

March 15, 1991

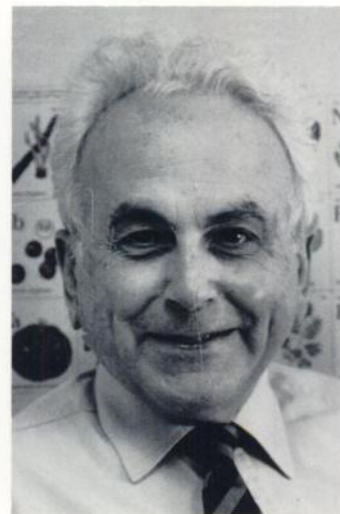
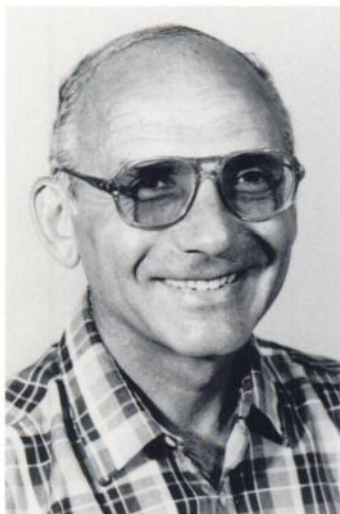
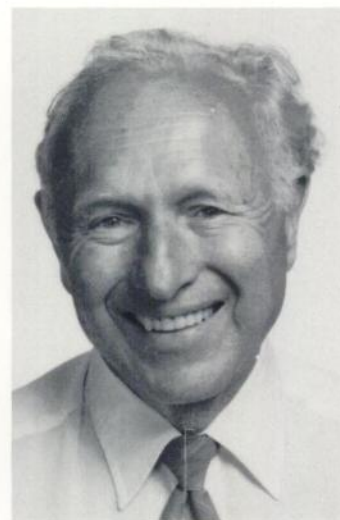
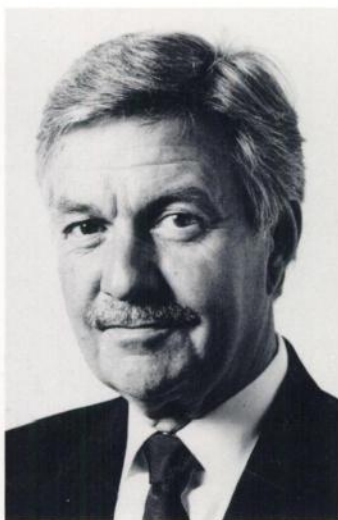
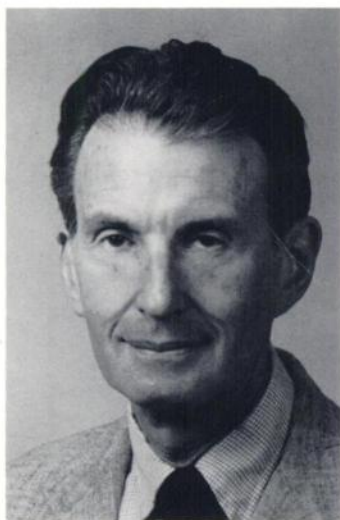


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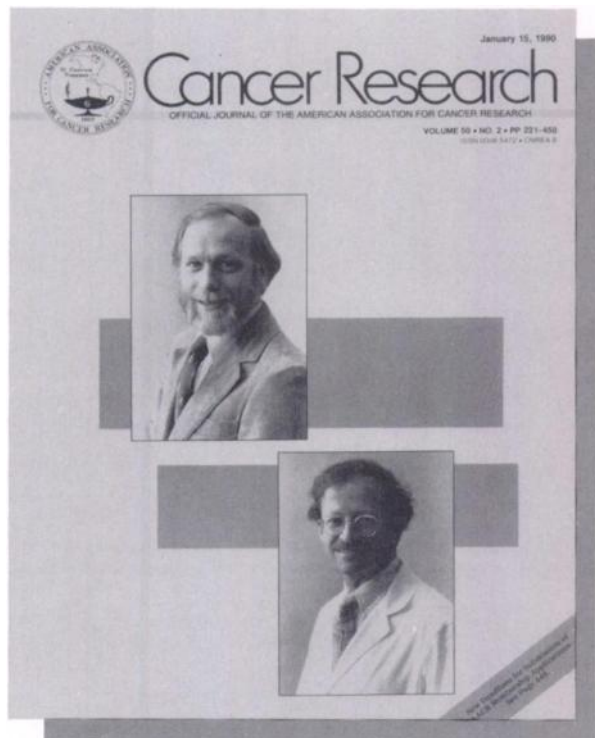


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COVER LEGEND



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The recognition of the role of the glutathione *S*-transferases in the metabolism and detoxification of xenobiotic carcinogens prompts consideration of the interesting prior history of this family of enzymes. In 1965, Brian Ketterer *et al.* (*Biochem. J.*, 103: 316–324, 1967) isolated a protein from rat liver that bound azo dye carcinogens. A few years later, Gerald Litwack and K. S. Morey (*Biochemistry*, 8: 4813–4821, 1969) and Irwin Arias *et al.* (*Proc. Natl. Acad. Sci. USA*, 64: 168–170, 1969) described proteins from the same source which bound cortisol and bilirubin as well as several drugs. Litwack and Morey showed that the cortisol-binding and the carcinogen-binding proteins were identical (*Biochem. Biophys. Res. Commun.*, 38: 1141–1148, 1970). Ultimately, the three hepatic proteins were recognized to be identical by Litwack *et al.* [*Nature (Lond.)*, 234: 466–467, 1971], who coined the term ligandin. Jakoby's group was interested in the reaction mechanism of a diverse group of enzymes, the glutathione transferases, and purified them to ho-

mogeneity from both rat and human liver (*J. Biol. Chem.*, 249: 7130–7148, 1974). Subsequently, Arias, Jakoby, and coworkers established the identity of ligandin with glutathione *S*-transferase B (*Proc. Natl. Acad. Sci. USA*, 71: 3879–3882, 1974), and Talalay *et al.* (*Proc. Natl. Acad. Sci. USA*, 74: 158–162, 1977) demonstrated that this transferase is identical to another enzyme, Δ -3-ketosteroid isomerase of rat liver.

Glutathione *S*-transferases comprise a family of enzymes with a broad substrate specificity, which participate in a variety of detoxication processes leading to excretion of xenobiotic agents as mercapturic acids. They achieve a special significance in their increased activities in early stages of hepatocarcinogenesis, thereby serving as markers of preneoplasia in liver and other organs. Glutathione *S*-transferases can be induced by certain carcinogens (Ding and Pickett, *J. Biol. Chem.*, 260: 553–559, 1985) but not by peroxisome-proliferator drugs (see *Cancer Research* cover, February 15, 1990). Enhanced production of the pi form characterizes many human neoplasms. Bueding *et al.* (*Cancer Res.*, 38: 4486–4495, 1978) found that glutathione *S*-transferase was greatly elevated in liver and other tissues by butylated hydroxyanisole and ethoxyquin. They have proposed that the potent anticarcinogenic effects of these substances are due at least in part to their stimulation of glutathione *S*-transferase activity.

Eleven subunits of the transferases have been described, as well as at least 4 heterodimers and 11 homodimers (Ketterer *et al.*, *Biochem. J.*, 260: 789–793, 1989). A comprehensive review by Kiyomi Sato is available (*Adv. Cancer Res.*, 52: 205–255, 1989).

Pictured are: Gerald Litwack, *lower left*; W. B. Jakoby, *upper left*; Brian Ketterer, *upper middle*; Irwin Arias, *upper right*; and Paul Talalay, *lower right*.

Sidney Weinhouse