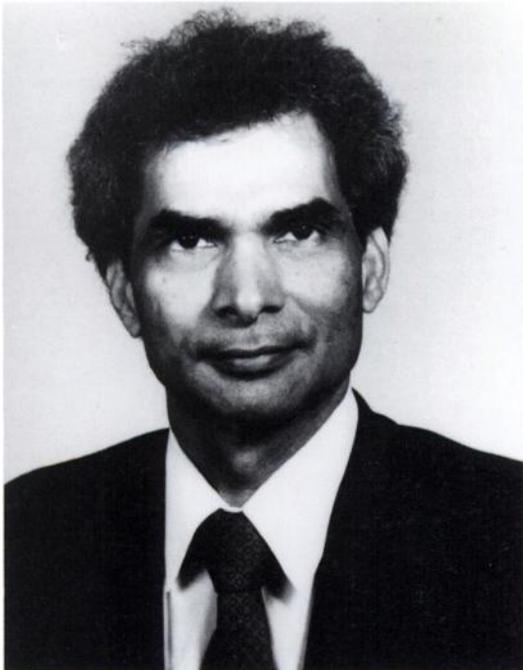
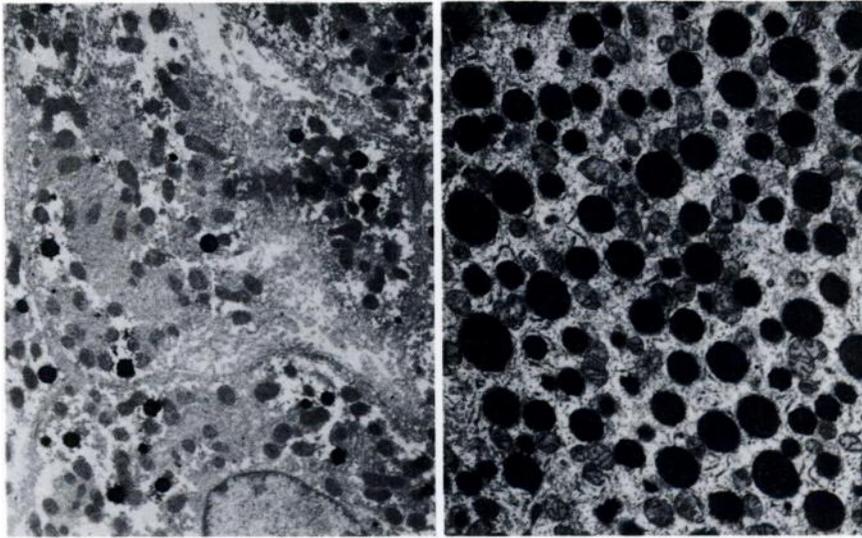


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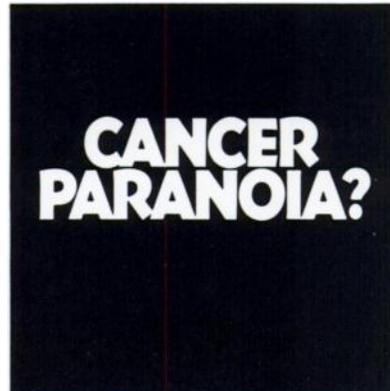
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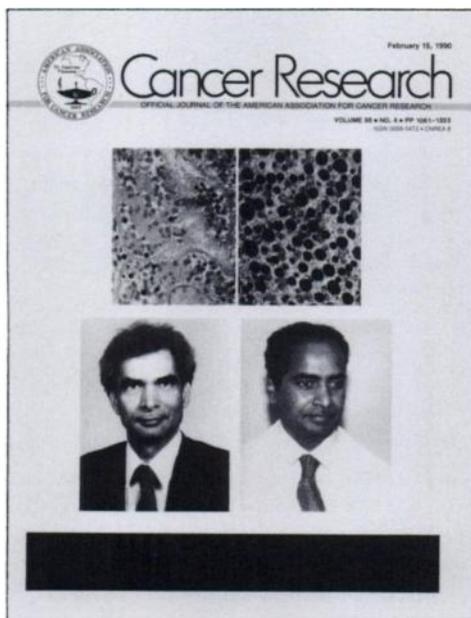
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COVER LEGEND



Displayed on this issue's cover are the peroxisomes, single membrane organelles, 0.2 to 1.0 μm in diameter, that contain a number of enzymes that yield or utilize hydrogen peroxide (de Duve and Baudhuin. *Physiol. Rev.* 46: 323–357, 1966). Their significance to hepatocarcinogenesis derives from their massive proliferation by certain substances of medical and industrial importance [Hess *et al.* *Nature (Lond.)*, 208: 856–858, 1965; Reddy and Krishnakantha, *Science (Wash. DC)*, 190: 787–789, 1975] and from the fact that these so-called peroxisome proliferators are potent hepatocarcinogens, acting by some unknown mechanism that does not fit within the generally accepted sequential pattern of initiation and promotion. Although peroxisomes are ubiquitous in animal and plant cells, their number in rodent liver cells is greatly enhanced by diverse chemicals, prominent among which are the hypolipidemic drugs (such as clofibrate, gemfibrozil, ciprofibrate, fenofibrate); plasticizers used in polyvinyl plastics, such as di(2-ethylhexyl)phthalate; and certain solvents and herbicides. Associated with the massive increase in peroxisomes are hepatomegaly, increased DNA synthesis, and marked augmentation (>30-fold increase) of the H_2O_2 -generating peroxisomal fatty acyl coenzyme A β -oxidation enzyme system. The peroxisomal catalase activity is increased less than 2-fold. The disproportionate increases in H_2O_2 -generating and degrading enzymes have been shown to cause severe oxidative stress in the liver.

Janardan K. Reddy and coworkers, during the mid-1970s, revealed that the hypolipidemic peroxisome proliferators produced liver tumors in mice and rats [Reddy *et al.* *Cancer Res.*, 36: 1211–1217, 1976; Na-

ture (Lond.), 283: 397–398, 1980]. Reddy's laboratory has been in the forefront of research in this area. A recent summary of his work and views may be found in the paper of J. K. Reddy and M. S. Rao, *Trends Pharmacol. Sci.*, 7: 438–443, 1986. [Other recent reviews are by Rao and Reddy, *Carcinogenesis (Lond.)*, 8: 631–636, 1987; Popp *et al.* *CIIT Activities (Chem. Indust. Inst. Toxicol.)*, 9: 1–7, 1989; and Lock *et al.*, *Annu. Rev. Pharmacol. Toxicol.*, 29: 145–163, 1989.]

Tumors induced by peroxisome proliferators, as well as the preneoplastic foci and nodules, are histologically indistinguishable from other chemically induced hepatic tumors. In marked contrast, however, the widely observed phenotypic markers, γ -glutamyltranspeptidase, the placental glutathione-S-transferase, and α -fetoprotein, are absent, and their mRNAs or inactive enzyme proteins are not detectable (Rao *et al.* *Cancer Res.*, 48: 4919–4925, 1988). No other tissue, except possibly kidney, responded like liver to peroxisome proliferators. Despite many efforts, peroxisome proliferators have not shown mutagenicity toward any prokaryotic or eukaryotic assays, nor have sensitive procedures revealed DNA adduct formation [Warren *et al.* *Cancer Res.*, 40: 36–41, 1980; Gupta *et al.*, *Carcinogenesis (Lond.)*, 6: 933–936, 1985]. They must act, therefore, by some mechanism different from that of direct DNA interaction. The absence of the usual phenotypic markers of liver neoplasia further implies a fundamental difference in the mechanism of gene regulation or in the cell type undergoing neoplasia. Reddy and Rao suggest that these nonmutagenic and nongenotoxic peroxisome proliferators must be considered as complete carcinogens and propose that these agents react with a cell-specific recognition molecule(s), translocate to the nucleus, and interact with DNA, leading to rapid transcriptional activation of selected genes. Chronic oxidative stress may lead to gene amplification or rearrangement. Alternatively, the peroxisome proliferators may be promoting spontaneously initiated liver cells [Popp *et al.*, *CIIT Activities (Chem. Indust. Inst. Toxicol.)*, 9: 1–7, 1989]. At the same time, all recognize some role of oxidative stress as a causal factor. The likelihood of a novel, hitherto unknown mechanism of hepatocarcinogenesis warrants further exploration.

Pictured are Janardan K. Reddy, *left*, and his colleague, M. Sambasiva Rao, *right*, both Professors of Pathology at Northwestern University Medical School, and electron micrographs of normal rat liver (*left*) with few peroxisomes, displaying black cytochemical reaction product due to catalase, and a portion of a hepatocyte showing peroxisome proliferation (*right*) after feeding a peroxisome proliferator to rats. Photographs were supplied by Dr. Reddy.

Sidney Weinhouse