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The history of carcinogenesis research is replete with observations suggesting a multistage mechanism of tumor formation. This was implied in the first published report on the etiology of cancer by John Hill in 1761: "Whether or not polypusses which attend snuff-takers, are absolutely caused by that custom, or whether the principles of that disorder were there before, and snuff only irritated the parts and hastened the mischief, I shall not pretend to determine..." (cf. cover legend, Cancer Research, February 1972). The work of Murray Shear, Peyton Rous, I. Berenblum, and J. C. Mottram established the two-stage mechanism underlying the promoting effect of croton oil in the development of epidermal neoplasms (cf. cover legend, Cancer Research, October 1970).

The two-stage model for the formation of skin tumors has proved useful for studying the molecular mechanism of carcinogenesis. The identification of certain phorbol esters as the tumor-promoting component of croton oil, largely through the efforts of Erich Hecker and his coworkers (Methods Cancer Res., 6: 439–484, 1971) and of B. L. Van Duuren (Progr. Exptl. Tumor Res., 11: 31–68, 1969) has greatly facilitated progress in understanding the role of promotion in tumor formation. The most effective ester, 12-O-tetradecanoylphorbol-13-acetate promotes skin tumors in mice at doses as low as 1 nanomole per application and is active in vitro in nanomolar concentrations.

The concept that tumor promoters act as a reversible derepressor (R. K. Boutwell, CRC Critical Rev. Toxicol., 2: 419–443, 1974) is exemplified by the ability of the tumor-promoting phorbol esters reversibly to induce ornithine decarboxylase (R. K. Boutwell, in Origins of Human Cancer, Cold Spring Harbor Symposium, 1977) and plasminogen activator (I. B. Weinstein, ibid). It is of particular interest that the induction of ornithine decarboxylase reaches a peak of 200 to 400-fold over the control level by 4 to 6 hours and that the induced enzyme has a half-life of only 17 minutes. Both of these enzymes are characteristic of the tumor phenotype, suggesting that a defect introduced by the initiating event precludes the rapid loss of the high level of an enzyme essential for cell division such as ornithine decarboxylase (O’Brien, Simsiman, and Boutwell, Cancer Res., 35: 2426–2433, 1975). We are indebted to Dr. R. K. Boutwell for the cover legend and other material.

Pictured, counterclockwise, are: Roswell K. Boutwell (Professor of Oncology, University of Wisconsin, Madison; born 1917 in Wisconsin); Erich Hecker (Director, Institut für Biochemie, Deutsches Krebsforschungszentrum, Heidelberg; born 1926 in Germany); and Benjamin L. Van Duuren (Professor of Environmental Medicine, New York University; born 1927 in South Africa).