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Development and the Environment: Clues to Carcinogenesis

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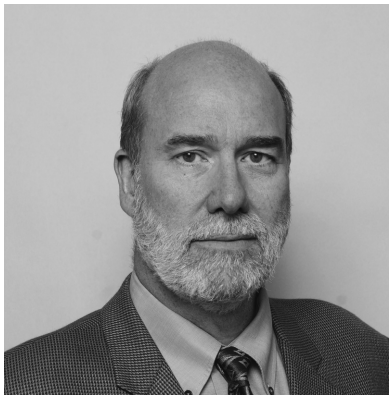

This commentary makes three points. First, the environment is a key determinant of developmental phenotype, with a wide variety of mechanisms that mediate this influence. Second, there is an intimate relationship between the biology of development and the biology of cancer, with many of the same signaling pathways, gene-expression profiles, endocrine and paracrine influences, and DNA modifications being involved in both. Third, although we have focused extensively on the role of DNA mutation in seeking to understand the role of environment in carcinogenesis, it is perhaps time to look more widely and to apply what we know of the environmental influences on development.

Since the Modern Synthesis was formulated, geneticists have dominated the argument about what determines phenotype. The answer seemed obvious: genotype determines phenotype. Other viewpoints, especially after the bizarre (and tragic) destruction of Russian genetics by Lysenko, were regarded as suspect at best, ignorant or even fraudulent at worst. Nonetheless, compelling evidence has accumulated over the 20th century: it is now clear that genotype, indeed, sets limits on the phenotype but, also, that there is marked plasticity within these limits; that many aspects of environment are key determinants of how that plasticity is further constrained; and that the influence of the environment is consistent and predictable in any given circumstance. Specific examples follow.

The larvae of the moth, *Nemoria arizonia*, develop on oak trees: Those that hatch in spring resemble the catkins (flowers), but those that hatch in the summer look like twigs (1). The level of tannins in the diet determines the phenotype although how the signal is transduced is not yet clear.

In the honeybee, a continuous diet of protein-rich royal jelly maintains the functions of the corpora allata, which produces juvenile hormones that delay metamorphosis; this, in turn, increases growth and ensures functional ovaries. This dietary regimen results in a new queen after the death of the old. The genotypes of queen and worker are the same; phenotypes differ markedly (2). The mechanism involves upregulation of energy metabolism genes (3).

Folate supplementation of dams ensures that the pups of the agouti mouse (heterozygous for the VY allele of the agouti gene) are dark pigmented and slender, whereas genetically identical mice from unsupplemented dams are fat and yellow (4). The mechanism involves alterations in DNA-methylation patterns (4). Alterations of methylation patterns also account for a higher number of glucocorticoid receptors in the hippocampus and an improved ability to respond to stress in rat pups that are maternally groomed, compared with those that are not (5, 6).

When the butterfly, *Araschnia levana*, emerges from its pupa in spring it has a different phenotype from the genetically identical adult that emerges in summer (so different that Linnaeus classified them as different species). This difference results from changes in day length and temperature (7) and is mediated by the larval levels of ecdysone, a hormone that also controls metamorphosis (8).

In mammals, sex determination is dependent on chromosomes. In many reptiles, amphibians, and fish, gonadal specification is determined by temperature (turtles and crocodilians) or social interaction (fish) and

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Dedication: This commentary is dedicated to my friend, the late and much missed Arthur Schatzkin, with whom I have discussed many of these issues and who, just a short while ago, gave me the book by Gilbert and Epel (9) that stimulated and clarified some of the ideas expressed here.

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mediated, in each case, by aromatase levels [see Gilbert and Epel (ref. 9), chapter 2].

Other sources of phenotypic variation, where mechanisms are less clear, include the following:

1) Predators [for example, specific amphibians respond to the presence of predatory larvae (10) and snakes (11) with survival strategies that alter phenotype (sometimes reversibly) and enhance survival];
2) Conspecifics [for example, there is a marked variation in phenotype of low- and high-density populations of tadpoles of the gray tree frog (12) and of locusts (13), where the effect is mediated by touch] and
3) Symbionts and parasites, which can alter a variety of outcomes, including sex determination, camouflage, angiogenesis, immune development, and fat storage [see Gilbert and Epel (ref. 9), chapter 2].

To this point, the discussion has been confined to the role of environment in producing variations in normal development, which involves a new organism from a single cell, followed by organ development from cells now committed as specific organ precursors. Adult tissues face a related problem to that of new organs, namely the maintenance (rather than the genesis) of tissue architecture and functional capacity in the face of cell damage, senescence, and turnover (14, 15). The failures of structure and function that characterize cancer are mediated by the disruption of many of the same pathways and mechanisms that are essential to development, including Hedgehog, Wingless, Notch, and fibroblast growth factor.

The focus of most environmental influences on cancer has been on the capacity for DNA damage and evidence of mutagenesis (16), despite the fact that many of the important agents known to cause human cancer do not mutate DNA (e.g., estrogen and alcohol). The environment is also a source of agents and processes that result in abnormal development, known as teratogenesis. A much more consistent pattern emerges when we consider the identity of known teratogens (disruptors of development) and known carcinogens (disruptors of adult tissue;

Table 1. Agents of disruption common to carcinogenesis and teratogenesis

Exposure	Human carcinogenicity	Teratogenicity	Mechanisms of teratogenesis
Heavy metals	Cadmium (22)	Methylmercury[a]	Impaired brain development (23)
Ethanol	Aerodigestive, colorectal, breast, etc.	Fetal alcohol syndrome (24) Reduced sperm count (25)	Abnormal apoptosis via loss of sonic hedgehog and FGF8 (26) Oxidative damage (27) Impaired cell adhesion (28)
Tobacco	Lung, aerodigestive, pancreas, etc.	Fetal growth (29) Lung growth (30) Brain growth (31) Sperm abnormalities (32)	Abnormal synapse formation (31) Premature aging of alveolar cells (30)
Pesticides	Non-Hodgkin lymphoma (33)	Atrazine in amphibians alters sexual development and reproductive capacity (34) and induces immune suppression (35) and skeletal malformations (36)	Induces aromatase—converts androgens to estrogens (34); the combination of immune suppression and subsequent trematode infection is a probable cause of the limb deformities (36)
Endocrine disruptors	DES—vaginal adenocarcinoma (37) Estrogens—endometrium, etc.	DDT in birds (38) DES in humans (39) Bisphenol A (40)	BPA binds to ER and results in major effects on sexual differentiation, aneuploidy in ovarian cells, genital-tract abnormalities, etc. (17) DES alters expression of *HOX* genes (41) DDT is a potent AR antagonist (42)
Retinoids	Lung (43)	Cranial anomalies (44) Specific anterior skeletal anomalies (45)	Alter relative anterior/posterior tissue distribution by alteration of *HOX* expression patterns (46)

Abbreviations: AR, androgen receptor; DDT, 1,1,1-trichloro-2,2-bis-(p-chlorophenyl) ethane, dichlorodiphenyltrichloroethane; DES, Diethylstilbestrol; ER, estrogen receptor.
[a]http://www.nimd.go.jp/archives/english/

ref. 14), including heavy metals, alcohol, tobacco, pesticides, endocrine disruptors (17), and retinoids. Table 1 outlines some of these agents and notes the nonmutagenic impact of each of these agents in teratogenesis. Some of these agents cause transgenerational effects (18–20), which also occurs in normal development (21), a mechanism that could apply (again without invoking mutation) at the stem-cell level (and thus in epithelial tissue architecture) in carcinogenesis.

Rather than remain fixated on DNA damage as a cause of cancer, we should work within a wider perspective and explore the role of environmental agents in cancer in the light of development and teratogenesis, duly noting that there are agents, pathways, and mechanisms in common, with a view to a less dogmatic approach to carcinogenesis and a more informed program of prevention, both of cancer and teratogenesis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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