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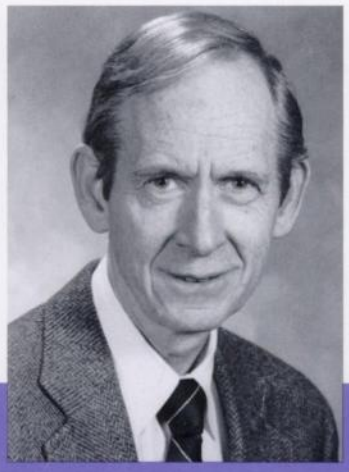

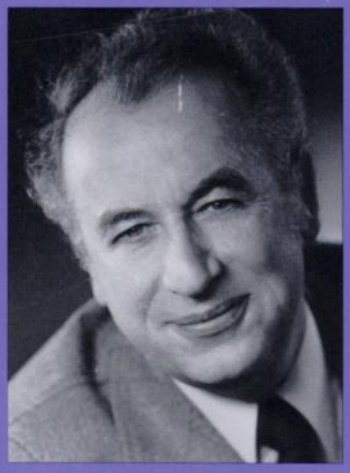

COVER LEGEND

In the history of occupational cancer, discovery of neoplastic disease in humans often precedes laboratory studies with the associated carcinogen. However, the reverse occurred with the α-haloethers. Van Duuren and associates, of the Institute of Environmental Medicine of New York University (NYU) (Cancer Research cover, December 15, 1988), known for their carcinogenicity studies of alkylating agents, performed systematic tests of a series of α-haloethers as a basis for establishing structure-activity correlations and discovered the powerful high yield, short latent period oncogenicity of bis(chloromethyl) ether (BCME) by application to mouse skin or subcutaneous injection in rats (Arch. Environ. Health, *16*: 472, 1968; J. Natl. Cancer Inst., *43*: 481, 1969). Confirmation followed shortly when Gargus and colleagues found that a single dose given to newborn mice yielded pulmonary tumors in six months (Toxicol. Appl. Pharmacol., *15*: 92, 1969). Inhalation tests by Laskin, Kuschner, Drew, and colleagues at the excellent facilities of NYU in suburban Sterling Forest demonstrated the remarkable potency of BCME. Inhalation of only 0.1 ppm, 6 h/day, 5 days/week, induced 40 neoplasms of the respiratory tract in 200 rats; 14 were in the lung, mostly squamous carcinoma, and 26 were nasal cancers; higher doses yielded more cancers (Arch. Environ. Health, *23*: 135, 1971; *30*: 70, 1975; *30*: 73, 1975). Leong *et al.* confirmed the carcinogenicity of inhalation of 0.1 ppm BCME (Toxicol. Appl. Pharmacol., *58*: 269, 1981).

Large scale industrial production of BCME and the related chloromethyl methyl ether (CMME), chemicals known for over 100 years, began during the late 1940s. CMME is less carcinogenic but usually contains BCME. In 1962, Weiss and Boucot of the Philadelphia Pulmonary Project were consulted by an occupational health physician, R. Megowan, about three cases of lung cancer death in young men in their thirties. Systematic studies of a cohort of 125 men by Weiss and a former resident in medicine, W. C. Figueroa, eventually led to the finding of 17 lung cancers, mostly oat cell carcinoma, and 2 laryngeal cancers in a group of 91 men belonging to the original cohort. There was a dose-response association and a mean latency period of 17 years, but the shortest was 8 years from the beginning of exposure (N. Engl. J. Med., *288*: 1096, 1973; JAMA, *234*: 1139, 1975; J. Occup. Med., *18*: 623, 1976; J. Natl. Cancer Inst., *69*: 1265, 1982). A German industrial physician, A. M. Thiess, described six lung cancers in a group of 18 workers in a pilot plant producing BCME (Zentralbl. Arbeitsmed. Arbeitsschutz, *23*: 97, 1973), and in Japan, Sakabe observed five lung cancers in workers exposed to several chemicals, including BCME (Ind. Health., *11*: 145, 1973). Thus, evidence for the high carcinogenicity of BCME in laboratory rodents, exposed by several routes, including inhalation, was followed shortly thereafter by clinical reports describing respiratory tract cancers stemming from industrial exposures in three different countries. Updated recent reviews are in *Journal of the National Cancer Institute* (*78*: 839 and 1127, 1987) and a book chapter (B. L. Van Duuren, *in*: Politzer and Roberts (eds.), Chemical Carcinogens, Amsterdam: Elsevier, 1988).

Top, *left* to *right*: William Weiss, M.D., Emeritus Professor of Medicine, Hahnemann University, Philadelphia, PA; W. G. Figueroa, M.D., Chief, Pulmonary Medicine, Lankenau Hospital Medical Building, and Clinical Professor of Medicine, Thomas Jefferson University, Philadelphia, PA; Professor Benjamin L. Van Duuren, Institute of Environmental Medicine, New York University, NY; *center left*, H. Sakabe, M.D., Japan Industrial Safety and Health Association, Japan Bioassay Laboratory, Kanagawa, Japan; *center right*, Professor Alfred M. Thiess, Director, Occupational Medicine and Health Protection, BASF, Ludwigshafen, Germany; *bottom*, *left* to *right*: the late Sidney Laskin; Marvin Kuschner, M.D., Dean Emeritus and Professor of Pathology, State University of New York School of Medicine at Stony Brook, NY; and Robert T. Drew, Ph.D., Health and Environmental Sciences Director, American Petroleum Institute.

We are indebted to Drs. Van Duuren and Weiss for background information and all individuals pictured for photographs.

John H. Weisburger