molecular weight is inherent in the overall species conglomerate of a commercial product, which may contain entrapped polymers of low molecular weight and free-radical-forming catalysts. Polymer breakdown may occur through a free-radical system involving oxygen (*29*).

The fate of the free radical in the polymer is best illustrated by the recently reviewed (*11*) elaborate studies on the silicas. In a three-dimensional formula for silica, every oxygen atom shares two silicon atoms and every silicon shares four oxygens up to the boundary, where free radicals are encountered. Most natural silica crystals and precipitated silicas contain SiOH (silanol groups) on the surface (*30*), indicating a reaction with the original free radical. Gas adsorption would be inevitable in the presence of free radicals. A precipitated silica with a three-dimensional random core has three possible degrees of —OH bonding at the surface: the silanol group, hydrogen-bonded water at the silanol groups, and an outside layer of free or adsorbed water. In this model and its extension to organic polymers, other polar substances could presumably replace water.

The potential carcinogenic hazard of the polymer free radical is based on a theorized transfer of unpaired electrons to molecules in the tissues surrounding the polymer. The free-radical chain reactions induced by radiation to produce cancer (*31*) as well as the formation of free radicals from carcinogens (*32*) are analogous processes. It is unlikely that a free radical would survive the distance between the polymer and the target cell (*33*), but it could exert its influence on cellular materials (*34*) from the area outside the cell wall.

Considerable experimental material with rodents (*35*) refutes the polymer free-radical theory of cancer. Comparative studies with true polymers containing free radicals and macromole condensation products (*35*) showed no difference in carcinogenic effects, e.g., a polyethylene polymer and cellophane, a polycondensate. On implantation of [^{14}C]-tagged polystyrene, polyethylene, and polymethylmethacrylate polymer disks in rats, small amounts of tagged degradation products were excreted in the urine (see section on *Disintegration of the Polymer in vivo*). The view that free-radical activity of the degradation product and not the original implanted polymer would initiate the carcinogenic process (*14*) was later withdrawn in favor of solid-state carcinogenesis (*36*). A more likely role of the free radical emerges when the polymer is engulfed by the phagocyte. With silica in the lung, the engulfing macrophage may die or release antigenic substances, which in turn produce antibodies in the reticuloendothelial system (*37*). For a similar defense mechanism involving the phagocyte see the section on *Polymer fume fever in humans* (p 883).

The lysosomes in polymer carcinogenesis. A unitary theory of carcinogenesis postulates that damage to the lysosome membrane by polymer hydrogen bonding, with release of a DNAase, would induce chromosomal mutation leading to cancer; radiation, the chemical carcinogens, and viruses all have been shown to affect the lysosomes (*38*). The theory does not explain nor derive support from the phenomenon of solid-state carcinogenesis.

By competing with the lysosome membrane for silicate polymers, polyvinylpyridine N-oxide (*39*) is a useful therapeutic tool in the prevention and treatment of silicate-dust pneumoconioses. With the silicas in rodents at the intrathoracic site, the reticulum cell sarcoma is the characteristic neoplastic manifestation (*30*). As indicated elsewhere in this review, water-soluble polymers are also suspect in reticulum cell sarcoma production, but the evidence is not conclusive.

Carcinogenic focus in solid-state carcinogenesis. The focus of sarcomatous proliferation has been ascribed to cells located outside the fibrous capsule that envelopes the implant (*41*), in the middle layers of the capsule (*42*), and inside the capsule at the internal surface adjacent to the implant (*36, 43*). In rabbits (*44*) and mice (*45*), there was evidence that the carcinogenic locus was not in the fibrous capsule but in cells residing on the implant. With subcutaneous implants of unplasticized vinyl chloride-acetate copolymer disks in mice of strains with and without a chromosomal marker, the preneoplastic unit first appeared in the fibrous capsule during the process of formation (*46*). At later stages clonal progeny could be found at the surface of the film and outside the fibrous capsule. These experiments seem to reconcile the apparently conflicting earlier observations in rats and mice; perhaps everybody was right. However, species difference and the use of unstable polymers leave undisclosed the focus of solid-state carcinogenesis, which cannot be established with certainty until highly unreactive substances such as gold, tin, and dotriacontane are used. Polyvinyl chloride copolymer is ill-suited for studying solid-state carcinogenesis exclusive of chemical factors. The vulnerability of the carbon-chloride bond, the breakdown of the polyethylene nucleus in vivo (*7*), the change in surface characteristics when bathed in body fluids, and the exchange of metabolites (or ingredients) (*47*) are not conducive to a study of basic mechanisms. After its sojourn in the body, chemical testing of the polyvinyl chloride copolymer was lacking. Since the process of polymerization is reversible, the carcinogenic potential of the monomer, polyvinyl chloride, is crucial in evaluation of carcinogenic studies with the polymer.

Rats exposed to a constant flow of air with 30 ml of vinyl chloride per liter for 12 months had a 65 to 70% incidence of cutaneous carcinoma in the area of the submaxillary and parotid glands, and a 20% incidence of lung carcinomas and bone osteochondromas. Such cancers did not appear in an equal number of 25 controls exposed to the same rate of air flow (*48*). Among the parenchymal lesions observed in the vinyl chloride-exposed rats were degeneration of the cerebellum, chronic hepatitis, interstitial pneumonia, and swelling of the kidney parenchyma. Tissue culture of normal and neoplastic mouse and rat tissue in media containing 0.02 to 0.1 mg of polyvinyl sulfate per ml demonstrated inhibition of growth as compared with controls (*49*). The polymer with a vinyl group cannot be thus regarded as inert. The difference in carcinogenic effect between it and glass, which is an inorganic polymer not affecting tissue culture (*50*) and having a mild local

tissue response (*11*), was demonstrated in comparative studies (*61*); the latent period for glass was much longer, 18 to 20 months for 50% tumor development (K. G. Brand, private communication). In a series of 43 mice, 25 developed tumors by the 12th month with vinyl chloride acetate copolymer implants (*55*). Glass coverslips were used as a control because their tumorigenic response was negligible during the observed time period for the copolymer (*51*).

Cyst[1] formation around implanted polymers in rodents. In tissue scaffolding experiments with glass tubes sheathed with nylon (*52*) or with indented buttons of silicone rubber or polyethylene (*53*), wells of serous fluid developed between the fibrous capsule and implant. Fluid was observed between implanted bakelite disks and the local sarcomas (*54*). In experiments with disk implants of cholesterol needles, cholesterol plates, glyceryl palmitate, cholesteryl palmitate, and dotriacontane in rats (*61*), the incidence of cyst formation to sarcoma yield was variable, with none for glyceryl palmitate (Table 2). Cyst fluid sometimes reached large volumes. The internal cyst layer was lined with sarcoma cells in some instances. This was observed also with organic polymers (*43*). The premalignant cells could originate on the implant, be released into the cyst fluid, and then invade the cyst capsule. In experiments with porous polymethylmethacrylate implants (*55*) the fibroblast in the fibrous capsule seemed to originate from mono-cytoid exudate cells in the cyst fluid. However, the saline wash of fibrous capsules seven months after polymer implantation recovered no malignant cells [Nothdurft, as quoted by Bryson and Bischoff, (*1*)].

The solid-state carcinogenic site. The preneoplastic rodent fibrous capsule around smooth surface solid implants is cell-poor and avascular, whereas the granulomatous reaction to fragmented implants is cell-rich, vascular, and noncarcinogenic. Different tissue responses may arise at different areas of the same implant. The original nodule in solid-state carcinogenesis does not overlap a sharp edge or corner of an implant (*56*), in keeping with the concept (*57*) that extended irritation has an inflammatory and anticarcinogenic influence. Evidence (*58*) that mechanical stress would induce more of an inflammatory area at the sharper curves was obtained for rats by studying the fibrous capsules surrounding subcutaneous implants of disks and spheres of rvc polymer or rubber for cell density at the surface adjacent to the implant. Forty minutes before sacrifice [^{3}H]thymidine was injected intraperitoneally and autoradiographic determinations of the capsule were made. Cell density for the spheres was random. For the disk the highest cell density occurred at the sharpest curve.

[1] Cyst formation around implants also occurs in humans. The following example was encountered in the laboratory of Dr. D. R. Dickson, Santa Barbara: After three years *in situ*, the sponge implants in the breast of a woman shrank and became hardened. Sectioned surfaces showed a peripheral yellow-white rindlike area 3 mm thick with a central spongy dull-yellow portion. On the costal surface of one there was a cyst, 13 mm in diameter and 3 mm thick, filled with clear fluid, located between the peripheral capsule and the implant.

Table 2. Cyst Formation Related to Sarcoma Yield

Implanted material	Sex of rats	Total local sarcomas	Local sarcomas with cysts
Glyceryl palmitate	♂	8	0
Dotriacontane	♀	6	4
Hydrated cholesterol plates	♂	5	1
Cholesterol needles	♂	6	1
Hydrated cholesterol plates	♀	4	3
Cholesterol palmitate	♂	8	3

Combination of chemical and solid-state carcinogenesis. The influence of gamma irradiation (100 megarads) and coating with paraffin on the production of local sarcomas by subcutaneous implantation of polycaprolactam disks in rats (*59*) indicated that a chemical reaction between the implant and surrounding tissues was one of the carcinogenic factors. Radiation of the disk was without demonstrable effect: 14/37 vs. 17/41 sarcomas for the nonirradiated series. The paraffin surface markedly decreased the sarcoma incidence, 2/41 vs. 17/41 for intact disks.

Extra- and intracarcinogens on implant carcinogenesis. In Swiss mice bearing subcutaneous implants of glass or Teflon, the injection of Trypan blue, which is a weak carcinogen and is taken up by the local fibrous capsule, and the addition of urethan (1 g liter) to the drinking water did not influence the incidence of local sarcoma development. Implantation of radioactive surfaces did not enhance carcinogenesis as compared with nonradioactive surfaces (*60*).

Disks vs. nets. In a study (*61*) in which 1140 Wistar rats of both sexes were implanted with solid disks of polyamide, polyester, polyethylene, and polypropylene, or with nets of the polyester, the results confirmed earlier work (*53, 62*) that the tumor incidence depends on the surface and size and is diminished when a foreign body giant-cell reaction persists (*57*). Knitted polyester nets (2 × 2 cm) made from Td 40 polyester yarn, when placed subcutaneously or over the liver intraperitoneally in male and female rats, elicited no local tumors during a 24-month period (*63*).

Local circulatory disturbances. Solid-state sarcomas are related to local circulatory disturbances that develop in the fibrous capsule around the implant after the latent period. Increased capillary formation, thrombosis, venous distortion and capillary distortion (*64*) and compression (*65*) have been described.

Cationic and anionic polymers. An attempt to correlate toxicologic including carcinogenic activity with physicochemical properties was made by comparing the long-term tissue reaction in rats to implants of a cationic polymer (polyvinylbenzyltrimethylammonium) chloride, an anionic polymer (sodium polystyrene sulfonate), and a complex coprecipitated by both of them (*66*). Because of the small number of rats, 16 in each series, conclusions are limited: The cationic film was significantly more tumorigenic than the neutral film. The weakness of the study lies in the sterilization of the films with formaldehyde. Since the polymers are 50% water, it is likely that, even after washing, some

formaldehyde remained in the polymer after implantation and would react with cells adjacent to the polymer. The importance of this early cellular reactivity has been emphasized (*67*). Also the comparison of the films is not strictly on a physicochemical (ionic) basis, because the styrene sulfonate group (thrombo-resistant in vivo) in one and the quaternary ammonium base in the other would have toxicologic implications related to organic structure. The anionic and cationic films produced ectopic bone formation in the nonmalignant fibrous capsules that engulfed them, whereas the neutral film did not. Since the electric surface charge of polymers is effectively nullified by the protein layer characteristically formed on implants, its influence as a carcinogenic factor would be unlikely. Cationic polymers enhance virus plaques by accelerating the movement of the viruses through the gels, which have become positively charged (*68*).

Human Solid-State Carcinogenesis

In addition to the human lung carcinomas associated with foreign bodies (*62*) and the sarcomas associated with bullets or shrapnel (*11*), other human cancers relating to solid-state surfaces include:

- A sarcoma arising locally 30 years after implantation of a relatively large metal bone plate (*69*)
- A chondrosarcoma occurring locally six years after bone-nailing (*70*)
- A giant cell tumor of the femur, probably malignant, three years after implantation of a Moore prosthesis (*71*)
- A meningioma surrounding a silver clip left in the area of the fronto-parietal-parasagittal lobe two years previously (*72*)
- A meningeal sarcomatous tumor (*73*) at the site of a 1-cm wire that pierced the skull of a male 20 years earlier
- A meningioma (*74*), with a latent period of 40 years, which arose at the site of a darning needle, in a 40-year-old male
- A foreign body-induced adenocarcinoma of the ciliary body (*75*) related to a nonmagnetic splinter from a detonator
- A tumor at the site of a bone splinter from the *Tabula interna* (*75*)
- A mammary carcinoma surrounding a needle engulfed in a pus pocket (*75*).

These tumors are related to inorganic solid surfaces. Local tumors ascribed to organic polymer implants follow a similar pattern. A human chondrosarcoma intimately associated with the fibrous capsule surrounding polymethylmethacrylate spheres, which were implanted as a plombage 16 years previously, gave rise to the classical picture of rodent solid-state carcinogenesis (*76*). Because of the limited life expectancy of most patients with occlusive vascular disturbances, there has been no latent period of 10 years to date among many patients subjected to polymer grafts. A fibrosarcoma of the thigh developed locally in a young man 10.5 years after the repair of a laceration of the left superficial femoral artery with a prosthesis consisting of woven Teflon–Dacron (*77*). A local carcinoma appeared four years after a mammoplasty with a Silastic implant preceded by simple mastectomy for chronic fibrocystic disease (*78*). Two patients with histories of fibrocystic disease who had simple mastectomies and silicone implants subsequently developed breast cancer, but not in immediate contact with the implants (*79*). Women with fibrocystic disease have a higher incidence of cancer of the breast than those without (*21*). Since isolated case histories, interesting as they are, rarely settle problems of carcinogenic epidemiology statistically, the role of the silicone implants as a carcinogenic factor remains in doubt in these two examples. In a survey relating to the relatively short-term carcinogenic potential of plastic foam implants in the human female breast, no substantiated malignancy occurred for 16,600 implants. One surgeon, however, reported three sarcomas after 103 implants (*80*).

Effects of Polymers as Prostheses and in Artificial Organs

Replacement of function, whether mechanical (*81*) or physiochemical, is the most important dimension in the physiology of polymer compatibility. A prosthesis ideally suited to replace a normal tissue should not be condemned for not functioning in an abnormal situation. If a living membranous surface of a heart valve is vulnerable to stenosis or fusion after bacterial inflammation, the ensuing living membrane that formed on a heart valve prosthesis would be similarly vulnerable. Since stagnation of blood in normal blood vessels can lead to clotting—bleeding causes fewer deaths than intravascular clotting (*15*)—a polymer blood vessel replacement would produce the same clotting under similar conditions. Conversely, the geometric baffling encountered with kidney and heart assistance or replacement devices poses a clotting problem in itself—a nonthrombosing surface at rest may induce clotting when active (*82*). (See section on *Clotting.*) A prosthesis may satisfactorily replace one or more functions of an organ, but it could hardly be expected to replace all of them. Thus an artificial lung will serve for adequate oxygen–carbon dioxide exchange, but lacks the regulatory mechanisms involving hormones and enzyme systems necessary to maintain all the functions of a living organ. The differences in pulsative vs. nonpulsatile pressure in heart action—problems with artificial hearts (*83*)—are reflected in peripheral pressure, lung, and kidney function. Here, density may preclude hydrodynamic flow. Sheet flow is thought to replace capillary action in the glomerular beds of the kidney and the alveoli of the lungs (*84*). The liver may have sheet-flow action too, hence capillary flow alone is an inadequate model for assessing blood transport problems.

As polymers are produced which are physically and chemically more akin to the adjacent cellular components that surround them after implantation, the proteins that become attached to their surfaces will be those that coat the adjacent cell surfaces; but because the polymer is not identical to the living cell there will be a kind of denaturation at the plasma membrane, which could very well evoke an autoimmune reaction ending in a rejection phenomenon. An example of this type of rejection involved nonpolymer subcutaneous

implantation. In groups of 30 female Evans rats, implants of 18-mm diameter cholesterol hydrate disks compared with dotriacontane disks of the same size produced a 53% and 10% incidence of rejection, respectively. The natural body constituent introduced in an abnormal physical state displayed less biocompatibility than the inert hydrocarbon (*11*).

With highly inert smooth-surface solids made from noble metals, tin, dotriacontane, etc., the initial inflammatory response after the implantation gives way to the formation of a fibrous capsule, which acts as a permanent barrier to metabolic exchange and may persist with its enclosed foreign body for the lifetime of the recipient. At some sites, this may lead to malignant degeneration (see *Human Solid-State Carcinogenesis*). A bone prosthesis that develops a layer of fibrous tissue introduces an unwanted complication. By using proper porous materials—a discontinuous solid-state surface—bone formation instead of the hyalinized collagen capsule is encouraged both within and without the prosthesis, and the prosthesis remains more biocompatible (*85*).

An ideal prosthesis would be one that takes over the function of the replaced tissue, stimulates the formation of the replaced tissue, and is itself ultimately resorbed. This would solve the problems of the two extremes—the autoimmune reaction and the fibrous capsule. Ideal suture materials are well known; these ultimately disappear from the site of application after they served the purpose of arresting bleeding or wound closure (*86*).

The Artificial Kidney

The cellulosic membranes used for repetative hemodialysis in patients with chronic kidney failure operate by passage of solutes through micro-holes. Best known of these is cellophane, reconstituted from the natural product cellulose. It can serve as a reference for synthetic organic polymer dialyzing membranes of the future. Permeability of cellulosic membranes is correlated with the molecular volume of the substance crossing the barrier. However, of two substances having the same molecular volume, it may not be desirable for both to diffuse through the barrier (*87*). When the sizes of molecules approach the size of the membrane pore, then surface forces come into play, so that, even with the cellulosic membranes, transfer may be influenced by factors other than pore size (*88*). Transfers across the cellophane membrane can be influenced by the composition of the dialysate. Sodium, calcium, magnesium, chloride, and acetate ions are added to the dialysing fluid to prevent their loss. Phosphate ions are omitted because their removal is a major problem (*89*). The films originally used in the artificial kidney are cumbersome and fragile, and the equipment associated with them has a large volume. Smaller equipment has been designed by substituting coils and hollow fibers, which increase membrane area and lend strength of support (*90*).

To duplicate more exactly the normal kidney, it would be desirable to develop membranes that would separate molecules on the basis of chemical properties as well as size (*87*). A considerable amount of research has been carried out to develop partition membranes for hemodialysis. Linear homopolymers, which have the desirable hydrophilic properties, do not have sufficient mechanical strength under the conditions of dialysis. Random copolymers gave no better promise. Block copolymers and cross-linked polymers can have both hydrophobic and hydrophilic properties (*88*). I have not been able to assess the extent to which permeable membranes have been used for human hemodialysis.

In addition to the dialyzing system, an artificial kidney requires heparinization, which must be adequately controlled (*91*). A practical device for connecting the patient's arterio-venous system with the artificial kidney is the extracorporeal shunt. An artery and vein are connected by plastic implants with a shunt tube, which is removable.

The problem of thrombosis associated with the artificial kidney is well appreciated; the washing out of constituents essential to normal metabolism by continued use of the artificial kidney is more difficult to assess, but probably is the limiting factor in the effective use of the artificial kidney. There is little information regarding the release, if any, of breakdown material or entrapped material from the dialyzing system. As the synthetic organic polymers replace the cellulosic membranes in the artificial kidney, the possibility of entrained toxic substances requires further evaluation.

Heart Valves

The natural heart valve in its action engenders a central flow in contrast to the lateral flow with certain types of prosthetic valves such as the caged ball, caged disk, or tilting disk attached to one side. Attempts have been made to use polymer cusp valves instead of aortic valve homographs, which have been useful (*92, 93*) but difficult to procure or replace. Knitted Teflon cusp valves tend to promote a fibrous reaction, with calcification, and to fracture (*83*). Silastic-impregnated cusp valves are in the same category (*94*). Both types may produce hemolysis. With the extensively-used ball valve, complications include (*83*) thromboemboli, obstruction, infection, detachment of valve, and anemia (see section on *Silicone* for lipid absorption by silicone heart valves).

Assessment of cloth-covered Starr-Edwards prostheses in 100 patients indicated that the hemodynamic function became unsatisfactory in many of these patients. Cerebral emboli, hemolytic anemia, and cloth and strut wear (*95*) have occurred. Thromboembolı formation and degeneration of the silicone ball used initially prompted its discontinuation in favor of a hollow stellite ball. Although the cloth covering is not identified in these experiments, earlier references (*96*) indicate that knitted Dacron fabric, Dacron struts, and Teflon orifices were used. In patients with Starr-Edwards valves, deterioration and fragmentation of Teflon has occurred. Some of the cardiac, cerebral, and other artifacts observed for patients with these valves may be Teflon emboli (*97*).

Artificial Hearts and Heart-Assist Devices

An excellent review on artificial hearts and heart-

assist devices (*98*) will not be elaborated upon. An artificial heart is designed to replace completely the circulatory function of a natural heart. A heart-assist device partially relieves a natural heart of its pumping activity, usually on a temporary basis. The heart-assist devices with in-parallel connections between the atrium and descending aorta, with in-series connections between the ascending and descending aorta, and with in-parallel connections between the left ventricle and descending aorta have not gained wide clinical acceptance or are still in the experimental stages. Intra-aortic balloons are readily installed by threading the ball and catheter by way of the femoral artery to the aorta (*99*). Such insertions have been made with promising results in about 200 patients. Among the polymers used for assist devices are Dacron, Dacron velour, epoxy resin, polycarbonate, polyurethane, polyurethane copolymers, and Silastic. Except for an artificial heart that kept a man alive 64 h, it has not yet found practical clinical use (*83*). Among the polymers used for making experimental artificial hearts are Dacron, Dacron velour, polyurethane, and polyvinylchloride.

Clotting and Cellular Destruction

Clotting, a basic problem in prosthetic replacement of blood vessels, hemodialysis systems, and heart-lung devices, is stimulated by stagnation or turbulence of blood flow, junctions of different materials, or by any foreign body. Depending on physical and chemical properties, each polymer prosthesis creates special problems. For the vascular system, the ultimate aim is a prosthesis that is negatively charged and semiconductive, semipermeable, and uniquely capable of absorbing, releasing, and exchanging ions with positive charges (*100*). Among the polymers having relatively less clot-promoting properties are polyurethane and Du Pont's "Delrin" acetal resin (*82*). Coagulation time is not decreased by a wettable surface as formerly believed (*101*), nor is zeta potential (*102*). The negative charge (−3 to −13 mV) of the blood vessel linings repels the platelets, which are similarly charged. Rupture of platelets attached to a damaged blood vessel or polymer initiates the clotting mechanism.

Heparin. Because heparin is a well-known anticoagulant, its incorporation into and release from polymers used as artificial organs has been extensively investigated both with ionic and covalent bonding systems. Most polymers such as silicone, Dacron, Teflon, polypropylene, polystyrene, polyurethane, polycarbonate, and the epoxides do not bind heparin, which has a negative charge. To promote binding, positively charged surfaces are prepared by a colloidal graphite coating that has absorbed benzalkonium chloride (Zephiran chloride) (*103*), by absorbing tridodecylmethylammonium chloride (TDMAC) (*104*), or by incorporation of γ-aminopropyltriethoxy silane (*82*). A covalent heparin bond to a polymer is achieved by means of the isocyanate radical (*105*). None of the devices that make use of ionic bonding have the necessary effective permanence; the covalent binding gives even less satisfactory results. So that the pool of heparin may be increased, the whole fabric is not bonded to, but instead impregnated with heparin (*82*), but the gain in effective time span is not sufficient for permanent devices. One of the problems with heparin is the change in physical properties of some polymers to which it is added in high concentrations. Heparin does not appear to function as an anticoagulant on the polymer surface, but must be released into the bathing fluids.

Homogeneous solutions containing a cationic polyurethane heparin complex are used to prepare thromboresistant *films on polyurethane tubing*. The new family of cationic polyurethanes are synthesized from commercial polyethers. The thromboresistance was evaluated by scanning electron microscopy for platelet adhesion rates. There was little quantitative difference between uncoated commercial polyurethane and medical-grade silicone tubing; the thromboresistance of the coating was demonstrated (*106*).

The living cell membrane. The fibrous capsule that develops around implanted foreign bodies does not induce the clotting mechanism, because it is made up of endogenous cells. A velour coating (*107*) has been used to induce a proliferation of living cells on polymer implants used in vascular systems. The original microclots are replaced by fibrous repair tissue. Instead of a velour, use of a mat of Dacron fibers and seeding with embryo fibroblasts of the same species accelerates the cell growth in vivo (*108*). The process may be begun in vitro (*109*). The drawback to living cell membranes is the lack of control over their growth. Too thick a layer of cells results in undernourished and dead cells with ensuing sloughs and potential emboli. Impedance of nutrient flow has been diminished by a very thin weave of polypropylene fibers anchored to silicone rubber or polyurethane (*83*).

Other anticoagulant mechanisms. Although heparinized and other surfaces designed to have negative charges are thromboresistant, a group of materials that does not fall into either of these categories has surface characteristics that achieve the same purpose (*110*). Pyrolytic carbon, graphite–polyurethane–polyvinyl or metallographic tallow surfaces, segmented surfaces (as with polyurethane–polyether or polyurethane–siloxane copolymer), and also albuminated polystyrene, fluorinated silicone rubber, or acrylic hydrogel fall into this category. Since virtually all foreign substances bathed in blood absorb proteins (*111*), the particular protein layer formed with these prostheses or devices apparently inhibits clot formation. An intrinsic common property of the surfaces of these materials that prevents clotting or induces adsorption of thromboresistant protein is yet to be ascertained. Nonionic detergents and wetting agents such as polyoxyalkylene derivatives of propylene glycol are incorporated in polymers such as polyurethanes and epoxides to create a layer of water on the embedded polymer; a barrier is erected against platelets and red cells. An albumin layer serves the same purpose. Silicone rubber, polystyrene, polyurethane, Teflon, and many other polymers can be treated to have albumin layers (*82*). "Pyrolite" carbons are highly thromboresistant when properly prepared; an adverse property for intravascular prostheses is their rigidity. Techniques have been developed to deposit adherent carbon coatings on flexible polymer substrates such as polyurethane (*112*).

An experimental artificial left ventricle made of a

contractile alloy, which simulates the heart muscle, would induce clotting unless coated with an ethylene vinyl acetate polymer. The contractile action overcomes the blood stasis problem inherent in hydraulic designs (*113*).

Red cell and white cell damage. Lysis of red cells shaken in glass with rather inert substances was described in 1884 (*114*). This phenomenon has been noted with implanted polymer heart valves (*115*) and is not subclinical in all cases. Hemolytic anemia has developed in patients with prosthetic heart valves and also from disruption of silicone rubber, Dacron, and Teflon aortic leaflets (*116*). Leukocytes are also injured by polymer interfacial contacts, but the clinical significance is not as clear as that for red cells (*117*).

Plasma Extenders and Water-Soluble Polymers

Polyvinylpyrrolidone

The polyvinylpyrrolidones (PVP), which for practical purposes range in molecular weight from 10,000 to 360,000 form colloidal aqueous solutions and hence belong to the group of water-soluble polymers. A PVP was used as a plasma extender in World War II in more than 500,000 cases, and rather extensively over the period 1939 to 1960. PVP polymers have also been designed to delay the resorption of penicillin, procaine, and insulin and to hasten the clearance of certain dyes from the reticuloendothelial system (*118*). PVP plasma extenders comprising a wide range of molecular weights (20,000 to 80,000) entail consideration of the fraction uncleared by the kidney (*119*) and the retention by the lysosomes of the reticuloendothelial system. Induction of latent hepatic lesions in humans who received a PVP solution (*120*) raises questions of toxicology as do the results of experiments on rodents that have allegedly produced cancer (*121*). (For a discussion of all types of plasma extenders see *Dispensatory of the United States of America*, 25th ed., J. B. Lippincott Co., Philadelphia Pa., 1955, pp 1811–1815.)

Thesaurismotic reactions. When administered parenterally to mice, rats, and rabbits, PVP was stored in many organs and tissues regardless of the polymer's molecular weight (*121*). Storage was most pronounced in rabbits, least in mice. Fatty tissue at the site of implantation, meninges, adjacent glial cells, lungs, endothelial cells in the blood vessels, myocardium, Kupffer cells, mediastinal and abdominal lymph nodes, spleen, renal glomeruli, and endometrium were observed to take up PVP. The retention involved parenchymal as well as phagocytic cells. Hyperplastic reactions were observed. Proliferation of cells was noted in ependymal, choroid, and meningeal cells, and multifocal adenomatosis in the pulmonary alveoli.

Polyvinyl Alcohol

The polyvinyl alcohols are generally water soluble or water–alcohol soluble and find use in the plastics industry for surface coatings of goods intimate to the human environment and as mixtures to produce elastomers. In the body, the storage distribution of polyvinyl alcohol, which had also been studied in dogs, was very similar to that of PVP (*122*).

Six water-soluble polyvinyl alcohol polymers, ranging in molecular weight from 35,000 to 240,000, were given subcutaneously to rats. All produced anemia and infiltrated the hypophysis and kidney. These common responses as well as chemical attraction for Congo red may be ascribed to chemical properties. The two polymers that caused hypertension, vascular lesions, and renal pathology had a lower solubility in cold water. There was no correlation of pathological effects with molecular weight, but those with vinyl acetate residues had the higher cold-water solubility (*123*).

Testing for Carcinogenic Hazards

A rather ambitious program of safety testing for water-soluble macromolecules was conducted at the National Cancer Institute (*121*) and included water-soluble PVP polymers and a polyvinyl alcohol preparation with an average molecular weight of 120,000. The conclusions drawn are not very convincing because of inadequate control. Although more than 1000 rats received polymers by various routes, there were only 200 normal controls. The 840 mice also used as controls had received wool fat, gelatin, tricaprylin, or test chemicals and approached the numbers that received polymers. Tumor incidence is given on the basis of beginning numbers, not effective numbers, which would be those that survived long enough to develop tumors. The sex of the animals is not given; control pathology indicates that some were females. The experiments were not performed concurrently. One of the candidates that was concluded to show a carcinogenic response was a PVP with a molecular weight of 30,000. It produced negative tumorigenic results in mice and rabbits (three experimental series). If the control rat colony is assumed valid for purposes of statistical analysis, chi-square with Yate's correction would indicate a carcinogenic response in only one of the three series. This assumption is not valid because the control colony was not observed concurrently. Because the control rat tumors were predominantly reticulum cell sarcomas with a rather high incidence, the observation of these same types of tumors in the series dosed with polymers is not compelling evidence for a carcinogenic effect. Of 460 rats that received PVP, 11.5% developed reticulum cell sarcomas; the control incidence was 5.5%. The challenge to the use of tumor incidence in the normal colony instead of concurrent controls is illustrated in Table 3 for lymphoid tumors (reticulum cell sarcomas and lymphomas). Although the females were followed longer than the males, the incidence of these tumors is lower in females than in males for each of the five series after 1966. Whether to pool the data for the two anatomic sites and whether to pool the two types of tumors, as was done in the Table, would be controversial.

Contraceptive and Erectile Devices

Polyethylene Polymers

The safety testing for polyethylene intrauterine contraceptive devices is more extensive than for most polymer uses.

Subcutaneous and intrauterine implants. On sub-

Table 3. Incidence of Spontaneous Reticulum Cell Sarcomas and Lymphomas in Evans Rats over a Six-Year Period

(F. Bischoff and G. Bryson)

Year (terminal)	Sex	Terminal age in in months	Number at start	Effective number	Intrathoracic tumors, %	Intraperitoneal tumors, %
1966	♂	18	30	27	11	7
	♀	22	47	35	6	11
1967	♂	22	41	29	24	3
	♀	24	38	28	4	14
1968	♂	18	36	36	17	11
	♀	19	35	27	11	0
1969	♂	23	40	26	39	8
	♀	24	77	59	31	0
1970	♂	19	41	30	33	0
	♀	22	36	26	15	0
1971	♂	20	79	71	16	1
	♀	23	76	57	10	2

cutaneous implantation in rats, a bilateral comparison of 10-mm diameter polyethylene disks made of a mesh of hard consistency with soft pliable films of the same material showed no significant difference in sarcoma yield during 18 to 24 months: 4/45 vs. 1/55 (*124*). The low sarcoma yield was predictable, because the size of the disks approached threshold size as evaluated by others (*68*). In comparing subcutaneous implants of a polyethylene segment (620 mg) with shredded polyethylene packed in gelatin capsules, there was no significant difference in local sarcoma production: 7/20 vs. 5/20 in CB stock rats. The mean time of tumor induction was eight weeks earlier for the segment. No tumors appeared in surgical controls or rats implanted with empty gelatin capsules (*125*). The packing would achieve the effect of a continuous surface to some degree and the sarcoma yields in both groups would be predictable on this basis.

Comparison of response to polyethylene polymer loops, spirals, and sheets on subcutaneous implantation in rats indicated a correlation of tumor incidence with degree of continuous surface (*126*). Under the same conditions, stainless-steel rings with a noncontinuous surface produced no tumors. In comparing similar intrauterine contraceptive device materials (*127*), local sarcomas were produced with both the polyethylene polymer and stainless steel. From a chemical standpoint, the stainless steel does not appear to have an advantage over the polymer. Since more relevant results (*127*) to the problem of intrauterine devices would accrue from intrauterine implantation, portions of stainless-steel and polyethylene intrauterine devices were surgically introduced into each uterine horn in two groups of 100 juvenile female Wistar rats. During a two-year period six epidermoid carcinomas arose in proximity with stainless steel and five with polyethylene; no such carcinomas developed in 400 control rats. Endometritis and endometrial squamous hyperplasia, which were concomitant with the development of epidermoid carcinomas in the rats, do not appear to persist in women with intrauterine devices. If they were a prelude to carcinogenesis in the rat, predictions for humans using devices are not forthcoming on this basis. Squamous metaplasia occurs from silk sutures and autologous or homologous skin grafts at the uterine site of the rat; this characteristic response rather than a solid-state surface effect may be more closely related to the production of the epidermoid carcinomas.

Intraperitoneal implants. Although uterine perforations by open-ended polyethylene intrauterine devices are rare, a study of the fundal portion of such loops introduced intraperitoneally in rabbits was made in order to evaluate the problem when it occurs in humans (*128*). In some instances the sterilized device was introduced directly into the peritoneal cavity, in others via the endometrial cavity or via the vagina, cervix, and endometrial cavity. The typical response was adhesion formation; this was not dependent on bacterial contamination. Seventy percent of the devices migrated to another area of the peritoneal cavity before becoming anchored by adhesion formation. Since there is a greater tendency for adhesion formation in rats than in rabbits, the results with the devices are considered of significant importance in predicting their fate if they herniated into the human peritoneum.

In earlier work (*17*), six local sarcomas developed in female Bethesda black rats implanted intraperitoneally with polyethylene polymer films. These sarcomas arose 16 to 24 months after implantation. On covering experimentally induced ulcers (1 × 1 cm) in the rat parietal peritoneum with polyethylene polymer sheeting, dense omental adhesions and marked fibroblastic activity, but no frank neoplasms, were observed (*129*). Because rats were killed only 3, 6, 9, or 12 months after implantation, few sarcomas would be expected.

Penile implants. Polyethylene has been used for the surgical treatment of human impotence. By implantation of polyethylene rods into the penis, an organ akin to that of the os penis of the dog has been achieved in 700 patients over a seven-year period. The practice, reported from the United Arab Republic (*130*), does not appear to have a wide following in the United States. Silicone and acrylic prostheses have also been tried for

this purpose. The ultimate fate of these implants would be of interest.

Tissue Adhesives

Polycyanoacrylate

The alkyl-2-cyanoacrylate monomers have been studied extensively as tissue adhesives (*131*) because they polymerize rapidly when exposed to tissues, forming a strong bond. However, local tissue irritation and necrosis has been an adverse effect with some (*132–137*).

The breakdown and resorption of degradation products of a polymer used as a tissue splint or hemorrhage deterrent is more desirable than one that is permanent, if the resorption process is not toxic (*86*). Theoretically, the breakdown products of the cyanoacrylates are formaldehyde, which would be bacteriostatic, and alkylcyanoacetate. The use of polycyanoacrylates in medicine depends on whether their breakdown is slow enough to minimize local and systemic toxicity. Blood polymerizes the cyanoacrylate monomers more rapidly than water. That the polymerization is via chemical bonding through protein amino groups is indicated because the resulting polymer was not extracted by polymer solvents. Tissue adhesives should have spreading characteristics that depend on surface, interfacial tensions, and substrate surface energy (*138*). Isobutyl and n-butyl cyanoacrylate polymerize rapidly and are less toxic than the methyl derivative (*139*), but they are not broken down rapidly in vivo (*140*). Isobutyl-2-cyanoacrylate formed a polymerizing adhesive with whole blood or blood fractions. The coagulation properties of blood were not affected by exposure to the formed polymer, a protein-polymer complex, or the monomer. Monomer sprayed on transected dog kidneys formed an adhesive layer, which progressively disintegrated with bleeding and concentration of leukocytes (*141*).

β,β,β-Trifluoro-isopropyl-cyanoacrylate appears to possess the desirable properties of both the methyl and higher homologs without their undesirable qualities, and is now under investigation (*131*). Although methyl-2-cyanoacrylate monomer has been used as a tissue glue since 1960, its application (*139*) as well as that of the higher homologs in clinical surgery has not been widespread.

Tissue reaction. Collagen formation preceded by fibroblast invasion normally occurs in wound healing and relates to tensile strength. In rats, a comparative study (*142*) of three cyanoacrylate monomers dispersed in implanted polyvinyl alcohol sponges showed that the methyl derivative inhibited collagen formation, whereas the hexyl and decyl derivatives did not. All three produced more edema fluid. The decyl and hexyl monomers did not disturb developing granulation tissue as did the methyl derivative. The local toxicity of methyl-2-cyanoacrylate polymer is the same as that of the monomer. There is a correlation between the rate of resorption and degree of local inflammation for the cyanoacrylates. Methyl-2-cyanoacrylate is the most histotoxic.

A study of several butyl cyanoacrylate tissue adhesive sprays intraperitoneally in dogs, rats, and mice showed a granulomatous reaction around the formed polymer, but no carcinogenic response existed. The dogs were followed for two years, the rats one year; the follow-up period for the mice is not given. Offspring of the rats developed no tumors (*143*). A high incidence of thrombosis developed in both arteries and veins of dogs when n-butyl-2-cyanoacrylate monomer contacted the lumen of the vessels (*144*).

Bucrylate (n-butyl-2-cyanoacrylate) was studied (*145*) as a potential ossicular adhesive in the middle ears of 12 cats. Because of the observed damaging effects to the middle and inner ears and the failure to achieve functional union between the ossicles, it was concluded that this cyanoacrylate was neither safe nor useful adhesive for the bones of the middle ear. In contrast to corneal injection experiments with rabbits, isobutyl-2-cyanoacrylate adhesive produced a pronounced granulomatous keratitis when used to close a perforated area in a markedly necrotic cornea of a human (*146*). In a study with rabbit extraocular muscles, the replacement of sutures with plastic adhesives (apparently isobutyl-2-cyanoacrylate) was found to be impractical because of inadequate bond strength and inaccuracy in measured replacement (*147*). Continuous suture microvascular anastomoses with 9-0 monofilament nylon were compared with end-to-end anastomoses by using isobutyl-2-cyanoacrylate adhesive and three stay sutures in studies with rats. One of the 24 of the nylon group failed, as compared with five of 28 of the cyanoacrylate group. The latter group showed degeneration of the intima and deposition of calcium in the vessels, and a more prolonged and intense foreign-body reaction (*148*). The injury to the arterial media by the isobutyl derivative was equal to that with the methyl derivative (*137*).

Polyurethanes

Polyurethanes and polyurethane prepolymers have been briefly studied as nonsuture adhesives (*149, 150*). Polyurethane was also studied as a bone glue (*149*).

Safety testing. Although the particular polyurethanes subjected to safety testing for carcinogenic hazards were not the polyurethanes designed for use as glues, they are reported here as representing a closely related class of organic compounds. In rats, a comparative study (*71*) of polyurethane sheets, foam, and powdered foam suffers from inadequate control. Here, the sheets and foam were different in that the former were aromatic, the latter aliphatic. Moreover, the foam contained castor oil, dimethylamine oleate, dimethylpolysilicone, and tri-β-chloroethyl phosphate. Results at the subcutaneous site were essentially negative. The foam when introduced intraperitoneally produced a significant number of adenocarcinomas arising from the cecal mucosa; powdered foam did not. The results obviously do not prove that polyurethane is a chemical carcinogen because the array of additives beclouds the issue. In female CC57W mice, intravaginal application of polyurethane or butadiene carboxylate latex sponges over a 10- to 20-month period induced premalignant changes in the cervical uterine and intravaginal epithelium (*150*). One hundred four Swiss albino mice that

survived one year after implantation of a polyetherurethane sponge beneath the mammary glands developed as local cancers. The sponges became distorted and shrunken and elicited a foreign-body reaction (*151*). One year would be too short for the evaluation of carcinogenic potential.

Self-Curing Resins

Clear polymers of methylmethacrylate are readily formed, and known in the industry as "Lucite," "Plexiglas," etc. Polymers and copolymers prepared from the monomer are used in dentistry. The monomer is the active ingredient in cements serving to implant ball and cup prostheses in orthopedics.

Use of Acrylic Polymers in Humans

"Self-curing resins" have been used in spine (*152*), hip (*153*), and elbow-joint surgery (*154*), and for containing intracranial aneurysms (*155*). A typical autopolymerising bone cement is formed by mixing a liquid containing methylmethacrylate monomer, ascorbic acid as a stabilizer, and dimethyl-*p*-toluidine as a catalyst with a powder containing polymethylmethacrylate and benzoyl peroxide as an activator. The monomer, methylmethacrylate, which may penetrate rubber gloves such as are used by surgeons and art technicians, can produce a dermatitis (*156*). In patch tests benzoyl peroxide and methylmethacrylate were positive. Because the polymerization process used to produce acrylic cement is exothermic, local temperatures, which can reach 100°C in orthopedic prosthetic fixation, may cause necrosis (*157*). Absorption of the monomer into the blood stream causes a fall in blood pressure and possible lung lesions. These effects are minimized by improved surgical techniques (*158*, *159*). In a study of 20 patients undergoing surgical replacement of arthritic hip joints in which a cold-curing methylmethacrylate cement was used at both the acetabulum and femur, a fall in systemic arterial pressure occurred in every patient, though not always with both procedures. In one case the fall in blood pressure was critical. The study was prompted by a death after the cement was used for replacement of a fractured femoral head. It cites incidents of cardiac arrest and cardiovascular collapse under comparable circumstances (*160*). Five communications concerned with bone cement and cardiac arrest or pulmonary embolism do not give the chemical composition of the cement (*161–165*); the responsibility for this failure rests with the editors of the journal that published these papers. In a study of 3,799 hip replacements (*162*) only four cases of cardiac arrest were reported; the absorption of the monomer, which has a very strong odor, can be minimized by not cementing too early, thus giving the monomer time to polymerize. The concentration of the monomer in the surgery atmosphere, as manifested by its odor, would obviously be of some concern to surgical personnel working with the cement because of its cytotoxicity. Earlier reports indicated that the implanted polymerized cements caused no serious adverse long-term reactions (*166*, *167*), nor was there pronounced decomposition (*168*). In the rabbit or monkey, self-curing methylmethacrylate produced no more adverse tissue reaction than "Vitallium" (*169*). In a study of 23 human patients who had bone-cement junctions and were followed for as long as seven years, newly formed areas of fibrocartilage at isolated points indicated transmission of load from cement to bone. Mechanical pressure on fibrous tissue stimulated development of areas of ossification. The presence of a giant-cell foreign-body reaction is not regarded as a rejection phenomenon because the success of the procedure was demonstrated over too long a period. Fat was stored within 10 μm of the cement, indicating absence of chemical irritation. Granulomatous or caseating areas were not observed (*152*).

Considerable heat is generated when methylmethacrylate is molded directly on the floor in orbital fracture repair (*170*) and the exact molding is difficult. Plates of this polymer, in various shapes and sizes, are therefore prefabricated and then surgically implanted, with excellent results (*171*).

A comparison of 9-mm disks of polymethacrylate with disks of 80% polymethacrylate and 20% anorganic bone was made in the skulls of Norway rats and showed that bone developed only with the latter. Polymethacrylate became surrounded by fibrous connective tissue. Neither the polymethacrylate nor the bone are completely identified as to chemical composition (*172*). Rats whose skin was painted three times weekly for four months with methylmethacrylate or subcutaneously embedded with pellets containing benzoyl peroxide developed no cancers (*14*).

Hematopoiesis in damaged bone. A prosthesis does not take over hematopoietic functions in bone replacement. With a partial replacement, influence on hematopoiesis and the carcinogenic potential of the solid-state surfaces of the prosthesis or of dead bone are to be considered. (See section on solid-state carcinogenesis.) Local environmental and traumatic influences on hematopoiesis have been studied (*173*) in rats by subcutaneously implanting living sternums and femurs obtained from littermates of a highly inbred strain. Rejection as sloughs was 12.5% (5 out of 40) over a 20-month implant period. Ten percent of the implants became necrotic but were not rejected over a 19-month period. Fourteen implants were viable with active hematopoiesis during a 5–20 month period. Necrotic areas of necrosis were observed in nine with periosteal inflammation and fibrosis in some. Chronic osteomyelitis occurred in four femurs. In sternum implants, two showed hypercellular bone marrow, and one lymphocytic hyperplasia in the marrow. An implanted femur gave rise to a benign exuberant fibrohistiocytic reaction. The absence of malignant degeneration associated with the living implants indicates adequate metabolic exchange or a noninhibited inflammatory reaction, conditions not prevailing in the environment of inert nonliving solid-state implants.

Safety Testing Polymethylmethacrylate

Subcutaneous, intraperitoneal, and intramuscular implants. A study of polymethacrylates and their copolymers that might find a use in dentistry, surgery, and opthalmology compared hard and soft resins, neutral or alkaline hydrocolloids, and solid or perforated plates at the subcutaneous or intraperitoneal site in

rats and rabbits. Only the solid plates produced local sarcomas. Negative results for the other forms indicate the absence of a chemical carcinogen (*174*).

The effects of intramuscular implants of stainless-steel and polymethylmethacrylate disks of three sizes (18, 12 and 4 mm in diameter) in four- to six-month-old Hartley guinea pigs and three-month-old Chester Beatty rats were compared (*175*). One hundred thirty-three guinea pigs developed no local sarcomas during a 20-month period; after prolonged implantation the fibrous capsules around the implants in this species thinned, with reduction of cellularity apparently correlated with degeneration of the inner margin. Confirming the work of others, sarcoma yield for the rat was correlated with implant size: The 4-mm diameter disks produced no cancers. *Local tumor yield for polymethylmethacrylate* was 34/153 for the large, 17/142 for the medium size disks, and 5/42 and 2/37, respectively, for stainless steel. Since solid-state-induced subcutaneous sarcomas in rats do not usually metastasize initially [they do after transplantation (*1*)], it is of interest that metastases were found in the lungs or mesenteric glands of 13 rats with sarcomas arising at the intragluteal implant site. Lack of local sarcoma production in the guinea pig might relate to subthreshold size, a prolonged latent period, or a species difference in response to a carcinogenic effect.

Plasma-cell tumor induction. Polymethylmethacrylate plastic disks, commercial mineral oils, 7-*n*-hexyloctadecane, squalane, and pristane were implanted intraperitoneally into BALB/c mice. All produced fibro- or oleogranulomatous reactions with obstruction of lymphatic drainage, local and systemic plasma cell hyperplasia and plasmacytomas arising in the peritoneal granulomas. Tumor yields ranged from 23 to 70% (*176*). The carcinogenic process apparently depended on stimulated plasma cell clonal derivatives trapped within granuloma, because material that migrated to the bone marrow, lymph nodes, spleen, and liver produced no neoplasms.

Polytetrafluoroethylene

This polymer is well known for its uses in the laboratory, both as a lining and as tubes. Vascular patches and tubes are noted in the section on *Effects of Polymers as Prostheses and in Artificial Organs*. The polytetrafluoroethylene (PTFE) polymers of commerce are linear fluorocarbon compounds. Because the carbon-fluorine bond is one of the strongest chemical linkages, these polymers are relatively inert, with high thermal stability and extremely low solubility. The useful temperature range is −75° to +250°C (*177*). At 325°C there is softening, and at 400°C a breakdown to the monomer occurs. Toxicologic investigations are concerned with the polymer itself when used at room and body temperature and with the decomposition products at elevated temperatures. Decomposition products resulting from heat processing in the production of polymer articles may be entrained in material utilized at room temperature.

Pyrolysis products. The chemical composition of a particulate fraction (fluorinated acids and olefins) produced by PTFE pyrolysis is influenced by the humidity of the air (*178*). By comparing filtered and unfiltered airstreams of PTFE pyrolysis products, it was demonstrated that particulate matter was associated with the toxic manifestations in test animals (*179*). The particulate material may have toxic components adsorbed on it.

Perfluoroisobutylene is the principal toxic agent formed 30°C above the lowest temperature that produces toxic products. The temperature at which toxic pyrolysis products develop depends on the molecular weight of the PTFE: polymers of higher molecular weight require a higher temperature. There is agreement that the rate of pyrolysis of PTFE is not substantial below 450 C (*180*). Carbonyl fluoride (fluorophosgene) is the principal toxic component at 550°C.

Tissue Reaction to Polytetrafluoroethylene

Safety testing. There was no significant difference in local tumor incidence in comparing plain with perforated PTFE (Teflon) disks on subcutaneous implantation into rats (*14*) or plain with fragmented disks in mice (*181*). Chemical factors were more important than the continuous surface in eliciting the carcinogenic response. The test conditions were comparable to those used for polyvinyl chloride polymer, Dacron, and nylon (*14*). The Teflon experiments in which the sarcoma incidence ranged from 13 to 24% indicated a chemical carcinogenic response, possibly through release of fluoride as an enzyme poison, the presence of entrained monomer, or pyrolysis products if the polymer had been subjected to heat treatment (*1*). In contrast, neither subcutaneous implants of Teflon mesh surgical outflow patches nor shreds of the same material (*182*) produced cancers in rats. For this particular material a chemical carcinogen was not indicated. The not-impenetrable *mesh, after implantation,* became covered with moderately vascularized, thin, hyalinized patches of connective tissue. The shredded material was engulfed in flattened mounds of granulomatous tissue. The results on safety testing for Teflon in three laboratories and two strains of rodents are thus in conflict, and may relate to possible product difference.

Parenteral in man. Intracordial injection of polytef (Teflon) for functional improvement of pathologic conditions of the human larynx may be followed by progressive fibrosis with either a receding or persistent foreign-body reaction. Recommended particle size of the Teflon for injection purposes is between 50 and 100 microns, because migration through the lymphatics and blood vessels was observed with pastes containing smaller particles (*183*).

Toxic Reactions to Pyrolysis Products

Test animals. The monomer, tetrafluoroethylene, and pyrolysis products of its polymer were subjected to toxicologic examination in rats and rabbits (*184*). The lethal monomer concentration in air is 2.5 to 4 vol %. The toxicity of depolymerization and pyrolysis products are ascribed to difluorophosgene, perfluoroisobutylene, and other highly toxic compounds. As tested in dogs and rodents the pyrolysis products of PTFE are moderately toxic, as evaluated by the Hine and Jacobsen toxicity scale. The pathological changes

associated with particulate material observed in lungs after exposure demonstrated an irritative effect more than seven days after inhalation. After the acute hemorrhage and edema, irreversible tissue damage demonstrated by focal emphysema and interstitial fibrosis ensues. Fatty degeneration of the liver was also observed in these experiments. The toxic effects of carbonyl fluoride are ascribed to its hydrolysis product, hydrofluoric acid (*180, 186*).

Chlorotrifluoroethylene. Toxicological studies with the pyrolysis products of polychlorotrifluoroethylene at 357° and 400°C indicated that the lethal effect may be due to inhalation of particulate products of hydrolysis. A chemical pneumonoitis was demonstrated in rats (*186*).

Polymer fume fever in humans. At the sintering temperature of 350°C, workers involved in the molding of PTFE developed a temporary influenza-like illness. These symptoms have not been reproduced in experimental animals (*178*). When cigarettes contaminated with fluorocarbon polymers, including fluorocarbon telomer aerosol, are smoked they can produce a polymer fume fever. Pyrolysis products are apparently the responsible agents (*187*). Fevers (*188*) classified as secondary result from dehydration, hypernatremia, and infection. So-called toxic fevers are classified as metabolic, induced either by thyroid extract, dinitrophenol, and pentachlorophenol, or by leukocytic pyrogens such as endotoxins, zinc oxide, or polymer decomposition products of PTFE. A worker who was exposed to PTFE-coated metal filaments and smoked on the job developed the latter kind of fever. Polymer fume fever is rare among those manufacturing the polymer, more common among those exposed to superheated products or contaminated cigarettes.

Domestic High Temperature Use

Teflon has been used to line cooking utensils: saucepans, dutch ovens, chicken fryers, skillets, griddles, muffin tins, and cookie sheets. In pan frying or griddling (*189*) the temperature ranges from 150° to 250°C. In roasting and baking the maximum temperature of the oven may exceed this range slightly but the food itself is below this maximum. Teflon-lined utensils and domestic heat appliances such as flatirons are a potential hazard if temperatures are accidently reached at which the polymer decomposes.

Uses and Abuses of Silicone

Solubility

The solubilities of a number of cosmetic materials, alcohols, and solvents in silicone fluids ("Medical Fluid 360") having viscosities of 20, 350, and 1000 centistokes (cSt), tested in ratios of 10 to 1, 1 to 1, and 1 to 10, are available (*190*). Data for lipids and a number of normal body constituents are given in Table 4 (1 stoke = 1 cm^2/s = 10^{-4} m^2/s).

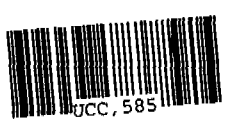
Endogenous Lipid Uptake

Uptake of lipids and other endogenous materials by injected liquid silicone in humans has not been reported. Such studies were made in conjunction with safety testing for carcinogenic hazards in rats and mice (*192*). A modified Zak procedure substituting 2-propanol for glacial acetic acid was adapted for cholesterol and lathosterol determination. Ultraviolet spectroscopy and the Zimmermann reaction served for detection of Δ^4-3-ketosteroids. The contents of

Table 4. Solubility of Natural Products in Dow Corning 360 (350 cSt) Silicone Fluid

Compound	Assay method	Temp., °C	Solubility, mg/ml
Carotene	spectrophotometry 454 nm[a]	38	0.24
Cholesterol[c]	Bowman & Wolf color reaction[b]	38	1.2
		25	0.7
Cholesterol palmitate	visual observation of precipitate[a,b]	48	1.5
		42	1.0
		38	0.5
Estradiol[c]	spectrophotometry 280 nm[a,b]	38	0.01
		38	<0.02
Estrone[c]	spectrophotometry 280 nm[b]	38	0.011
Olive oil	visual turbidity[a]	38	>10
Progesterone[c]	spectrophotometry 231 nm[b]	38	1.1
Riboflavin	visual color[a]	25	<0.002
		100	<0.002
Testosterone[c]	spectrophotometry 232 nm[a,b]	38	0.16
		38	0.25
Tripalmitin	visual observation of precipitate[a,b]	56	6
		53	2.4
Urea	visual observation of precipitate[a]	38	<0.04

[a] From undersaturation (*191*).
[b] From supersaturation (*191*).
[c] (*81*).



large cysts were removed for chemical analysis. Multilocular cysts and silicone granulomas were not analyzed because the silicone subjected to analyses had to be free of formed elements. The silicone cyst contents was diluted with spectro grade 2,2,4-trimethylpentane and scanned for ultraviolet absorbancy against a control containing the original silicone in the same dilution. The silicone samples from six rat cysts taken 12 to 21 months after injection into the mammary tract showed 0.7 to 2.0 mg of cholesterol per milliliter of silicone. The cholesterol values, 0.2 to 0.7 mg/ml of silicone, for eight mice 11 to 17 months after dosage into the mammary tract are lower than are those for rats. The values actually exceed the solubility of cholesterol in the silicone in some instances. This reflects either the uptake of some esters of cholesterol, or the enhancement of solubility in the injected silicone by the uptake of other lipids. Four rat and two mice silicone cysts demonstrated no Δ^4-3-ketosteroids by ultraviolet spectroscopy. Two showed concentrations of 0.6 and 1.6 mg/ml, calculated as progesterone. This was confirmed in one by the Zimmermann reaction, which also indicated 0.1 mg of a 17-ketosteroid. There was no measurable lathosterol in either the mice or rat silicone from cysts. Since lathosterol in the color test gives about 0.6 the color at its peak (386 nm) that cholesterol does at its peak (530 nm), the minimum amount of detectable lathosterol would be 10% of the cholesterol value.

The uptake by silicone of a substance with the ultraviolet absorbance characteristics of a Δ^4-3-ketosteroid and the Zimmermann test characteristics of progesterone is of clinical interest. In female humans, fat depots take up a higher percentage of ingested progesterone than of estradiol (*193, 194*). The correlation of endometrial carcinoma with obesity may be related to the uptake of progesterone by the fat, thus prolonging the estrus effect; estrogen-secreting tumors enhance the incidence of this type of cancer (*193*). The affinity of liquid silicone for progesterone [at 38°C, progesterone is more than 50 times as soluble in liquid silicone as is estradiol or estrone (*21*)] must be considered in evaluating its carcinogenic potential as indicated in the studies with mice.

Liquid Silicone as an Oxygen Carrier

The solubility of oxygen (30 vol %) at 37°C in Dow Corning 200 silicone with 1 cSt viscosity is 12.5 times that in isotonic saline (*195*), and of the same order as that in perfluorobutyltetrahydrofuran. The solubility thus exceeds that of the volume of oxygen taken up by whole blood (20 vol %). At 25°C a silicone fluid with 20 cSt viscosity dissolves 6.3 times as much oxygen as water (*196*). Hamsters immersed in certain perfluorinated organic liquids or silicones saturated with oxygen are able to survive variable periods of time ranging from 10 min to 24 h. Pulmonary changes such as leukocytic infiltration of focal atelectatic areas, alveolitis, bronchitis and alveolar and perivascular edema and hemorrhage were more extensive and lethal with the silicones. The silicone with a viscosity of 10 cSt showed phagocytized material in foam cell formation; the silicones with 1 and 5 cSt viscosity produced a fiberlike precipitate in the alveoli (*197*). The 10 cSt silicone was better tolerated than the 1.0, 1.5, and 5.0 cSt silicones. Mice, cats, and dogs have also survived after breathing oxygenated fluorocarbon liquids (*198*). The saturated perfluorocarbons have no hydrocarbon linkages.

Tissue Reaction to Liquid Silicone in Rodents

Following interscapular injection of liquid silicone into a mouse, macrophages formed a local tumor and demonstrated engulfed silicone, described as a siliconoma (*199*). This phenomenon was confirmed with the same species at the same injection site. Clear vacuoles were seen in the cytoplasm of the macrophages. Local subcutaneous injection of liquid silicone in a human produced a local reaction. In the discharged fluid, white cells showed vacuoles similar to those which developed in silicone-injected mice. It was possible to produce the same effect by shaking human blood with liquid silicone (*200*). Local atrophy of fat cells with phagocytes containing clear vacuoles are observed following subcutaneous injection of liquid silicone into laboratory animals. After both subcutaneous and intraperitoneal injection of silicone into mice, their adrenals, lymph nodes, liver, kidneys, spleen, pancreas, and ovaries showed focal infiltration of macrophages with large clear cytoplasmic areas (*201*). Fourteen weeks after intraperitoneal injection of silicone into adult mice, silicone granulomas appeared at the corticomedullary junction of the adrenal. Generalized foci of fat atrophy were also observed, the phagocytized silicone was transported to regional lymph nodes and distributed through the reticuloendothelial system (*202*). Phagocytosis of silicone also occurs in baboons; red cells of rats dosed with silicone also show vacuolization (*203*). A granulomatous reaction was observed after injection of liquid silicone into the peritoneal cavity of rats (*204*). The phagocytosis of liquid silicone by cells of the reticuloendothelial system has its counterpart in the role of the macrophages in siliosis and asbestosis (*11*). The analogous pathologic defense mechanisms may relate to structural chemical similarities between the silicones and the silicates.

Effect on Experimentally Induced Adhesions

Medical-grade silicone fluids of 20, 350, and 1000 cSt viscosity, applied intraperitoneally to the bowel, did not prevent but augmented intestinal adhesion formation induced in rats by sandpaper abrasion. Granulomatous reactions to silicone were observed seven weeks to four months after silicone application (*205*).

In rabbits, silicone fluid (300 cSt) appeared to augment postoperative pelvic adhesions as evaluated two to four weeks after silicone administration (*206*).

In rats, either locally applied hydrocortisone or silicone (20 cSt) diminished the number of standardized experimentally induced peritoneal adhesions (*207*). The period of observation, only three weeks, seems too short to evaluate ultimate effect, in view of the longer-term results of the same silicone in rats (*205*).

Release of Drugs from Silicone Depots

Gradual, continuous liberation of small amounts of certain hormones (simulating endogenous release) markedly increases their physiologic effectiveness as compared with a sudden release of the same total amount, flooding the target cells (*208, 209*). The subcutaneous injection of regular insulin illustrates the sudden release whereas the injection of an insoluble insulin such as histone insulin shows the slow release. The augmentation effect may be achieved by divided dosage—many injections over a period of time. Thus, three injections of estradiol-17β per day for three days produced a 72% augmentation of uterine weight in the immature rat as compared with one injection per day of the same total amount of estradiol (0.15 μg).

Except for the organic polymers, no attempt will be made to review the extensive literature on the various hormone and drug preparations designed to delay resorption and minimize the number of injections. It should be noted that all hormones do not demonstrate the augmentation effect (*210*).

Because of their solubility in silicone rubber, many drugs, hormones, and other compounds may be diffused at rather uniform rates through silicone rubber carrier depots, whether implanted parenterally or inserted into the blood stream. The less polar compounds diffuse more rapidly (*211*), in keeping with increased solubility of nonpolar compounds in liquid silicone (see page 883). Gaseous anesthetics swell the silicone rubber, which returns to its original size after the gas has been released. A silicone rubber capsule containing powdered triiodothyronine and isoproterenol implanted in the myocardium of dogs with heart block produced a pacemaker effect for a week. The effect was reinstated by transplanting the rubber capsule to another area after removing it from the fibrous capsule that had been forming (*212*). This experiment demonstrates the diffusion through silicone rubber. It also illustrates an inherent liability to its practicability: the lessening of diffusion by the ensuing foreign-body reaction. In contrast, silicone capsules containing melengestrol acetate, implanted intramuscularly into sheep, abolished ovulation over a two-year period (*213*). Among the compounds shown to produce pharmacological activity after diffusing through a silicone rubber barrier that has been implanted parenterally or inserted into the bloodstream are amines such as DL-epinephrine, L-phenylalanine, histamine, atropine, and piperazine; steroids such as estradiol, progesterone, testosterone, and cortisol; and gaseous anesthetics such as ether, nitrous oxide, and cyclopropane (*211*).

It has not been practical to extend the action of a single injection of a depot insulin beyond the period of a day because of the uncertainty of resorption into a variable vascular bed. Depots designed to release a fixed amount of hormone over days, weeks, months, or years constitute a considerable hazard if conditions develop in which all of the depot is released at one time. With the silicone rubbers, the problems of disintegration, uptake of lipids, foreign body reaction, and local vascular changes will have to be met if parenteral implantations are to be effectively used in humans.

Under study are a plastic device that glaucoma patients may insert under the eyelid to release impregnated pilocarpine for a uniform release during 24 hours, and a polymeric intrauterine capsule that releases a reservoir of enclosed progesterone during a year. The released progesterone is completely metabolized by the uterus, so the menstrual cycle is not affected. The polymers comprising these devices were not identified (*214*).

Silicone Carcinogenesis

A solid-state silicone surface will produce local sarcomas when implanted in rodents, as do all solid-state surfaces (*53, 14*). The question whether this effect is solely related to the solid state or reinforced or inhibited by local chemical effects is best evaluated by studies with liquid silicone. A summation of the extensive safety testing for silicone rubber and gum (*11, 16, 17*) in rodents is of special interest because the surfaces involved are not rigid. With a rubber that had a tendency to crumble at the subcutaneous site, two epicardial mesotheliomas in addition to local sarcomas, 10/30, were found in rats. A similar tumor type, a pericardial mesothelioma, was induced in a mouse by intrathoracically injected diatomaceous earth (*1*). The induction of mesotheliomas remote from the test site is possibly an example of chemical carcinogenesis, whereas the local mesothelioma associated with diatomaceous earth injection would relate to physical carcinogenesis. Also of interest is the correlation of high local tumor yield with a low inflammatory response as elicited by silicone rubber, *viz.*, the potential carcinogenic role of inhibited inflammatory activity (*215, 57*). Most experiments with liquid silicone were not carried out long enough to evaluate carcinogenic potential (*11*).

Long-term effects, including the carcinogenic, of injected Dow Corning 360 dimethylpolysiloxane medical fluid of 350 cSt viscosity were studied in both Long-Evans rats and Marsh mice (*21, 192*). Each experimental group was comprised of 36 to 76 animals of one sex with an equal number of littermate controls receiving the same volume of isotonic saline at the same site. The injections were made at 2-3 months of age and the experiments were terminated 17 to 21 months after dosage, depending on the survival rate assuring an effective number. Effective numbers, those developing tumors plus those surviving, ranged from 22 to 64.

The intraperitoneal route. This route was tested in male and female rats and mice. Female rats received 1.0 ml of liquid silicone, the males 2.0 ml. Female mice received 0.4 ml, the males 1.0 ml. On the basis of effective numbers, 8/34 of the silicone-dosed female rats developed reticulum cell sarcomas in the lung or peritoneal cavity, and one intraperitoneal adenocarcinoma during 17 months. Of 27 controls, one reticulum cell sarcoma and one mixed type arose. For the male rats that were observed for 18 months, the significant trend for the females was not observed: 7/34 lung or intraperitoneal reticulum cell sarcomas for the silicone series, 8/36 for the saline controls and 4/35 for undosed controls. However, the silicone series developed one fibrosarcoma of the lung. In female mice 22 were living 18 months after dosing; 23 saline-dosed controls survived the same period. One malignant

histiocytic proliferation, one fatty degeneration, two instances of extramedullary hematopoiesis of the liver, and one local fibrosarcoma developed in the silicone series; also an infiltration of lymph nodes and a local necrosis with focal calcification. The controls did not show these types of pathological changes. Twenty of the male mice that received silicone intraperitoneally were living 19 months later. For the silicone series, 4/22 lymphoid tumors vs. 1/29 for saline-dosed controls is not significant. Not only was there a lipogranulomatous reaction, but also leukocyte infiltration, calcification, and necrosis were observed at the intraperitoneal silicone dose site. Twenty-one mice showed one or all of these reactions.

The subcutaneous site. This site was studied in male mice that received 0.4 ml of liquid silicone. The mammary-gland site was studied in both female rats and mice, the former receiving a 1.0-ml injection, the latter 0.2-ml injections each in two mammary ares. For the rats the effective numbers for dosed and controls, 21 months after dosing, were 64 and 57, respectively. There was no indication of a carcinogenic effect: one silicone dosed and one control developed breast adenocarcinomas. A local follicular adenoma, akin to a similar clinical entity of women with fibrocystic disease of the breast was probably due to blocking of the ducts by silicone, a deposit of which was encased in a fibrous wall in the center of the adenoma. Local silicone cysts showed a granulomatous reaction. The effective number of female mice that received liquid silicone injections in the mammary tracts was 43. In contrast to the rats, one fibrosarcoma, one spindle cell sarcoma, one pleomorphic sarcoma, one malignant fibrohistiocytic neoplasm, one adenocarcinoma and one hamartomatous epidermal cystic inclusion developed at the local liquid silicone site. No corresponding local tumors developed in the controls (effective number, 51). The adenocarcinoma cannot be ascribed to the silicone because its appearance is characteristic for the colony where mothers are rebred. This carcinoma, however, was riddled with silicone deposits. At the subcutaneous site in the male mice one each fibrosarcoma, neurofibroma, diffuse lymphoma, ulcerating benign hyperplasia of the skin, and heterotopic bone formation developed at the liquid silicone dose site. These manifestations were absent in the controls.

The seven local cancers of mesenchymal origin that developed at the liquid silicone injection site in the mice cannot be attributed to chance because none developed in the controls. A species difference is indicated because such tumors did not occur in the rats. However, in the female rat injected at the intraperitoneal site, liquid silicone induced an increase in lung and peritoneal lymphoid tumors. A similar trend was also observed for the male mice. It is concluded that liquid silicone has a low-grade carcinogenic potential in rodents, the specificity depending upon the site. Qualitatively the response is akin to that of the silicates (see *Tissue Reaction to Liquid Silicone in Rodents*). Note the mesothelioma for crumbled silicone rubber. In silicosis, the phagocyte that engulfs the silica particle in the lung dies; the engulfing process is repeated with ensuing massive fibrosis and ultimate carcinogenesis. At the subcutaneous site in rodents, asbestos produces the local sarcomas of mesenchymal origin. The rupturing of silicone cysts with formation of new ones may be analogous to the traumatic effect of repeated local injections, which leads to carcinogenesis in rodents.

Human Considerations

Food. Circumstantial clinical evidence suggests that foods may take up methylpolysiloxanes when cooked in proprietary brands of cooking oils containing this type of silicone. The effectiveness of anticoagulation drugs like warfarin or phenindione as measured by a thrombotest was markedly reduced at periods during which such foods were ingested by patients (*216*).

Lipid uptake by silicone heart valves. The critical obstruction of Silastic (silicone) heart-valve balls observed in a number of patients is ascribed to the increase in volume of the balls as a result of lipid absorption (*217*). Solubility studies in which the balls were equilibrated in a simple lipid solution similar to human plasma showed a 1.5% maximum volume increase occurred in eight weeks. Larger volume increases were observed in balls after chronic implantation in humans. Analyses for five patients with variant and obstructive Silastic occluders showed total extractable lipids ranging from 6.2 to 16.1%. In analyses of balls which showed a volume increase greater than 1.5%, the lipid distribution was 60-65% cholesterol esters, 15-20% triglycerides, 5% free fatty acid, and 10% cholesterol. Atrophy and fracture of the silicone ball has also been reported in patients more than 21 months after aortic valve replacement (*218*). The effects of curing, addition of a silicon dioxide filler, and the use of other polymers are to be considered in evaluating the biocompatibility of heart valves.

Mammaplasty. Augmentation mammaplasty in humans has depended on the implantation of a prosthesis or the injection of a fluid that has or develops the consistency of body fat. The prosthesis may be a rubbery polymer or a pretilled or inflatable bag filled with liquid silicone. A silicone fluid that gels by some catalytic process, a preformed gel, or a pure liquid silicone have been injected. This technique is now outlawed in the United States. Complications that may arise with the silicone gel include extravasation of blood, lumpy nodular breasts, migration of the gel, silicone mastitis (*219*).

Because liquid silicone has a tendency to migrate from an injection site, additives were introduced to produce more of a local inflammatory reaction, an effect believed to enhance anchoring. The exact chemical nature of the additives has only been inferred—vegetable oils, or possibly mineral oils (*220*). Because liquid silicone takes up endogenous lipids, it would be difficult to establish categorically whether the original injected silicone carried a lipid additive unless its history was on record. A wealth of clinical material demonstrates the serious complications that may arise when liquid silicone is injected locally into human females for mammary amplification (*220-222*). The local tissue reaction would be influenced by the general reaction to a foreign substance, the chemical activity of the silicone, and the relative solubility of endogenous

local tissue and fluid metabolites in the silicone.

Bilateral granulomatous mastitis developed after repeated injections of liquid silicone into two women (*222*). The histiocytic reaction to silicone droplets was similar to that of a paraffinoma. Axillary lymph nodes were affected. Loss of both breasts preceded by a delayed allergic reaction ensued after augmentation with liquid silicone (*220*). A bilateral inflammatory reaction to a polyethylene bladder implanted for mammary augmentation was noted (*222*).

Other uses of silicone. Silicone frames are used for reconstruction of the external ear; numerous adverse reactions with induration and serous drainage have been reported (*223*). Liquid silicone as an artificial lubricant for osteoarthrotic joints of humans was *not* superior to saline. There was no difference in reduction of stiffness as measured with a knee arthrograph. In experiments with rabbits, induced cartilaginous defects did not heal faster when silicone was injected into the joint, and obstruction to lymphatic outflow was indicated by use of a tagged protein for the objective measure (*221*). Emboli of silicone were found in the capillaries of the heart, brain, and kidney in 10 humans who died after open-heart surgery involving perfusion equipment that used a silicone antifoaming agent (*225*).

Bone resorption was observed in 11 of 25 patients who had plastic implants in the chin. Of these showing resorption, silicone rubber was used in seven (*226*).

Silicone rubber tubing as a shunt has been used successfully in hydrocephalus for draining cranial fluid to another part of the body. Two hundred thousand Americans have been so treated (*82*). The tissue reaction to two silicone rubber shunts with the formation of a hyaline collagenized capsule, a typical foreign-body reaction, is illustrated (*1*).

Food Packaging and Polymer Dishware

In addition to the packaging of raw or uncooked foodstuffs, polymers are also used in their storage, protection from bacterial contamination, in keeping them warm, and to enclose them while they are being cooked. Although subject to Federal Drug Act approval, there is comparatively little safety testing of these polymers reported in the scientific literature. Polymers involved with one or more of the above-described purposes include polyvinyl chloride, polystyrene, polystyrene fortified with rubber, nylon, and polyester. Permeability to gases, such as water vapor, and thermal stability have to be considered in designing their application. The parenteral sites of the animal body are surprisingly hostile to the stability of various polymers, as described elsewhere in this review. More information is necessary on the effects of the proteins, fats, and carbohydrates and the other constituents of foodstuffs in prolonged contact with polymers at various temperatures and oxidative conditions. The amounts of unreacted monomer and other ingredients used to induce polymerization or produce the desired product, as well as the decomposition products of the latter are also important.

Routine safety testing by the Food and Drug Administration for phthalate ester plasticizers has not revealed ill effects, but the safety of food-packaging materials containing them will have to be re-evaluated in light of the uptake of phthalate esters in human organs (*227*) (See section on *The Use of Polymers in Clinical Chemistry*.) A sensitive tissue culture test for biocompatibility of plastics extracts the plastic with plasma. Peritoneal macrophages from the rat and calf kidney, as well as chick embryo fibroblasts, are used in the cell cultures to which the plasma extract is added (*228*).

Polyethylene. A scheme for the identification of antioxidants in polyethylenes for plastic food containers uses four solvent systems to simulate food types: water, dilute (3 ml/100 ml) acetic acid, ethanol-water (10:90 by vol), and ethyl ether. Antioxidants from several products tested migrated to one or more of the solvent systems (*229*). Aqueous and oily extracts of commercial polyethylenes such as are found in the home and in the food industry were fed to mice for four weeks. The skin of the mice was then painted with 3,4-benzpyrene. No co-carcinogenic effect was observed in the malignant transformation of the induced papillomas (*230*).

Canadian chrysotile (an asbestos) absorbed oil from polyethylene bags when stored in them. A constituent of the oil was converted to diphenoquinone. The relationship between the weak carcinogenic activity of organic material extracted from the asbestos and the oxidation products of the polyethylene was not resolved (*231*). Although food was not stored in these polyethylene bags, the demonstrated exchange from the polyethylene is relevant to the problem of food packaging.

Polystyrene. A study on the exposure of human volunteers to styrene (*232*) gives some measure of human tolerance. Since intake was by way of the respiratory tract, the test only qualitatively assesses effects of intake by way of the gastrointestinal tract—a possible route involving styrene polymers as food containers. Human subjects were exposed to 23 to 85 μl/l of ethyl benzene or 22 μl/l of styrene for 8 h in a gas chamber. No exhaled styrene and only traces of ethyl benzene were detected in expired air when the vapor-inhalation phase of the experiment was ended; during vapor inhalation about two-thirds of the vapors were retained. Urinary excretion of the hydrocarbons was negligible. The main excretory product for both hydrocarbons was mandelic acid with some phenylglyoxylic acid, also some methylphenylcarbinol for ethyl benzene. Under the experimental conditions the metabolic degradation of these hydrocarbons apparently does not produce harmful end products and only slightly toxic intermediate products. When the exposure to humans exceeded the amount used in the tests, complaints of fatigue, sleepiness, headache, and mild irritation of the eyes and respiratory tracts were observed. Dermatologic lesions in workers exposed to styrene used for the production of resins may be caused by other substances.

See section on *Uses and Abuses of Silicone* for possible effect of silicone in cooking oils.

The Use of Polymers in Clinical Chemistry

Plastic AutoAnalyzer cups. Serum calcium is ad-

sorption on plastic AutoAnalyzer cups for serum storage when the pH of the serum rises above 8.0. More calcium was adsorbed by polystyrene cups than by polypropylene cups. Ten percent of the calcium may be lost under optimum adsorption conditions. If serum is stored at 4°C with minimal pH change, this sampling error is avoided (*233*).

Polymer syringes. Uptake and diffusion of oxygen occurs with polymers such as polypropylene, polystyrene and S.A.N. copolymer. In oxygen tension determination, glass syringes are preferable for blood collection and storage. For true values to be obtained, blood must be injected into the electrode within seconds after it is collected in the plastic syringes. Losses from glass syringes occur at a considerably slower rate (*231*).

Phthalate ester plasticizers. Of the 850 million pounds of phthalate esters currently produced in the United States, plastic manufacture consumes the bulk. Plasticizers like some phthalate esters may leach or even volatilize from plastics. A number of diesters of phthalic acid are used as plasticizers in the manufacture of plastic transfusion packs. Di-(2-ethylhexyl)-phthalate plasticizer was recovered from plasma (11.5 mg 100 ml) stored 21 days in a polyvinyl chloride pack (*235, 236*). The LD_{50} intraperitoneal dose in mice, greater than 75 g per kilo, vastly exceeds the amount a human would receive in a transfusion. Whether the amount of a lipid-soluble plasticizer has any adverse effect when received in a transfusion is not known. Blood from laboratory and surgical tubing for hemodialysis and heart-lung-bypass systems extracted phthalate ester plasticizers (*237*). Plasticizers were also found in the tissues of patients that had received transfusions. The rat liver was able to desesterify butylphthalylbutyl glycolate to glycolyl phthalate; di-(2-ethylhexyl)-phthalate remained intact under similar experimental conditions, but accumulated intracellularly (*237*).

Phthalate ester residues have been found in waters and marine animal life in industrial localities, also in hatchery fish. Toxicity studies indicate that a very low concentration of di-(2-ethylhexyl)-phthalate inhibits the growth and reproduction of the water flea studied. Absorptions in guppies and deaths of zebrafish were produced by food containing phthalate esters (*238*). Di-(2-ethylhexyl)-phthalate, apparently as an optically active isomer of the commercial product, has been identified in the mitochondria of the heart-muscle cells of cows, dogs, rabbits, and rats. Since the liver of rats can synthesize phthalic acid and certain bacteria can esterify it, it is not established to what degree the phthalate ester comes from the external environment (*239*). The toxicology brought to light by the above studies suggests, nevertheless, a re-evaluation of the environmental impact of phthalate esters.

Discussion

This review refutes the myth that the silicones are biologically inert when introduced parenterally into mammals. The local tissue reaction is analogous to that of other polymers with similar physical and chemical properties. The extraction and release of endogenous lipids by silicones involve abnormal shifts in local concentration gradients. The migration of injected liquid silicone and its uptake by the reticuloendothelial system appear rather insidious. Certainly the silicones do not qualify as safe food additives. The human race does not always profit by past experience. In a past era, the debacle following the injection of paraffin for cosmetic effect should have been a warning that liquid silicone, with its similar physical and chemical properties, would follow a similar pattern. Pandering of Madison Avenue to the "little boy" mentality of so many American males must be held accountable for the wholesale tragedy resulting from silicone mammary amplification. In other cultures the hypertrophied female breast is recognized as a disease. At the classical Japanese Kabuki theater it serves as comedy relief. In Ireland "breasts are for babies," and in Argentina, North American females selectively bred for large breastedness may be referred to as cows. The desire of the American female to cater to her infantile boyfriend or husband led to the silicone craze. While the aftermath—deaths by emboli, necrosis, lumpy breasts, and breast amputations after silicone injections—will hopefully sober the exuberance for indulging this form of sexual variance, the genetic outcome of preoccupation with the female breast may perpetuate a race of top-heavy rather than intelligent women. The effect of surgically implanted silicone and other breast prostheses—falling in love with a bag of silicone—is in the same category as silicone injections when related to mental health. Plastic surgery with the organic polymers has reached the dubious state of art where humans can be outfitted with a dog-like penis and pig-like breasts.

The overview of silicone toxicology changed when silicic acid was recognized as an essential body constituent. Because of the close structural relationship to silicic acid, the silicones could conceivably act as blocking agents in silicic acid metabolic processes, as the sulfa drugs block *p*-aminobenzoic acid (*62*). The carcinogenicity of liquid silicone in mice, as described in this review, may stem from such a blocking phenomenon: the metabolic processes dependent upon silicic acid and the cancers derived through silicone both involve cells of mesenchymal origin.

It is rather unique that in cancer testing for polymers there is no disagreement between results of various workers; the objective measure, the production of a cancer, is not controversial. The long latent period for solid-state carcinogenesis in the rodent (*22*) and the rarity of cancers associated with foreign bodies in humans suggest that the life span of most persons after implantation of solid polymers would be too short for them to develop this type of cancer. In humans, the intrathoracic site is more susceptible as evidenced by the high carcinogenic potential of the avascular fibrosis associated with silicosis and asbestosis. Such formations, analogous to the rodent subcutaneous histological foreign-body reactions, are likewise characterized by a long latent period for cancer, 20 to 30 years (*11*). Medicolegal complications probably deter the reporting of some human case histories involving solid-state or chemical carcinogenesis related to implants. The list of cases in this review includes some that were overlooked by earlier reviewers. Much potential clinical material is never followed through, either post-surgically or postmortem.

Reports on the clinical applications of the polymers were often meaningless because they did not identify the exact chemical composition of the polymer used. It was frequently difficult to evaluate the extent of clinical application of polymers as is exemplified by the cyanoacrylates studied for use as surgical glues (*138, 240*).

One surefire means of raising money for cancer research is to proffer the cure or test for cancer—just around the corner. Apparently this funding strategy also works for artificial heart research.

With some notable exceptions, the polymers that have become a part of the human scene do not produce manifestations of acute toxicity. Degradation for any one polymer is slow enough that body defense mechanisms are able to cope with it. However, the sum total of such breakdowns of all the polymers to which a human is exposed could conceivably overtax the defense mechanisms. It is too early in this age of the polymers to assess whether such an insidious process will be forthcoming. With polymer dishware, unforeseen complications may occur with uses to which they may be inadvertently subjected and for which they were not designed:

- microwave heating of materials not designed for high temperatures
- acidic foods or beverages stored in non-acid-resistant materials
- alcoholic beverages placed in alcohol-extractable polymers
- dishwashing in strong detergents and high temperatures of material designed for "throwaway" after one use

Volatile plasticizers from polyvinyl chloride upholstery used in cars have been held accountable for the fogging of car windows as shown by gas chromatographic analysis of windshield deposits (*241*). The plasticisers act as binders for airborne materials. The effects on humans who inhale these plasticizers is a matter of concern.

Summary

Linkages vulnerable to hydrolysis contribute to polymer breakdown in vivo and depend on the hydrophilic nature of the polymer. Free radicals in tissue metabolism may induce rupture of a carbon-to-carbon linkage, as in the polyethylenes. Oxidation reduction reactions involving alcohol and aldehydes, degradation reactions such as decarboxylation, and cleavage of double bonds are possible. Tagged polymers demonstrated breakdown after implantation in rodents.

All organic polymers tested as solids with smooth surfaces of critical size produced solid-state carcinogenesis at the rodent subcutaneous site. At the subcutaneous site, humans are not as susceptible as rodents to this type of cancer; human serous membranes are. Free radicals in polymers do not appear to constitute a carcinogenic threat. A polyvinyl chloride acetate copolymer, vinyl chloride, polycaprolactam, some brands of Teflon, and liquid silicone acted as chemical carcinogens in rodents.

The factor limiting effective continued use of the artificial kidney probably is the washing out of constituents essential to normal metabolism. Crucial problems with heart-assist devices and artificial hearts involve clotting and destruction of cellular elements of the blood. Polymer prostheses physically and chemically akin to adjacent cellular components risk an autoimmune reaction ending in a rejection phenomenon.

Polyvinylpyrrolidone plasma extenders tested in rodents produced thesaurismotic reactions. In humans receiving a fraction, liver lesions occurred. The storage of polyvinyl alcohols in the body was similar to that of the polyvinylpyrrolidones; some produced anemia and vascular lesions in rats. In rodents, safety testing for human cancer is inconclusive.

Safety testing for polyethylene intrauterine contraceptive devices demonstrated the usual solid-state carcinogenic effect at the subcutaneous and intraperitoneal sites. The intrauterine response—endometritis, squamous metaplasia, and carcinoma—appears to be characteristic of foreign bodies in the rat at this site.

In contrast to self-curing methylmethacrylate resins used as bone cements, rapidly polymerizing alkyl-2-cyanoacrylates and prepolymer polyurethanes have not found extensive clinical application as tissue adhesives. Toxicological problems relating to methylmethacrylate at the time of application need further resolution both for patients and surgical staff. Once successfully installed, the long-term results are promising. No chemical carcinogenic effect was noted for the monomer in safety testing.

Polytetrafluoroethylene used at high temperatures or its contamination of cigarettes can produce a polymer fume fever in humans inhaling the pyrolysis products. Safety testing of polytetrafluoroethylene produced a variable response, indicating a chemical carcinogenic effect for some products.

The uptake of endogenous lipids has limited the usefulness of silicones as heart valves. Similar uptake by liquid silicone depots correlated with a local carcinogenic response in mice. A wealth of clinical material demonstrates the serious complications possible from local liquid silicone injections for mammary amplification in women. Bone resorption has followed silicone implants in the human chin. Liquid silicone is phagocytized by cells of the reticuloendothelial system.

Long-term adverse effects from polymer food wrappers and dishware are yet unknown. The toxicity of phthalate ester plasticizers in some packaging materials needs re-evaluation. The antioxidants contained in some polyethylene food containers are extractable under certain conditions. Since styrene is toxic to humans at critical concentrations, the long-term effects of using polystyrene dishware should be appraised.

Polystyrene and polypropylene AutoAnalyzer cups used for serum storage may adsorb calcium at a pH above 8.0. Glass syringes are preferable to some polymer syringes for collection and storage of blood for oxygen tension determination. Phthalate esters in polyvinyl chloride transfusion packs have been recovered from stored plasma.

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