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Pitot H C & Sirica A E. The stages of initiation and promotion in hepatocarcinogenesis. *Biochim. Biophys. Acta* 605:191-215, 1980.
[McArdle Laboratory for Cancer Research, The Medical School, Departments of Oncology and Pathology, University of Wisconsin, Madison, WI]

The evidence for and the characteristics of the stages of initiation and promotion in hepatocarcinogenesis in animals and the human was reviewed. The analogies between the stages of initiation and promotion in rodent hepatocarcinogenesis and epidermal carcinogenesis were compared. The potential implications of the stages of carcinogenesis and their characteristics to human risk were explored. [The *SCI*® indicates that this paper has been cited in more than 480 publications.]

The Multistage Nature of Carcinogenesis

Henry C. Pitot
McArdle Laboratory for Cancer Research
University of Wisconsin
Madison, WI 53706
and
Alphonse E. Sirica
Department of Pathology
Medical College of Virginia
Virginia Commonwealth University
Richmond, VA 23298

Although distinct stages in the development of cancer had been recognized by several laboratories in the 1940s using epidermal carcinogenesis in the mouse as a model, a more general appreciation of the multistage nature of the development of cancer in vivo was not appreciated until the 1970s. In that decade, the demonstration of the promoting action of phenobarbital in rat hepatocarcinogenesis by C. Peraino and his colleagues,[1] as well as the use of single, subcarcinogenic doses of diethylnitrosamine coupled with a mitotic stimulus that induced enzyme-altered focal lesions, as reported by E. Scherer and P. Emmelot,[2] laid the foundation for the development of multistage models of hepatocarcinogenesis in the rodent. A model based on these two studies, which was completely analogous in format to the earlier studies in multistage epidermal carcinogenesis, was first reported from our laboratory.[3] In the years just before and after the publication of this model, a number of other models of multistage hepatocarcinogenesis in the rodent were published. Thus, at the invitation of the editor of *Biochimica et Biophysica Acta*, we reviewed the evidence for the multistage nature of neoplastic development in rodent liver to that time. This review included references to the evidence for the multistage nature of carcinogenesis in several other organs and tissues in the experimental animal, alluding to a similar multistage nature of cancer in the human. In addition, the first efforts at comparison of the multistage nature of neoplastic development in murine liver and mouse skin was presented, demonstrating that the similarities far outweighed the differences in this process in the two different tissues of two different species. The importance of the spontaneous initiation of the carcinogenic process in the absence of exogenous experimental carcinogenic influences was also emphasized for the first time in the oncologic literature.

In reference to this review, it is of interest that, during the 1980s, our knowledge of the mechanisms and the characteristics of multistage carcinogenesis in a variety of different tissues has expanded dramatically. Furthermore, even more important are the potential practical applications of a knowledge of the characteristics of the stages of carcinogenesis, initiation, promotion, and, as newly defined, progression.[4] The relationship of the genetic characteristics of neoplastic development to this multistage nature of carcinogenesis has placed our understanding of cancer in a much more defined light. The reversible nature of the intermediate stage of promotion which is likely important in the development of the more common types of human cancer, is critical to the rational development of effective methods for cancer prevention in the human. In all, as our understanding of the multistage nature of cancer development increases and the action of specific agents (chemical, physical, biologic, and genetic) at each of these stages becomes defined, our ability to prevent, diagnose, and ultimately control cancer as a disease in the human is being greatly enhanced.[5]

1. **Peraino C, Fry R J & Staffeldt E.** Reduction and enhancement by phenobarbital of hepatocarcinogenesis induced in the rat by 2-acetylaminofluorene. *Cancer Res.* 31:1506-12, 1971. (Cited 380 times.)
2. **Scherer E & Emmelot P.** Kinetics of induction and growth of precancerous liver-cell foci, and liver tumour formation by diethylnitrosamine in the rat. *Eur. J. Cancer* 11:689-96, 1975. (Cited 145 times.)
3. **Pitot H C, Barsness L, Goldsworthy T & Kitagawa T.** Biochemical characterization of stages of hepatocarcinogenesis after a single dose of diethylnitrosamine. *Nature* 271:456-8, 1978. (Cited 415 times.)
4. **Pitot H C.** Progression: the terminal stage in carcinogenesis. *Jpn. J. Cancer Res.* 80:599-607, 1989.
5. **Hendrich S, Glauert H P & Pitot H C.** The phenotypic stability of altered hepatic foci: effects of withdrawal and subsequent readministration of phenobarbital. *Carcinogenesis* 7:2041-5, 1986.

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