SPECIAL REQUIREMENTS FOR PLASTIC DEVICES

By

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ABSTRACT

The safety testing for polymers in contraceptive devices already in use, at the human pilot test stage, or proposed is appraised. At the subcutaneous and intraperitoneal sites in the rat, polyethylene did not demonstrate chemical carcinogenicity; in the uterine horn endometritis was a prelude to epidermoid carcinoma development. In rodents, polyvinyl chloride copolymer, vinyl chloride, liquid silicone, and other polymers may respond as chemical carcinogens. A polyvinyl chloride resin produced local uterine squamous cell carcinomas in rats and leiomyosarcomas in mice. Intrauterine implants produce a characteristic foreign-body reaction in all species studied, including man, and secondary infection in rats and mice. Solid-state carcinogenesis can no longer be regarded as a phenomenon exclusive for rodents. Because it depends upon a minimum implant period in situ and a long latent period, its appearance in humans should occur only after many years and only if the implant has resided more than temporarily.

When safety testing fails because of differences in response between species and/or anatomical test sites, evaluation of the effects of polymers already used for other purposes in humans and over long periods of time may be a necessary recourse. The tendency of the silicone prosthesis to mechanically erode its way through body tissues and to absorb lipids suggest general lack of biological inertness.

The development of a fibrous capsule around parenteral implants may decrease metabolic exchange and limit the use of polymer-hormone depots.
Introduction

This review covers synthetic organic polymers, inorganic macromolecules such as metals in solid form, and silicones – organic-inorganic hybrids. In contraceptive safety-testing, polymers present special problems not shared by the oestrogens and progestins. Normal body steroid hormones or chemically related steroids are readily transported to their target sites and metabolized in due order. Polymers fated to a long sojourn at the deposition site are essentially in a mutually hostile environment. The relative damage of this environment and the polymer to each other is assessed in safety-testing. Steroids are prepared mostly in pure form with no deleterious contaminants; polymers may contain plasticizers, fillers, stabilizers, catalysts, antioxidants, inhibitors, suring agents and unreacted monomers. Some monomers are quite toxic. When steroids are rendered highly insoluble by esterification or other chemical modification and can form depots by virtue of this insolubility, they tend to share more of the problems concerned with the polymers.

The dilemma in testing for carcinogens

The chemical carcinogens

The negative tumorigenic response of the rhesus monkey to a number of the classical "carcinogenic hydrocarbons" is a serious challenge to the whole concept of safety-testing for cancer (Food Protection Committee 1960). The rat was more sensitive than the mouse, the guinea-pig and hamster were resistant to the production of carcinoma of the breast induced by the carcinogenic hydrocarbons (Huggins 1961). The stimulus required for malignant degeneration by the carcinogenic hydrocarbons is present in the rodent but lacking in the primate (Bischoff 1969) although the locally induced fibrosis is the same for both (Vasiliev et al. 1962).

Other differences in response between species, strain, young and old, and sex relate to the oestrogens. The higher breast-cancer rate associated with human fibrocystic disease is ascribed to endogenous progestin inhibition resulting in continuous endogenous oestrogen stimulation (Bischoff 1969). About 20% of human male cancer of the breast is associated with gynaecomastia caused by the inability of the liver to destroy oestrogens (Gilbert 1933). Exogenous oestrogen, as in the treatment of carcinoma of the prostate and formerly for the treatment of cardiovascular disease, may be a cause of breast cancer in the male (Bischoff 1969). There is little evidence that exogenous oestrogen treatment of the human adult female produces breast cancer (Bryson & Bischoff 1969); however, adenocarcinoma of the vagina in young women whose mothers received stilboestrol treatment during their foetal development
illustrates the factor of age (Folkman 1971) and carcinoma of the endometrium linked to oestrogen-producing neoplasms, the factor of site (Bischoff 1969). A rat strain which may be resistant to dimethylbenzanthracene, may be more sensitive to oestrone in the production of carcinoma of the breast (Bryson & Bischoff 1969). Oestrogen administration to C57 mice was non-tumorigenic (Shimkin & Andervont 1942).

Carcinomas induced by foreign bodies (solid-state carcinogenesis)

In rodents implants of critical size and texture composed of highly inert substances such as tin, gold, platinum and dotriacontane produce local sarcomas (Bischoff 1972). More reactive substances including polymers also produce this effect under comparable conditions, but a combination of solid-state and chemical effects must be considered. Thus intramandibular carcinomas in mice were produced by introducing hair, steel wire or Nylon threads into the alveolar pockets (Hollander & van Rijssel 1963), as were adenocarcinomas with glass tubing introduced into guinea-pigs’ gallbladders (Petrov & Krotkina 1947). Squamous carcinomas arose from cyst walls produced by dermal penetration of grass seeds in Merino sheep (Carne et al. 1963). In rats and mice the smooth shell of Cysticercus crassicolis led to sarcoma formation (Dobberstein 1960).

Calcifying epitheliomas, arising from sebaceous or cutaneous cysts (Bischoff & Bryson 1964), and scar cancers in the lung may be associated with cholesterol crystal deposits (Rössle 1943). Carcinoma of the human gallbladder is correlated with gallstones (Moore 1945).

Previous work on polymer safety-testing

Polyethylene

At the subcutaneous site in the rat, local sarcoma production was correlated with the magnitude of continuous polyethylene surfaces of loops, spirals, sheets (Southam & Babcock 1966), powder or textile (Oppenheimer et al. 1955). Comparison between commercial polyethylene containing a plasticizer and pure polyethylene showed no difference in effect (Oppenheimer et al. 1952; Bering et al. 1955). Threshold size for solid-state carcinogenesis (under 10% sarcomas) (Shulman 1963) and the effect of packing shreds which contributed to a local continuous surface (Carter & Roe 1969) were demonstrated. In summation, these studies did not indicate chemical carcinogenicity for polyethylene.

At the intraperitoneal site in the rat, local sarcoma yield was correlated with surface area in a comparison of powder, cubes, disks, and films of polyethylene. The minimum latent period for cancer development was 13 months.
(Hueper 1961). No sarcomas arose in experiments carried only to 12 months (Bridges & Whitting 1966).

**Local tissue reaction in the rat and rabbit.** Pronounced fibroblastic activity with adhesions to the omentum ensued when ulcers were covered with polyethylene sheeting at the rat parietal peritoneum (Bridges & Whitting 1966). When the fundal portions of sterilized polyethylene intrauterine devices (IUD’s) were introduced directly into the peritoneum of rabbits or by way of the cervix, vagina or endometrium, the typical reaction was adhesion formation. Initially 70% of the devices migrated in the peritoneal cavity before becoming anchored (Echenberg & Ledger 1968).

**The intrauterine site in the rat.** When portions of IUD’s consisting of stainless steel or polyethylene were introduced into the uterine horn of groups of 100 young rats, 6 and 5 epidermoid carcinomas, respectively, developed locally in those surviving over 19 months (Corfman & Richart 1967). Endometritis and endometrial squamous hyperplasia were a prelude to carcinogenesis.

**Miscellaneous polymers**

*Polyurethane or butadiene carboxylate latex administered* intravaginally in repeated doses into CC 57W female mice as sponge particles produced pre-malignant changes in the uterine cervix and vagina for both groups with possible malignant transformation with the carboxylate (Vol’fson 1969).

*Stainless steel.* As contrasted with continuous polyethylene surfaces which produced local subcutaneous sarcomas in rats, stainless steel rings with discontinuous surfaces were not tumorigenic (Southam & Babcock 1966) whereas other steel rings were (Corfman & Richart 1967).

*Polyvinyl chloride.* In three species of rodents, a mixture of polyvinyl chloride resin and melted paraffin was injected or inserted on impregnated tapes of cotton or strings of silk into the uterus. The paraffin-polyvinyl chloride was not carcinogenic in the rabbit. Five squamous cell carcinomas appeared in twelve rats impregnated with the coated strings; in 14 mice no local uterine carcinomas but four leiomyosarcomas arose (Baba & von Haam 1967). In 14 rats one leiomyosarcoma developed when strings coated only with paraffin had been placed in the uterus; marked pyometra was noted in 8 (Baba & von Haam 1971). Vinyl chloride acts as a chemical carcinogen (Viola et al. 1971) and polyvinyl polymers or copolymers are not inert (Bischoff 1972).

**Silicone**

The polyvinyl chlorides and similar polymers have inorganic groups which are not part of the polymer skeleton as they are for the silicones. The struc-
tural similarities between the silicones and the silicates suggest that the silicones could block silicic acid in essential metabolic processes (Bischoff 1972) such as periosteal and endochondrial calcification (Carlisle 1972).

**Lipid solubility.** The uptake of lipids by silicone heart valves (McKenry et al. 1970) in chronic human implantations was greater in some patients than in *in vitro* equilibrations. Variant and obstructive silicone occluders showed total extractable lipids ranging up to 16.1%. In rodents, injected liquid silicone took up cholesterol and Δ4-3-keto steroids. Measurable amounts of carotene, cholesterol, cholesterol palmitate, olive oil, progesterone, testosterone and tri-palmitin (Bischoff 1972) were determined in solubility studies with liquid silicone at 38°C.

**Carcinogenicity.** A solid silicone surface of critical area and texture, as all solid-state surfaces, produces local sarcomas when implanted in rodents (Nothdurft 1961; Oppenheimer et al. 1955). Whether humans will respond in a similar manner remains to be seen. For polymethylmethacrylate, a local human chondrosarcoma developed 16 years after spheres were implanted as plombage (Thompson & Entin 1969); for a Teflon-Dacron prosthesis used to repair an arterial laceration (Herrmann et al. 1971), a local fibrosarcoma developed 10.5 years after implantation. A number of local neoplasms have been reported after mammary amplification with prostheses (Bischoff 1972). A study of six cases of human cancer of the breast previously implanted with materials used for mammary amplification lists polyvinyl alcohol, polyurethane, silicone sponge, silicone gel and silicone liquid as implant materials (Minakawa & Kudo 1971). In a series of 93 patients, one carcinoma arose at the injection site of an unidentified fluid used for mammary augmentation (Ortiz-Monasterio & Trigos 1972).

In Marsh mice, six local cancers of mesenchymal origin developed following injection of liquid silicone subcutaneously, with none in control series (Bischoff 1972). In rats no neoplasms developed at this site. However, when given intraperitoneally, increases in lung and peritoneal lymphoid tumours occurred in female rats. In addition to 10/30 local sarcomas produced by silicone rubber implantations at the subcutaneous site in rats, two epicardial mesotheliomas arose (Hueper 1961). In conclusion, besides the solid-state carcinogenic effects of silicone, there is evidence for a chemical carcinogenic effect.

**Phagocytosis.** The uptake of liquid silicone by macrophages and other cells was observed in mice (Rees et al. 1967), rats, baboons (Rees et al. 1970) and humans (Andrews 1966). Polyvinylpyrrolidone in colloidal solution was taken up by phagocytes in mice, rats and rabbits (Hueper 1959).

**Local tissue reactions.** Induration and serous drainage with silicone frames used for reconstruction of the external human ear (Curtin & Bader 1969) and
bone resorption at the site of silicone implants in the human chin have been reported (Robinson 1972). With liquid silicone mammary amplification, skin necrosis (Perlman 1965) and mastitis (Symmers 1968) among other complications have been observed. An adverse characteristic of silicone used for the reconstruction of body parts is a tendency of “mechanically eroding its way through body tissue” (UPI, San Francisco 1972). This may relate to silicone’s chemical resemblance to silicic acid and illustrates a problem created with substances which resemble adjacent cellular constituents at the implant site (Bischoff 1972).

A benign biologic response attributed to the chemical inertness of polydimethylsiloxane is challenged on the basis of observed damage to nervous tissue. At the vitreo-retinal interface, liquid silicone would create a two-phase system promoting water swelling with disruption of mitochondria cristae (Mukai 1971).

Silicone rubber tubing used as a shunt in treating hydrocephalus evokes the typical foreign body reaction with formation of a hyaline collagenized capsule (Bryson & Bischoff 1969).

When safety-testing fails

When the responses at a particular anatomical site for humans and the test animal are at variance, another anatomical site which manifests analogous responses may be considered. Thus, cellular reactions during inflammation at the serous membranes in humans resemble those elaborated by foreign body surfaces at the rodent subcutaneous site (Bischoff & Bryson 1964).

In many instances materials considered for intrauterine devices have been used clinically at other sites over long periods and for large statistical populations. In considering steel and other metals and alloys at the intrauterine site, there is the experience with metal heart valves (Reis et al. 1970), bone prostheses (Bischoff 1972), bone nailing (Bauer 1960), embedded shrapnel and other metal foreign bodies. The reaction of the human uterus to foreign bodies is known. Discounting any difference between the effect at the intrauterine biologic environment and that at the other body sites already tested remains a risk.

The myoma, being of mesenchymal origin, bears some similarity to pathologic fibrosis although in this case fibroblasts are not involved. Leiomyosarcoma may begin in a myomatous uterus. Endometritis is sometimes associated with submucous myoma as well as being a possible sequel to intrauterine contraceptive devices (Novak & Woodruff 1967). Sarcomas arising from surgical scars (Ju 1966), sarcomas, related to osteitis fibrosa, osteitis deformans or
fibrous dysplasia of the bone (Schwartz & Alpert 1964), carcinoma of the liver associated with cirrhosis of the liver (Gall 1960) and with haemochromatosis, as well as lung cancers related to tuberculosis scars and pneumoconioses (Bryson & Bischoff 1967) illustrate a possible aetiology related to pathologic fibrosis.

The lumen of the bladder in mice has produced positive tumorigenic results with foreign-body implants, without complications such as the endometritis and pyometra that beset the intrauterine experiments. Pellets of paraffin, stearic acid, or cholesterol when introduced in the lumen of the bladder produced carcinoma of the bladder with varying incidence up to 9% in experimental series of 34 to 89 (Clayson 1966). The solid state is implicated as the aetiologic agent with the bladder epithelium serving as the carcinogenic locus.

Chronic endometritis was noted in 17% of a series of women with intrauterine contraceptive devices (Rozin et al. 1967). The Gräfenberg ring produced chronic inflammatory responses (Jessen et al. 1963). Endometrial biopsy of 518 Japanese who were wearing or had worn intrauterine devices over periods as long as 16 years, indicated only a slightly higher incidence of inflammatory changes as compared with 75 controls (Hata et al. 1969). In 210 women aged 17 to 46, using IUD’s endometrial biopsy showed endometrial hyperplasia in 9 and proliferative or secretory conditions involving infiltration of lymphocytes or polymorphonuclear leukocytes in 27 (Rimdusit et al. 1970). Stromal oedema beneath IUD’s sometimes with a fibrous reaction was noted (Bonney et al. 1966). Of 1240 women subjected to endometrial biopsy, 5.3% showed chronic endometritis (Dumoulin & Hughesdon 1951) associated with conditions as varied as pregnancy, abortion, tuberculosis, endometrial or fibroid polyp, foreign body, or chronic salpingitis. A non-specific foreign body reaction to intrauterine implants was noted for all species studied and relates to the antifertility mechanism. Inflammatory cells in the endometrium and/or uterine fluid are associated with biochemical changes in the uterus. Mice and rats are subject to secondary infections with intrauterine foreign body implants in contrast to rabbits (Sahwi & Moyer 1970).

Our involvement in the problem

Our interest has focused primarily on polymer carcinogenesis, hormone release simulating physiologic conditions (Bischoff 1972) and hormonal interplay (Bryson 1971). Our test animals have been mice, rats and rabbits. The desirability of tree shrews as small primates comparable in size to the smaller rodents was offset by their irascible nature both to humans and each other. Larger primates because of their cost and longer life span are not practical. The process of safety-testing is longitudinal; the test animal must be followed

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throughout its normal life span. The number of experimental animals must be sufficient for statistical analyses. The exhaustive short-term (two or three years) study of a few primates may be appropriate for metabolic studies but does not satisfy the requirements for safety-testing.

The sites studied by us were the subcutaneous (including mammary tracts), intrathymus, intraperitoneal, intrathoracic and intracerebral. Control of even minute intervening variables is crucial. With implants, there are surgical controls subjected to the same surgical manipulations, viz., incision, exploration and suturing. With mice, the number of animals per cage has been shown to be crucial (Chouroulkov et al. 1969). Endometrial sarcomas and mammary carcinomas were significantly more frequent in isolated mice than in those caged in groups of 10. Isolated mice show behavioural disturbances such as aggressiveness and irritability. The endometrium and breast are endocrine linked, and isolation effects the pituitary-gonadal-adrenal axis (Bryson 1971).

Publication in Federation Proceedings, Proceedings of the American Association for Cancer Research, Research Communications in Chemical Pathology and Pharmacology, and Abstracts of Papers presented at American Chemical Society Meetings has achieved our goal of rapid communication of pertinent safety-testing data and human studies. Because safety-testing data are dispersed over such a wide area of publications, some data get overlooked.

The over-all approach

It is to the interest of industry to assess the clinical value of any product which it has developed. Distribution of new material for assessment to clinicians at large does not invariably net meaningful results, because of uncontrollable variables in the every day patient-doctor relationships. Industry by employing physicians especially trained or gifted for conducting clinical trials under rigidly controlled conditions can achieve the same standards as government agencies or university medical schools. It is important to have checks and balances between industry and governmental regulatory agencies.

As an ideal, acute tissue and organ toxicity, chronic tissue and organ toxicity, carcinogenicity and mutagenicity should be tested before pilot clinical trials. Since the longer life span of animals such as dogs and monkeys would delay the completion of clinical trials for a considerable number of years, it is necessary to take a calculated risk; particularly so when the urgency, as for effective contraceptive devices, is world wide and of high priority. Pilot clinical trials would thus begin after a two to three-year test period on rodents. Because of the limitations of safety-testing, new products will inevitably involve calculated
risks. Ultimately, past experience based on related phenomena is a necessary and reliable criterion.

Regulatory standardization of toxicity requirements for any new contraceptive product should be flexible, regardless of type, and dependent upon the exact chemical and physical nature of the device. A type may be an intrauterine depot reservoir releasing a hormone or hormone-like material. The depot reservoir and the hormone present independent problems. In cases where these problems have already been resolved, safety-testing would focus on the combination.

The clinical experience with various heart valves indicates the difficulty of predicting polymer wear at inherently hostile body sites before actual clinical trials (Bischoff 1972).

**Contraceptive devices considered**

In lieu of the “pill” there have been a number of alternatives involving uniform release of steroid hormones over comparatively long periods from subcutaneous or intrauterine implants of a polymer depot containing the steroid. To be considered are the local sarcomas which arise in mice at the subcutaneous injection site of steroid hormones, whether through local irritation (Loeb et al. 1937) or non-specific stimulation of cellular proliferation (Lacassagne 1937). The intrauterine depot has the theoretical advantage that the amount of required hormone is small enough that extraterine increases of this hormone need not occur.

The development of the fibrous capsule around the implant is a problem. In dogs, a silicone rubber capsule containing triiodothyronine and isoproterenol implanted in the myocardium demonstrated a pacemaker’s effect for only a week. Implantation to another area after removal from the fibrous capsule restored the activity (Folkman & Long 1964). In sheep, intramuscularly implanted silicone capsules containing melengestrol acetate were effective for two years in preventing ovulation (Dziuk & Cook 1966). In a preliminary short-term study in human females implanted with subcutaneous silicone capsules containing a synthetic progestin to be released in micro quantities, no serious local or systemic complications were noted (Tatum 1970).

A uterine contraceptive progesterone system is being investigated (Alza Corporation 1973). A polymer impregnated with progesterone serves as a core with a barrier of ethylene copolymers in this T-shaped device. The release of 50 micrograms of progesterone daily has been demonstrated for a year. The uterine capsule is smaller and softer than conventional intrauterine devices (Alza Corporation 1971).
Chemical methods of fertility control by introducing chemicals into the Fallopian tubes, cervix and vagina (Battelle Memorial Institute 1973), a progestin released from a vaginal ring (Mishell 1972) and injection of liquid silicone into the Fallopian tubes to block passage of sperm by forming a rubbery solid are being investigated. The latter has been tested on rabbits and monkeys and awaits clinical trial (Franklin Institute 1973).

In rats, the subcutaneous implant must remain in situ during a critical period, about 1/5 the life span, for sarcomas to develop. Removal of the implant after this period does not prevent the development of a sarcoma in the fibrous capsule many months later; the mean latent period is 50% of the life span. In humans, mesotheliomas arising at the site of asbestosis (Wagner 1959) and pulmonary scar carcinomas related to an embedded foreign body (Strauss et al. 1963) have long latent periods, about 30 years. At other human sites, foreign-body-induced cancers had latent periods in the 10-year range. An implantation period of a year or less for contraceptive devices involving plastics would likely be too short for solid-state cancer to develop. However, repetitive implantations may have an accumulative effect.

A false sense of security may arise from the implication that adverse effects of polymer implants are predictable with the sophisticated tools of science, without validation by long-standing experience through the ages. Synthetic polymers may have raised more ethical problems than chemical ones, not only in terms of safety but of application. Fertility control has centered on the refinement of contraceptive methods. The use of reproductivity by the vested interests of Judeo-Christian agencies (Chisholm 1948) to confer acceptance and status and the system of legal and extra-legal sanctions against non-reproductive sexuality must be reappraised.

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DISCUSSION

Goodman: I would like to comment on the previous paper primarily from the standpoint of a polymer chemist. I cannot make valid remarks concerning the nature of the pathological effects described. In our laboratories at the University of California, San Diego, we are concerned with the synthesis and characterization of organic polymers prepared in a traditional manner from highly purified monomers. We are primarily interested in biopolymers and biomedical materials.

This paper comes across to me as bad polymer chemistry. Materials are inadequately described. Numerous effects are included which cannot be related to the polymer systems used. In the section on polyethylene, variations of the form of the polyethylenes and resultant effects are presented. Polyethylenes can differ substantially from each other. Stabilizers, antioxidants and other additives may or may not be present. The structures of these organic molecules can be very different in polyethylenes dependent upon the molecular characteristics of the polymer. This reader

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cannot deduce scientifically valid generalizations from the diffuse discussion about the polyethylenes. No explanation is included to establish the nature of the commercial polyethylenes or the so-called pure polymers. What is meant by “pure”? Is it really reasonable to compare stainless steel devices with polyethylene and deduce pathological effects attributable to the device?

The sections on miscellaneous polymers are presented in a confused manner. Polyurethane and the latex are said to produce pathological effects. The nature of the polyurethane and the latex are not given. An effect is included based on stainless steel where construction appears to be important. Once again we have no amplification concerning the chemistry of the polyvinyl chlorides employed. Categorical statements are included about vinyl chloride monomers and polymers which are unsupported. What is the meaning that polyvinyl polymers are not inert? (See page 299).

Silicones vary in structure and properties. As in other sections of this paper, results are given as if there was just one silicone polymer. We are presented with numerous effects, some of which have nothing to do with carcinogenicity, such as the uptake of lipids by silicone heart valves. The authors fail to point out that while this may happen in some cases, the silicone-based heart valves do indeed work and help many people live longer as functioning people.

The authors are taking a shotgun approach, bringing into question many aspects of the use of synthetic materials for medical applications. Many of their deductions are based upon ill-defined materials or commercial materials simply taken from the shelf. Their premise that the purity of the polymer plays little role in the production of pathological effects is unsubstantiated. Their belief that polymers which are similar to natural macromolecules are intrinsically deleterious is also not supported by solid scientific evidence. It is not sufficient to refer to a United Press International (San Francisco) news release of 1972, in which an effect is described and pathological consequences implied. Such evidence is less satisfactory than full, detailed accounts in reputable scientific journals. I am not questioning the right of the San Francisco Chronicle or any other representatives of the media to investigate and report on scientific matters. I am worried that conclusions not based on extensive scientific investigation are promulgated. Biomedical materials play an important role in modern medicine. It is essential to support fundamental research on the understanding of the nature and properties of these materials. It is possible to design and synthesize specific biomedical materials which are biocompatible and effective in terms of the specific use envisaged. I trust that the authors of this manuscript will reconsider their broad and diffuse attack on synthetic polymers. It is not, as the authors suggest (on p. 305), a question of ethics or of vested interests of Judeo-Christian agencies but rather a problem of research and discovery.

Bischoff: I have drawn the structural formulae for polyvinyl chloride and polydimethylsiloxane on the blackboard to score the difference in the position of the inorganic groups of these macromolecules in relation to the polymer skeletons. The silicon-oxygen linkage occurs in the silicone skeleton as well as in the normal body constituent silicic acid. The chlorine in polyvinyl chloride is not regarded as part of the polymer skeleton because cyano or other groups replace it in other vinyl polymers. I think we are not talking about the same thing.

We have quoted two references (Oppenheimer et al. 1952; Bering et al. 1955) in which pure polymers were studied. When this pure polymer was compared with a polymer that contained some plasticizer, both polymers acted in the same way. So we have brought up pure polymers and polymers that are not pure.
Bryson: It is not the intention of this paper to condemn the purity of polymers or the capabilities of the polymer industry in making pure compounds. As a matter of fact, the variety of compounds that we took, as it was suggested, from off the shelf, was not to try to raise the spectre of impurity or chemical complexity, but rather to point out that, pure or not, there are certain carcinogenic mechanisms related to a non-specific phenomenon called solid state carcinogenesis. I think Dr. Goodman has missed the major thrust of this paper if he has centred upon the issue of purity, because that was not our issue and in this sense we have no issue. What we are essentially trying to say is that because of the fact that polymers can be made pure and they can be made in ways that resemble body constituents does not preclude the risk of solid-state carcinogenesis. There is a particular hazard when resemblance to natural body constituents produces a phenomenon where there is protein adsorption giving rise to de-naturization and, in turn, to an immune reaction leading to implant rejection. This does not happen when you have a greater degree of difference between the implant and adjacent body tissues. We did an experiment comparing a pure paraffin, dotriacontane, with cholesterol hydrate. The normal body constituent as a solid was rejected to a greater degree than the paraffin which did not closely resemble the body constituent (Bryson & Bischoff 1969). This has been observed to be the case with polymers (Bischoff 1972).

The major thrust of our paper, however, concerning the carcinogenicity issue is the effect of solid-state carcinogenesis, of which we were pioneers. We are stressing here that it is the physical characteristics of the implant in a particular relationship with specific tissue sites that are a hazard, and we would like to alert people to this concept. The hard data base relates to that more than it does to the spectre of impurity.

With respect to the use of popular media, especially the San Francisco Chronicle report, Mr. Perlman was able to get data that the medical profession had been unable to obtain. In terms of interviews with particular persons, he was able to report not only about their subjective feelings about silicone injections, but medical findings which were related frankly to this science writer. Such information has not been forthcoming in the medical literature because the medical profession has been hampered by a possible spectre of malpractice suits in reporting adverse effects in relation to liquid silicone implantation.

Kirton: Earlier, the case of ectopic pregnancies and intrauterine devices was alluded to. Are there any published data concerning the incidence of malformations of offspring born with uterine devices in situ?

Mishell: Yes, in an article by Lewit (1970), reporting results of a long series in which the incidence of congenital defects in infants born with mothers who became pregnant with an intrauterine device in situ was no different than individuals who became pregnant after an intrauterine device was expelled. She concluded that the presence of the intrauterine device did not cause any increased incidence of congenital malformations.

Lei: I would like to show a few slides of endometrial biopsies taken from women wearing intrauterine devices for rather long periods. This work was done by a group of gynaecologists, not by myself. I am not a gynaecologist, so I can only give a brief summary. The two series of clinical observations consist of about 900 cases with polyethylene or stainless steel intrauterine devices, and quite a number of them had the device in their uterus for 5–10 years. In brief, what we could see in the endometrium macroscopically and microscopically, were mainly changes due to pressure from the
Fig. A.
Endometrial epithelium denuded forming superficial ulcer.
From The Capital Hospital, Peking, China.

Fig. B.
Spindle-shaped change of the stromal cells. From the International Peace Hospital for Women and Children, Shanghai, China.
intrauterine devices and some degree of solid infiltration due probably to mechanical irritation. On the whole, the changes were of a mild degree or moderate degree. Changes of an advanced degree, such as necrosis of the endometrial tissue, were relatively uncommon and, if present, were limited in extent. No signs of endometrial malignant changes were ever observed. However, sometimes the epithelium is eroded and denuded, actually, forming a superficial ulcer as a result of the device, as shown in Fig. A.

Again, sometimes, very rarely, as shown in Fig. B, spindle-shaped changes of the stromal cells can be observed.

Our observations lead to the general impression that the polyethylene and stainless steel intrauterine devices may be relatively harmless as far as endometrial changes are concerned. The changes are of mild or moderate nature, and necrosis of the endometrium, if it occurs, is rather limited in extent. Of course, we cannot guarantee that the intrauterine devices are absolutely safe on prolonged use, because the time of observation is not long enough and serious changes might not be evident until some years later, but the gynaecologists feel that it probably may be safe to use the devices for 5-10 years, provided the subject can tolerate it well and has no clinical manifestations.

Tuchmann-Duplessis: Dr. Lei, you have shown us a fair number of biopsies of the endometrium which are very heterogeneous. Fortunately, all the changes are benign changes. Is there a relationship between the variety and severity of the changes observed and the duration of time with the device in utero? Secondly, is there a relationship between the age of the woman and the type of the changes? The most drastic changes I have seen here are the spindle cell reactions (p. 310).

Lei: I am not very much familiar with the details of this work, as this was done by two groups of gynaecologists, as mentioned before, but I have certain impressions. Of course, the time relations exist. The slides I showed are from long-time users. The reactions are of the chronic type. In recent cases, some of the subjects had to have their devices removed after a short period of application, since they showed inflammation or cellular infiltration of an acute type. The cell type is mainly polymorpho-nuclear, and as far as I can remember, the type of changes does not show much difference between different age groups.

Remmer: Does anybody know what is the amount, in plastic devices, of polychlorinated biphenyls, now highly discussed, because we find them in any plastic material.

Goodman: I do not think I could give you a meaningful answer in quantitative terms.

Remmer: Is this compound present in the plastic material which is used as a contraceptive? It is well known that it is eliminated very slowly and can reach toxic levels.

Goodman: I doubt that it is. Such a plasticizer is not used when materials are designed to release drugs. Biomedical materials generally are fabricated without additives.

Benirschke: I would like to come back to the criteria for carcinogenicity. I was surprised about the frequent occurrence of sarcomas and carcinomas after implantation of what seem relatively inert materials. It is often difficult to differentiate local, at times violent, tissue reactions that only look like carcinomas. What criteria were used
to determine if there were carcinomas or sarcomas that arose as results of implants of steel devices into the uteri of rats, etc?

Bryson: In addition to our pathology studies, we have found that these tumours will metastasize if they are disturbed. They are also quite transplantable, for several successive generations of tumours. I would like to stress again that the observation of true malignancy associated with these implants speaks to the mechanism of solid-state carcinogenesis. In addition to being a phenomenon, solid-state carcinogenesis is also being offered as a theoretical construct having implications for safety testing.

In passing, I also wanted to consider the silicone that Dr. Goodman mentioned as having absorbed lipids under abnormal hydrodynamic stresses. In our laboratory we have tested liquid silicone, and it has been shown to take up a variety of compounds under normal atmospheric conditions in equilibration studies. The relevance of this to our discussion here is the fact that not only the breast – in which case silicone has had wide application – but also uterine tissues are very oestrogen sensitive, and variations in local oestrogen concentration caused by these silicone devices are a possible hazard that would not only affect normal metabolic processes but might also have greater effects in terms of drug applications pejorative to their intended design.

Fairweather: First of all, I would like to compliment Dr. Bryson on what is an extremely interesting experimental pathology paper, but this is the reason why I wish to sound a word of warning to the interpretation of such data. To my mind, the pathology contained within this paper is extremely exotic and undoubtedly is part and parcel of a pathologist's dream. It is also reminiscent of the work carried out by Roe et al. (1964) with respect to iron dextran and subcutaneous sarcoma, in which large doses of iron were given locally and at multiple sites producing lesions which at the time incriminated the drug. Therefore, once we see such exotic pathology in animals, such as leiomyosarcoma and indeed malignant plasmacytoma, I am prompted to ask Dr. Bryson, what does he think the relevance of his findings is to man? What would he suggest, what test, what investigation should be carried out during life to predict any of these findings?

Bryson: First of all, your apt criticism of the work on iron dextran relates more to the topic of experimental design than to the production of bizarre pathology. We are not dealing with that. I consider largely resolved the problems of experimental design in the solid-state carcinogenesis experiments. There are also clinical studies, such as the one mentioned with plombage and one of a series of 11 pulmonary scar carcinomas (Strauss et al. 1963) which was not mentioned, but I might mention it now anecdotally. It concerned a person having a broken knife in the chest cavity as a result of a street fight. Later on it was discovered to have produced a carcinoma in the patient, who complained of "stabbing pains". Anyway, there are a lot of clinical corollaries to experimental models with these highly inert substances, and they too offer a warning about long term application of plastics in a biological environment.

With respect to the other part of your question, relating this model to human usage, its practical application has already given rise to an interpretation of asbestos engendered cancer. For many years the oncologists were seeking an explanation for asbestos engendered cancer from the trace elements, maybe minute amounts of iron. Some of the work you cited in respect to the iron dextran was related to studies on iron contamination in asbestos. We suggested through our model that the serous membranes or the pleural cavity behave in an analogous fashion to the rodent sub-
cutaneous test site and that the asbestos fibrosis picture was very similar to the fibrosis picture in general elicited by the foreign body via an inert foreign body capsule (Bryson & Bischoff 1967). This interpretation, relating to the mesotheliomas produced by classical asbestososis, has been largely accepted as the mechanism responsible for asbestos engendered cancer rather than the trace elements (Stanton & Wrench 1972).

Goldzieher: I was a little startled by Dr. Bryson’s remark, which implied that transplantability was necessarily related to malignancy.

I further would like to comment on a relevant situation which happened at an early period of oral contraceptive use. There was a paper from the Mayo Clinic reporting cases of endometrial sarcoma in pill users. It turned out that these were the usual effects of the agents being given at that time, and the histology had nothing whatever to do with sarcoma. It was rather embarrassing. This underscores the problem of the interpretation of histological changes, which I think has been amply discussed.

Frohberg: In addition to the remark of Dr. Fairweather, I would also wish to raise some doubt concerning the relevance of the findings from experiments after subcutaneous implantation in small rodents, because you mentioned, Dr. Bischoff and Dr. Bryson, that different chemical compounds were able to produce sarcomas in rats, for instance. We know, however, also that other compounds and other products, as for instance human bone, are able to produce sarcomas in rats. According to the work done by Oppenheimer and Notdurft, only the physical stage might be responsible (Notdurft 1955a,b, 1956, 1962; Notdurft & Mohr 1964; Mohr & Notdurft 1958; Oppenheimer & Oppenheimer 1948; Oppenheimer et al. 1952; Oppenheimer et al. 1953a,b; Oppenheimer et al. 1955, 1957, 1958, 1959, 1961; Fishman et al. 1961; Oettel 1957, 1958, 1959, 1963; Oettel & Hofmann 1966; Ott 1970).

Bryson: I might point out that one of the ways that we have proposed in getting around the species difference problem is by differentiating between anatomical sites. Histologically-analogous sites in different species may behave similarly. We have suggested that in humans the serous membranes behave similarly to the rat subcutaneous test site. That is one of the ways of getting one’s foot through the door of species difference and still utilizing the rodent’s short life course for safety testing. This need not be an embarrassment, but something upon which to capitalize. In humans, the subcutaneous site with its lengthy history of foreign body inclusions is highly defended against the kind of histological reactions that one sees in small rodents, but at the serous membranes there is an analogous tissue reaction.

With respect to Dr. Goldzieher’s comment about transplantability, this transplantability was also accompanied by the frank clinical signs of invasiveness and the well-known histologic criteria of pleomorphism, mitosis, etc. You do not have the frank ambiguity in these types of sarcomas, in terms of malignancy, as you do with the well-known endometrial situation which is a classic pathologist’s nightmare.

References:


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