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TO: Dr. Watson B. Ackart, BB

DATE: March 30, 1978

RE: Review of Literature
on Polyethylene Toxicity

Attached is a list of articles and abstracts compiled from NLM systems (TOXLINE, TOXBACK, and CANCERLINE) and from Chemical Abstracts back to 1963. In my judgement, based on reviewing these abstracts, there is no evidence of significant hazard. The articles by Kogan, Komarek et al., and Lavorgna et al., relate to the well-known Oppenheimer phenomenon.

The Oppenheimers and others have shown that numerous materials implanted subcutaneously in rats produce tumors (principally sarcomas) which are related to the size and shape of the implant, not the chemical composition. I have a pertinent abstract from CA and a brief discussion by R. E. Eckardt enclosed.

I believe the abstracts in the list are copyrighted. I do not know what implications this has on their use.

Please let me know if I can be of further assistance.



Elton R. Homan, Ph.D.
Group Leader

ERH/jm

Attachments

TOXICOLOGY OF POLYETHYLENE

- 1) Investigation of the Toxicity of High-density Polyethylene Used in the Food Industry and in the Home. Braun, D. D. Gig. Sanit., 1968, 33(6) 34-39 (Russ). No observed physiol. effects were observed during 1 year in which 2 types of lab. animals were fed food and water that had been stored in P4007 polyethylene stabilized with SAO-6 [2,2'-thiobis(4-methyl-6-tert-butylphenol)].
- 2) Possible Cocarcinogenic Effects of Extracts of High-density Polyethylene Designed for Household Use and for Use in the Food Industry. Braun, D. D. Vopr. Pitan., 1968, 27(5), 78-82 (Russ). Aqueous and oil extracts of commercial polyethylene, stabilized by 2,2-thio-bis-4-methyl-6-tert-butylphenol (SAO-6) or unstabilized, were fed to groups of mice for 4 weeks, prior to skin painting with 3,4-benzpyrene (BP). Controls were fed water and oil prior to BP application. The results in all groups were the same. The first skin papillomas developed 12 weeks after the beginning of BP treatment, and the papilloma incidence was 100% after 33 weeks; malignant transformation of the papillomas was first seen in all groups after 24 weeks, and the survival times were the same. Males were more sensitive than females to BP carcinogenesis. It is concluded that these polyethylene extracts had no cocarcinogenic activity.
- 3) Effect of Polyolefin Antioxidants on the Tumor Induction by Benz(a)pyrene. Braun, D. D. Gig. Sanit., 1975, 6, 18-22 (Russ). In a lengthy test carried out on mice, the effect of water and fat extracts of polyolefins (polyethylene of high density, polypropylene), containing maximal quantities of substituted phenol antioxidants was studied on the induction of tumors with benz(a)pyrene. The test was carried out on male and female mice. Indices such as the time of appearance of papillomas, their increase in number and malignization and the length of the animals' life were used. The antioxidants apparently have only an inhibiting effect on the onset and development of the tumor process under experimental conditions.
- 4) Toxicological Studies of Photosensitizer Agents and Photodegradable Polyolefins. Caprino, L., G. Togna, M. Mazzei. Eur. J. Toxicol. Environ. Hyg., 1976, 9(2), 99-103. The plastic photosensitizer 1,1,4,4-tetraphenylbutadiene (I) [1450-63-1], its degrdn. products benzophenone [119-61-9], benzopinacol [464-72-2], and benzaldehyde [100-52-7], and I-activated polyethylene [9002-88-4] had low acute toxicities, had no adverse cardiovascular effects, and were nonirritant to eyes as detd. in animals. The LD50 values of I were >14,000 and >10,000 mg/kg, resp., in mice after oral and i.p. administration.

- 5) Canine Tissue Reaction to TFE-fluorocarbon Resin (Teflon), to High-density polyethylene, and to Vitallium. Evarts, C. M., A. D. Steffee, L. J. McCormack. J. Surg. Res., 1970, 10(2), 91-94. Screws made of Teflon, of RCH-1000 (high-d. polyethylene) and of Vitallium were inserted into the long bones of eight anesthetized dogs and specimens of the affected tissues examined at 3, 5, 6, 7, 10, 12, 13, and 14 months after implantation. RCH-1000, toward which canine tissue had a high tolerance, had suitable phys. properties with regard to strength, elasticity, and hardness, and could be sterilized, offering great promise as a component of the Steffee metacarpophalangeal joint prosthesis.
- 6) Toxicology of Medium-pressure Polyethylene. Kalinin, B. Y. and L. P. Zimnitskaya. Toksikol. Vysokomol. Mater. Khim. Syr'ya Ikh Sin., Gos. Nauch.-Issled. Inst. Polim. Plast. Mass., 1966, 41-47 (Russ). A certain amount of material is extd. from medium-pressure polyethylene (I) by water, causing an increase of the oxidizability of the aq. exts. The migration of reducing agents into water is more intensive at 60° than at 20°. The exts. obtained at 60° contain small amounts of Cr. A single administration of I into the stomachs of white mice in a dose of 2500 mg/kg did not produce any toxic effects. A prolonged intake (over 1.5 years) of aq. exts. of unstabilized I together with the food did not result in any changes in white rats as compared with the control animals. White mice exhibited slight changes with respect to the wt. dynamics and the conditioned reflex activity. No pathol. changes of internal organs of white mice and rats connected with the effect of aq. exts. of I could be observed.
- 7) Assessment of Morphological Changes in the Lungs of Experimental Animals Caused by the Dust of Some Powdered Polymers. Kechetkova, T. A., O. I. Vasil'eva, A. D. Promyslova, A. N. Sergeev. Gig. Sanit., 1971, 36(7), 75-78 (Russ). Pneumoconiosis, gigantic cells which carry out phagocytosis, granulomas, and inflammation appeared in the lungs of rats who had inhaled the dust of certain powdered polymers. Morphol. changes were apparent at 6 months after a single inhalation of dust and were greatest in rats exposed to polyformaldehyde dust, least in those inhaling fluoroplast (polytetrafluoroethylene) dust, and intermediate in severity in rats who inhaled polyethylene or polypropylene.
- 8) Plastic(-induced) Carcinogenesis. Kogan, A. K. Tr. 1 (Pervogo) Mosk. Med. Inst., 1969, 66, 118-123 (Russ). Small capsules of nylon 6, polyethylene, Teflon, polystyrene, poly(Et terephthalate), poly(vinyl chloride), cellophane, rubber, collagen, fibrin, or glass were implanted into 2100 rats s.c. The clin. observation of the implants after 12-27 months showed 34.6% incidence of blastomogenesis. The histol. examination of the abnormal tissues revealed a preponderance of sarcomas and fewer carcinomas and papillomas. The differences between blastomogenetic activity of the tested materials are discussed.

- 9) Tissue Reaction and Neoplasia of Rats When Implanting Polyethylene and its Copolymers. Komarek, J., S. Holanek, M. Nevole, J. Sracek, Z. Nedbal. Acta Vet. (Brno), 1969, 38(2), 183-189 (Eng). Flat plates from a copolymer of polyethylene with vinyl acetate filled with 20% BaSO₄ sterilized with radiation from ⁶⁰Co and from a high-pressure polyethylene were implanted s.c. in 6-month-old rats. After 60 days collagenous fibrous capsules enclosed the polyethylene implants. During 24-month expts. with the polyethylene-copolymer implants in rats, similar capsules were formed; in addition, blastomatous swellings in 3 of 10 rats were found. These tumors were of the same character as the fibroadenoma of mammary glands. The tumors did not appear to have been caused by direct mech. irritation since there was no connection with the fibrous capsules; however, the tumors may have been induced by the residual micro-radiation from sterilization of the copolymer by the ⁶⁰Co. For practical implantation into the subcutis and muscle polyethylene objects are not suitable because of chronic inflammatory irritation.
- 10) Rejection of Metal to Metal Prosthesis and Skin Sensitivity to Cobalt. Munro-Ashman, D., A. J. Miller. Contact Dermatitis, 1976, 2(2), 65-67. Metal to metal prostheses give satisfactory results of 90% of patients. About half of the failure rate may be due to allergic reaction to the metals involved, particularly cobalt. A total of 35 patients in this unsatisfactory group have been patch-tested; 16 were positive to metals, 13 to cobalt, 4 to nickel, and 2 to chromate. Only two patients showed any skin lesions -- one a localized dermatitis round the knee joint from nickel sensitivity, and one to cobalt who had a widespread scattered circular erythematous lesion suggestive of a generalized allergic vasculitis. Patients requiring a metal/metal prosthesis should have a careful history taken for metal sensitivity and be patch-tested with the metals. All the patients in this investigation had metal/metal prostheses and no reaction was seen after metal/high density polyethylene implants. Titanium 318 may be a satisfactory substitute for cobalt chrome alloy if reactions are encountered.
- 11) The Carcinogenesis of Plastics Used in Orthopedic Surgery: An Assessment of the Incidence in Rats and the Possible Relevance to Man. Lavorgna, J. J., N. A. Burstein, A. L. Schiller, W. H. Harris. Clin Orthop. Related Res., 1972, 88, 223-227. High-density polyethylene, methyl methacrylate, epoxy castino resin and glass were studied in terms of carcinogenic activity of implanted solid discs in the abdominal wall of Wistar rats. The incidence of fibrosarcoma formed in those rats surviving 6 months or more was 10% from high-density polyethylene, methyl methacrylate and glass. No sarcoma formed in relation to the epoxy resin. While the constraints upon the interpretation of these data are noteworthy, follow-up data of the effects of implantation of plastic materials in man are too short to be meaningful. Neither is it clear whether this test method in rats should be used for screening plastic implant materials for use in man.

- 12) Ingrowth Kinetics of Bone in Porous High-density Polyethylene. Sauer, B. W., M. Spector, W. R. Flemming. Proc. Annu. Conf. Eng. Med. Biol., 1975, 17, 38. Bone growth into high-density polyethylene (HDPE) implanted in canine femora was minimal after 1 week and restricted to the endosteal region of the implant. (9002-88-4 Polyethylene). However, after 2 weeks significant bone ingrowth had occurred, completely bridging the HDPE pellet in the endosteal region. By 3 weeks developing bone was obsd. throughout the entire implant and after 8 weeks extensive remodeling of the ingrown bone was obsd. In the 8 week implants bone spicules located in the cortical region of the implant were significantly larger than those located in the medullary region in contrast to the 3 and 4 week implants in which there was no difference in the ingrown bone in the 2 regions. Biopsy samples taken from 1 and 2 year specimen indicate that the ingrown bone has been maintained.
- 13) Experience in Sanitary Evaluation of the Use of Polyethylene Pipes for Rural Water Supply Lines. Sheftel, V. O., V. G. Sinitskii. Gig. Sanit., 1973, 38(3), 111-113. Under laboratory conditions, low density polyethylene stabilized by C did not have a significant effect on the organoleptic, physicochemical and microbiological indices of water quality. Over 300 analyses of water from 8 water supply lines were carried out over an 8 year period.
- 14) Preparation and Characterization of Wear Debris of Orthopedic Materials for Biocompatibility Studies. Wagner, C. N., A. H. Shabaik. J. Biomed. Mater. Res., 1976, 10(5), 653-670. In order to test the biocompatibility of wear debris of orthopedic materials, a method has been developed to produce artificial debris of stainless steel, cobalt-chromium alloy, and high-density polyethylene. In this process, called the accelerated rubbing process, two cylindrical blocks of the same alloy were held under normal pressure in triply distilled water. One block remained stationary while the other rotated at approximately 4000 rpm. The water with the metal debris was recirculated between the rubbing surfaces. To prepare debris from polyethylene, a stainless steel block was rubbed over a polyethylene block submersed in liquid nitrogen. The shape of the metal debris was granular, whereas the polyethylene debris had a shred-like shape. The size distributions were determined from scanning electron micrographs, and it was found that the particles of the metal debris (stainless steel or cobalt-chrome alloy) ranged in sizes from 0.1-10 μ with 75% of all particles less than 2 μ in diameter. The size of polyethylene debris, expressed as the volume of an ellipsoid, ranged from 10-20,000 μ^3 with 45% of all particles in the range of 400-2500 μ^3 . The x-ray diffraction pattern revealed that the debris of stainless steel consisted primarily of the face-centered cubic (fcc) alloy with small amounts of body-centered cubic (bcc) alloy and Fe304, whereas the cobalt-chrome debris consisted of the fcc alloy with a small amount of Cr203. The structure of the polyethylene debris was quite similar to that of the solid sample used in its preparation. The percent crystallinity P_c and the size of the crystalline regions D were slightly smaller in the debris than in the solid sample, i.e., $P_c = 52$ and 55% , $D = 90$ and 130 A, in the debris and the solid, respectively. To test the suitability of the artificial debris for biocompatibility studies, stainless steel debris was implanted into knees of adult female New Zealand rabbits. Bacterial challenge studies indicated prolongation, but not increased susceptibility to infection.

- 15) Comparative Evaluation of the Toxicity of Initial Polymer Products (poly(vinyl alcohol), polyethylene, polypropylene) Used in the Preparation of Synthetic Fibers. Zaeva, G. N., V. I. Fedorova, M. D. Babina, and V. A. Shirskaya. Toksikol. i Gigiena Vysokomolekul. Soedin. i Khim. Syr'ya, Ispol'z. dlya ikh Sinteza, Leningrad, Sb., 1964, 34-36 (Russ). A single intraventricular injection of poly(vinyl alc.) (I) in a dose of 5000 mg/kg caused the death of 30% of mice by the 10th-13th day; polypropylene (II) caused no deaths, and polyethylene (III) caused 33% deaths. Dust of I, II, or III caused slight hyperemia in the mucosa of the eyes. Products of thermooxidative destruction of I arrested body weight gain and increased the excitability of the central nervous system; such products from II caused morphological alterations in the lymph follicles around the bronchia and vessels, while those from III irritated the mucous membrane of the eyes and upper respiratory tract. Standards should be established for the gas mixt. of products of thermooxidative destruction formed in spinning synthetic fibers of II and III. A permissible concn. for aldehydes (calcd. on basis of acetaldehyde) in the air is 0.0005 mg/l.
- 16) Hygienic Study of Rubbers Intended for Contact with Food Products. Shumskaya, N. I., K. P. Stasenkova. Gig. Sanit., 1973, (8), 28-30 (Russ). When administered orally to rats at 20-200 mg/kg/day for 6-12 months, neozone D [135-88-6] or golden yellow [49625-2i-0], components of rubber products, showed significant cumulative properties, whereas the cumulative effects of low mol. polyethylene or polyfruit were weak. Trimethylthiourea [2489-77-2] (150 mg/kg/day), antioxidant 4010NA [101-72-4] (50 mg/kg/day), or ionol [128-37-0] (50-500 mg/kg/day) had embryotropic effects when administered orally to rats during pregnancy. The higher the dithiocarbamate level in the tested rubber products the greater was the toxicity of their exts.
- 17) Action of Powdered Unstabilized Polyethylene ND and Polypropylene on Animals. Shvedchenko, V. S. Gig. Vop. Proizvod. Primem. Polim. Mater., 1969, 104-112 (Russ). Powdered Polyethylene ND and polypropylene [9003-07-0] given in a single oral dose (3-7 g/kg) to mice, or in a single intratracheal dose of 50 mg to white rats, or inhaled 100 mg/m³ for 9 months by rats and rabbits showed weak toxic effects revealed in bronchitis, peribronchitis, bronchiolitis and a weak diffused sclerosis of the lungs. A concn. of 8 mu/m³ is considered as admissible for the factory buildings.

Fluorine in urinary tract calculi. J. R. Herman, B. Mason, and I. Light (Albert Einstein Coll. of Med., New York, N.Y.). *J. Urol.* 80, 283-8(1958).—The relation of F to urinary tract calculi was studied. Materials from 100 cases of urolithiasis were obtained and the F analyzed. The F content varied from nil to 1800 p.p.m. and was not correlated with the patient's sex, age, or race. The F content found in different anatomical portions of the urinary tract is not significantly different. If the Ca content of the calculus is 5% or less, the F content is less than 100 p.p.m. The presence of F in urinary calculi is not related to systemic fluorosis.

Oxalic acid excretion in oxalate lithiasis. J. F. McIntosh and M. K. Read (Roy. Victoria Hosp., Montreal, Can.). *J. Urol.* 80, 272-4(1958).—Ca oxalate calculi from 11 patients were hydrolyzed, extd. with Et₂O and titrated with ceric sulfate. The 24-hr. excretion of oxalic acid varied from 21 to 48 mg., the av. 30.1 mg. The results were within normal limits.

Carcinogenesis in the Syrian hamster. Philippe Shubik (Chicago Med. School). *Acta Unio Intern. contra Cancrum* 15, 554-8(1959); cf. C.A. 51, 6828h.—9,10-Dimethyl-1,2-benzanthracene (I) induced melanotic tumors in Syrian hamsters after a single application of 50 γ to the skin, and squamous cell papillomas and carcinomas after multiple applications. Injection or feeding of urethan produced melanotic tumors. I given endotracheally resulted in epidermoid and adenocarcinomas.

The application of wave mechanical methods to the study of the mechanism of carcinogenesis by chemical substances. Odilon Chalvet, Raymond Daudel, and Carl Moser (Pasteur Inst. Radium, Paris). *Acta Unio Intern. contra Cancrum* 15, 577-80(1959).—The electronic charge of the K region of a series of benzacridines correlated directly with a tumor index (% of animals developing tumors/time in days for tumor appearance). In general the more carcinogenic hydrocarbons were more strongly bound to proteins by the K region while weaker carcinogenic or inactive hydrocarbons were bound through the L region or by neither.

Breast tumor formation as a response to graded doses of methylcholanthrene and the effect of this drug on the pituitary glands of rats. Charles Harris, Harry Shay, Margot Gruenstein, and Joseph L. Ciminera (Temple Univ. Med. School, Philadelphia, Pa.). *Acta Unio Intern. contra Cancrum* 15, 595-602(1959); cf. C.A. 51, 10724h.—Oral doses of 2 mg. of methylcholanthrene (I) in 0.5 cc. of olive oil were administered daily. There was no correlation between the duration of treatment, the no. of animals that developed tumors, and the no. of breasts that developed tumors. While 100% of animals given I for 12 months developed tumors, the stimulus may have been submaximal since only 30% of the exposed breasts developed tumors. The wt. of the pituitary gland tended to decrease after prolonged administration of I.

Carcinogenesis by cholesterol and its derivatives. I. Hieger (Roy. Cancer Hosp., London). *Acta Unio Intern. contra Cancrum* 15, 603-6(1959); cf. C.A. 52, 13954a.—Purified cholesterol was variably carcinogenic for subcutaneous tissues of C₃H mice when injected in soln. in lard or olive oil. The following were not appreciably carcinogenic in C₃H mice: Δ^4 -cholestene-3-one, Δ^4 -cholestene-3,6-dione, 6-hydroxy- Δ^4 -cholestene-3-one, and 6 β -hydroperoxy- Δ^4 -cholestene-3-one.

The cigarette smoke-arsenic-cancer of the lung problem. Robert H. Holland, Russell H. Wilson, Antonio R. Acevedo, Mary Sue McCall, Dale A. Clark, and Henry C. Lanz (Southwestern Med. School, Dallas, Tex.). *Acta Unio Intern. contra Cancrum* 15, 608-11(1959).—The As content of American cigarettes was found to have increased 200-600% in the past 25 years, and represents a dangerous impurity of possible etiological significance in relation to lung cancer. Uptake of As⁷⁴ by smokers ranged from 2.2 to 8.6% of the total added to a cigarette as Na₂HAsO₃.

Exogenous and endogenous factors in the pathogenesis of lung cancer. Paul Kotin (Univ. of S. California, Los Angeles). *Acta Unio Intern. contra Cancrum* 15, 613-18(1959); cf. C.A. 50, 17119h.

The induction of leukemia in C₃H1 mice after painting the dorsal skin with short-chain fatty acids, fatty acid esters and with squalene. Friedrich Krenning (Max Planck Inst., Göttingen, Ger.). *Acta Unio Intern. contra Cancrum* 15,

619-26(1959)(in German).—Hexanoic acid, heptanoic acid, mixed decanoic and lauric acids, ethyl hexanoate, or squalene was painted on the skin 6 times a week for periods up to 3 months. A high percentage of leukemic tumors of the lymphocytic type were obtained. Leukemia developing after large doses of x-irradiation to a fold of skin or after application of these compds. appeared later than after whole or partial body irradiation.

Organ culture as a tool in the study of carcinogenesis. Ilse Lasnitzki (Strangeway's Research Lab., Cambridge, Engl.). *Acta Unio Intern. contra Cancrum* 15, 627-31(1959); cf. C.A. 52, 15715f.—A review of the author's studies on chem. modification of growth of tissue cultures.

A correlated histological, cytological, and cytochemical study of the sequence of events in the bronchial epithelium from mice exposed to cigaret smoke. Cecilie Leuchtenberger, Rudolf Leuchtenberger, William Zehrun, and Patricia Shaffer (Western Reserve Univ., Cleveland, O.). *Acta Unio Intern. contra Cancrum* 15, 632-9(1959); cf. C.A. 52, 12182g.—A review of the authors' studies.

The nature of the interaction of biologically active agents with tissue constituents. R. Mason (Univ. Coll., London). *Acta Unio Intern. contra Cancrum* 15, 650-1(1959).—The electronic structure of carcinogen-protein mol. complexes was examd. theoretically and the possibility of charge transfer in the complex discussed. A banded-electronic model of a protein suggests that electron transfer within such a mol. complex will take place only when the energy levels of the mols. of the complex are closely matched. Aromatic carcinogens satisfy a precise criterion for such matching of levels, and carcinogenesis is to be asso'd. with the induction of conducting properties in the protein.

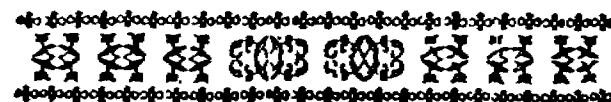
The new test for rapid biological assay of certain carcinogenic substances. S. Neukomm (Romand Anticancer Center, Lausanne, Switz.). *Acta Unio Intern. contra Cancrum* 15, 654-8(1959).—An oil soln. of the compd. to be screened is injected under the skin of the newt's tail. After 6 to 20 days the tail is cut and examd. microscopically. The types of reactions produced are described. The presence of hyperplasia with infiltration is interpreted as a positive result. A fair correlation between the mouse skin sebaceous gland suppression index and the newt test was found for a number of carcinogens.

The mechanism of carcinogenesis by plastic films. B. S. Oppenheimer, E. T. Oppenheimer, A. P. Stout, I. Danishefsky, and M. Willhite (Columbia Univ.). *Acta Unio Intern. contra Cancrum* 15, 659-63(1959); cf. C.A. 52, 6596i.—The chem. compn. of the imbedded plastic was not important, but the phys. form and duration of exposure were crit. Mucopolysaccharide turnover of tissue encapsulating implanted films was higher than that of surrounding tissue.

Metabolic variations within a clone of mouse fibroblasts transformed to neoplastic cells in vitro. Katherine K. Sanford, Benton B. Westfall, Mark W. Woods, and Wilton R. Earle (Natl. Cancer Inst., Bethesda, Md.). *Acta Unio Intern. contra Cancrum* 15, 675-9(1959); cf. C.A. 52, 13943a.—One cell was isolated from a culture of subcutaneous adipose and connective tissue of a male C3H mouse and the resulting clone culture divided during subsequent transplantations to establish 17 independent cell lines. Two lines were selected for study: the 1st produced sarcomas in 1% of mice on injection (low line clone, A) and the 2nd (high line clone B) produced sarcomas in 97% of mice on injection. Two sublines were derived from B. Their arginase activity was 20 and 400 times that of B. The rate of anaerobic glycolysis of B was considerably higher than that of A. Three low-line clones were derived from A. Two of these lines produced a higher percentage of sarcomas in mice than A. A high glycolytic activity in high-line clones correlated with rapid growth of these cells to produce palpable tumors.

The lower glycolytic activities of low-line clones correlated with increased tumor latent periods. Inhibition of anaerobic glycolysis by a fraction of *Podophyllum peltatum* was min. with a high-line clone but increasingly effective with low-line clones, suggesting that differences to antiinsulin hormonal restraints may be a detg. factor in their different growth response *in vivo*.

Morphological alterations in the mouse skin induced by synthesized surfactant-type tumor promoters. Kai Setälä,



C A N C E R S C R O T I.

RAMAZINI has written a book *de morbis artificum*; the Colic of Poitou is a well known distemper; and every body is acquainted with the disorders to which painters, plumbers, glaziers, and the workers in white lead, are liable: but there is a disease as peculiar to a certain set of people, which has not, at least to my knowledge, been publicly noticed; I mean the chimney-sweeper's cancer.

It is a disease which always makes its first attack on, and its first appearance in, the inferior part of the scrotum; where it produces a superficial, painful, ragged, ill-looking sore, with hard and rising edges: the trade call it the foot-wart. I never saw it under the age

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Industrial Carcinogens

By R. E. ECKARDT, M.D., Ph.D., F.A.C.P.

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animals washed five minutes after the oil was applied received greater protection than animals washed six hours after the oil was applied. Even washing six hours after application of the oil did provide some reduction in the potency of the oil, when compared with those painted on their back and washed on their belly. In similar experiments, designed to test whether protective creams provide any real protection, none was demonstrated.

SUBCUTANEOUS TISSUES

The rather lengthy discussion of skin carcinogenesis in the preceding sections may be equally applicable to experimental subcutaneous carcinogenesis and need not be repeated here. There are, however, certain factors specific for subcutaneous experiments which require special mention.

The use of the subcutaneous tissues of animals as a test site in experimental carcinogenesis has few direct corollaries in human cancer, and especially in occupational cancer. In general, human exposures, especially in industry, occur by application to the intact or abraded skin, by inhalation or by ingestion. Exceptions to this occur when various metals or plastics are introduced subcutaneously by the physician as supporting structures for bones or other mesenchymal tissues such as arteries. In this case, the materials are placed in direct contact with the bones or arteries. In addition, subcutaneous or intramuscular administration of medications may deliberately introduce various materials into the subcutaneous or deeper tissues. Finally, trauma with resultant lacerations and abrasions may accidentally introduce various substances into the subcutaneous or deeper tissues. High pressure air hoses may at times inject materials into the subcutaneous tissues of man, but this occurs rarely and, especially with greases, leads to an extensive cellular reaction. In treatment, extensive incisions are usually necessary and the foreign material is probably ultimately removed with the inflammatory exudates which it produces. Experimentally, the advantage of the subcutaneous tissue resides in the fact that carefully controlled dosage can be administered with little chance that the dose can be removed or that it can be ingested.

The most extensive work using the subcutaneous tissues has been done with rats and mice. Of the two species, the rat subcutaneous tissue is so highly susceptible to the production of sarcomas that it seems an unwise species to use in this type of experiment, unless it is supplemented by

additional species. Thus, 25% sucrose injected subcutaneously into the rat may lead to sarcoma formation. The significance of the recent observations that the subcutaneous implantation of certain plastics in rats and mice results in sarcoma formation is as yet unknown. Whole sheets of some plastics will produce such tumors, but sheets in which holes have been punched, or the plastic in powder form do not lead to sarcoma formation. Perhaps the continued pursuit of these observations may lead to the elucidation of a physical mechanism of malignancy formation rather than a chemical one. In this respect, these experiments hold promise of opening new vistas to our understanding of the mechanisms of malignancy production and hence should be pursued vigorously. On the other hand, they are far too preliminary and far too little understood at present to constitute more than interesting phenomena. Certainly if such plastics are used in humans, such as for wrapping aortic aneurysms or providing artificial valves for the heart, careful post-mortem observations of the tissues in immediate contact with them should be made. However, the conditions for which they are used are so serious, and offer such a threat to the longevity of the patient that it is wholly unwarranted at this stage to advise against their use when the only evidence of their carcinogenicity has been in the subcutaneous tissues of the rat or mouse. To suggest that these observations have any significance in terms of other types of cancers seems wholly unwarranted.

The subcutaneous tissue of the mouse, on the other hand, appears to have about the same general sensitivity as the skin. The work of Bryan and Shimkin represents perhaps the most quantitative approach to carcinogenesis available in the literature. Their data were plotted in a dose-response curve for three polynuclear aromatic hydrocarbon carcinogens which has been reproduced in Figure 19. In these experiments, of course, the total number of tumor-bearing animals are used rather than the total number of tumors produced, the presumption being that only one subcutaneous tumor per mouse is produced. Data of this type provide very nice estimates of relative potencies of different carcinogens. It is important to point out that the relative order of potency of a group of carcinogens to the skin may not be the same as the relative order of potency of the same materials to the subcutaneous tissues.

Little work has been done with the subcutaneous tissues of other species, so that use of other species seems unwarranted until they have been studied adequately.

Although the subcutaneous tissues provide an easy, simple method.