THE ROLE OF INHIBITED INTERCELLULAR COMMUNICATION IN CARCINOGENESIS:
IMPLICATIONS FOR RISK ASSESSMENT FROM EXPOSURE TO CHEMICALS*

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Introduction: A Crisis in Paradigms

With the reality that humans cannot live without chemicals and that the number of new chemicals to which we are exposed is increasing, the justified concern over the potential harm of any one or mixture of these chemicals to human health is also growing every day (Steering Committee, 1984). In addition, the harsh reality is that these chemicals cannot all be tested, in an absolute fashion, for their potential toxicity as an acute toxicant, teratogen, carcinogen, neuro- or reproductive toxicant. Constraints, such as (a) our lack of basic understanding of the mechanisms by which chemicals might lead to various toxic endpoints; (b) the reliance on short-term assays and animal model surrogates for human exposure; (c) limited resources (human, financial, technical) to perform the toxicological tests; and (d) imprecise ability due to species, genetic, developmental stage, sex and nutritional/occupational/environmental background, to extrapolate from short-term test or animal bioassay results to the unique individual human situation, put great uncertainties in any risk assessment process.

In recent years, concern over this major problem has led to an accelerated attention to, and development of, concepts, techniques and strategies to attack this problem. Among the massive research activity in the fields of toxicology stimulated by this concern, the introduction of the concepts of "carcinogenesis as mutagenesis" (Ames et al., 1973) and of "genotoxicity" (Ehrenberg et al., 1973) has to be viewed as the major spark that ignited the energies of many scientists for the last fifteen years.

The paradigm that mutagens can induce cancers has, in our opinion, paralyzed our ability to develop a understanding of the process of carcinogenesis and of the practical issue of risk assessment after exposure to chemical agents (Trosko and Chang, in press). From experimental studies, in vitro and in vivo, and from genetic predispositions to human cancer, it is obvious that mutations (genes and chromosomal) can play a role in carcinogenesis (Trosko et al., 1985). However, equally obvious is the realization that (a) not all toxic chemicals are mutagenic and (b) carcinogenesis is more than mutagenesis (Trosko, in press; Trosko, 1984). It is this fact that we believe has been glaringly neglected in the design of the NTP bioassay protocol to
test chemicals for their carcinogenic potential, in the design and interpretation of short-term assays, and the interpretation of results testing the concordance of the short-term results to the bioassay results (Trosko, in press).

The basis for our opinion can be illustrated by the recent evaluation of the results of the National Toxicology Program to test the mutagenicity/carcinogenicity of 300 chemicals (Tennant et al., 1987). Three of the "most potent carcinogens produced no genetic toxicity in any of the four short-term tests studied" (Tennant et al., 1987). The question is "Why?"

Carcinogenesis: A Multistep Process Involving Both Mutagenic and Epigenetic Processes

Carcinogenesis has been viewed, in both experimental animal studies and during the clinical course of tumor development in human beings, to consist of multiple and distinct phases (Fialkow, 1974; Foulds, 1975; Cairns, 1975). Conceptually, these stages have been classified as initiation/promotion/progression (Boutwell, 1974; Pitot et al., 1981; Weinstein et al., 1984). Although these operational concepts, derived from whole animal studies, do not specify any particular mechanism, it appears that the underlying cellular and molecular mechanisms of initiation and promotion are very different (Trosko and Chang, 1983; Trosko et al., 1983; Trosko and Chang, 1985).

Because initiation, by operational definition, is an irreversible event, and because many known mutagens are good initiators, it has been postulated that mutagenesis is the cellular basis for initiation (Trosko and Chang, 1978). On the other hand, promotion appears to be an interruptible or reversible process in its early phase. Because agents or conditions which can stimulate a sustained stimulation of growth of an initiated cell (surgery, wounding, cell death, normal growth or exposure to mitogenic chemicals), mitogenesis appears to be a necessary, if not sufficient, factor in tumor promotion (Trosko et al., 1983) [Fig. 1].

Based on phenomenological observations, it has been hypothesized that initiation is the process by which a single normal stem cell is irreversibly altered, such that it cannot terminally differentiate (see later discussion). However, as long as it is surrounded by, and communicating with, normal cells, it can be suppressed from further growth and expression of its altered genotype. Until and unless, it is released from the suppressing effects of its normal neighbors by agents or conditions which can inhibit gap junctional communication, this initiated cell will remain in a quiescent or latent state (Yotti et al., 1979).

If intercellular communication is inhibited by endogenous (i.e., growth factors, hormones) or exogenous factors (i.e., cytotoxicants, non-cytotoxicant modulators of gap junctions), these initiated cells can proliferate (self-renew, but not differentiate). If these inhibitors are removed before a "critical mass" of the initiated cells is attained, the clonal expansion is stopped or even reversed (Reddy and Fialkow, 1987). If during the promotion process, a single initiated cell acquires a phenotype, via either another genetic (Trosko and Chang, 1980; Potter, 1981; Moolgavkar and Knudson, Jr., 1981; Hennings et al., 1983; Reddy and Fialkow, 1983; O'Connell et al., 1986; Taguchi et al., 1984; Jaffe et al., 1987; Chu et al., 1987) or epigenetic (Kerbel et al., 1984) alteration, which makes it independent of exogenous promoters, it can be said to have reached the progression stage.