The *Journal of Theoretical Biology* Papers

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Cancer and Evolution: Synthesis

Cancer has certain characteristics that lead me to conclude that it functions as an "enforcer" of the genetic program and, as such, played a major role in the origin and evolution of the Bilateria. In this theoretical conception of the cancer process, each juvenile specimen capable of getting the disease can be viewed as a "black box" in which the input of a carcinogen results in the output of cancer. Ames' correlation (Ames *et al.*, 1973) permits the substitution of "mutagen" for carcinogen, and cancer's lethality suggests that the output can be labeled "genetic death." Although the precise cellular mechanisms involved in carcinogenesis are not considered here, it is assumed that within a target pre-mitotic cell the following sequence takes place: (a) the mutagen causes a mutational event and (b) oncogenes (Bishop, 1982) initiate transformation to the cancerous state following mitosis. It follows from this sequence that virtually all selected defenses against cancer would have enhanced the ability of the genomes to create organisms in which the genetic program is expressed with great fidelity in all somatic cells.

If, as I believe to be the case, all Bilateria have oncogenes in every cell and descended from species that endured significant losses to mutagen-induced cancer, then all Bilaterian specimens possess an extensive array of characters that function both as cancer defenses and replication enhancers. There would seem to be five basic means by which selected characters would carry out these two functions: (1) minimize pre-reproductive mitosis, (2) avoid exposure to mutagens, (3) provide morphophysiological

protection against mutagens, (4) repair mutagen-induced damage before transformation, and (5) destroy or contain transformed cells. Examples of such mechanisms and comments on their replication-enhancive character follow.

Pre-reproductive mitosis avoidance is evident in the strict control over somatic cell production in Bilateria. Compared to plants and many species of tissue-level animals, most Bilaterian specimens lack phenotypic plasticity, regenerate damaged tissue less flamboyantly, undergo diminishment in mitosis following (likely) sexual reproduction, have many fixed post-mitotic cells (neurones and muscle cells) and, in the insects, exhibit polyploidy and polyteny. The possibility of replication errors is decreased when somatic cell production is minimized by these devices.

Minimization of exposure to mutagens is evident in the Bilateria's unique (for multicells) history of sun avoidance. The earliest Bilateria lived either in the sea bottom or on its surface (Valentine, 1973). All of the animals in the latter habitat were equipped with non-cellular outer coverings that protected them from any mutagenic, and carcinogenic, radiation that penetrated the layers of water above. Descendants of those first complex animals all reflect selection of devices that protect against radiation: habitats, including parasitical sites, affording good shelter; shells, chitinous scales, exoskeletons, feathers, hair and skin pigmentation; small body size, which would have minimized the likelihood of a single lethal, i.e., cancer-inducing, "hit" of radiation; or they were equipped with a "fail safe" immunological system.

Efficacious repair of damaged DNA by repair enzymes functioning in somatic cells would both avoid death from cancer, as I have conceptualized it, and enhance somatic expression of the genetic program.

Complete destruction of malignant cells would eliminate effects of the mutational event that initiated the cancer process. Harshbarger (1968) has suggested that some invertebrates may use autectomy to rid the body of tumors or encapsulation to contain them; metamorphosis, during which diseased larval cells could be discarded, was mentioned by Gateff and Schneiderman (1968) as a factor which might account for low cancer rates in

insects. Such disposal or containment of cancer cells would be enhancive of precise replication since these processes, if successful, would help juveniles to survive to reproductive age without being devastated by the effect of a single error in replication.

The evolution of efficient cancer-specific immunological defenses in all vertebrates would have enabled those species to adapt characters, functions, etc.. which might have increased the incidence of cancer *initiation*. The following all suggest the lowering of first line defenses against cancer in vertebrates: increased mitosis as evidenced by large body size and extended pre-reproductive life, increased exposure to radiation as the result of migration from aquatic to terrestrial habitats, and the elimination, in many mammalian species, of opaque external protection from UV radiation. Bilaterian invertebrates do not have a lymphoid system which, according to Good & Finstad (1968), has as its primary *raison d'etre* surveillance against malignancy. Unlike animals equipped with such immune systems, the invertebrate germ lines seem not to have produced any large, long-lived terrestrial specimens, and none seem to have shed ancestral radiation-protective shielding to the extent found in some vertebrate species. On the other hand, as noted by Gateff & Schneiderman (1968), experimental data suggest that in the largest group of terrestrial invertebrates, the insects, somatic cells exhibit karyotypic and genetic program stability greatly in excess of that found in vertebrates.

If evolutionary theory is modified to include the assertion that cancer established, about 700-800 million years ago, the imperative that only those Bilaterian genotypes capable of extreme precision in the construction of multi-celled organisms could possible survive to participate in the struggle for existence, and ruthlessly enforced that imperative ever since, then evolutionary theory is strengthened. It would offer, as it does not now, a mechanistic explanation for a generally ignored, but nonetheless perplexing problem: why, if they had access to the same mechanisms as the Bilateria, did the germ lines of plants, Porifera and Coelenterates not create multicells with complex vital organs? Or, conversely, if tissue-level multicells were sufficiently adapted to ensure the survival of their germ lines for

hundreds of millions of years, why do organisms of so much greater complexity exist in such abundance in the Bilateria?

D.A.Buyske, W.Bock and R.Milkman commented, helpfully, on earlier drafts. J.C. Harshbarger, R.Dawkins, J.E.Trosko, A. Zeitlin and R.G.Brenner gave me helpful advice or information.

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The following second Letter appeared in the March 21, 1984 edition, volume 107, number 2, on pages 341-343

of the journal:

Cancer and Evolution: Amplification

To amplify the ideas expressed in "Cancer and Evolution: Synthesis" (Graham, 1983) I suggest that all Bilaterian genetic material can be divided into four groups: oncogenes, anti-oncogenes, adaptive pro-oncogenes and those that are cancer neutral.

Genes that are cancer neutral are those whose selection was followed, for whatever reasons, neither by an increase nor a decrease in the incidence of cancer in the organisms equipped with them. These genes have no value in this theory.

In this context "oncogenes" are cellular oncogenes. These are further defined as having the potential for killing the organism in whose genetic program they are present, such deaths being initiated by the occurrence of a mutational event in a single somatic cell. This theory states that oncogenes, thus defined, have been present in every cell of every specimen of every species of the Bilateria that ever existed, and that they have existed nowhere else in nature. Although it has been assumed by many "...that c-onc genes serve some essential purposes in uninfected cells" (Bishop & Varmus, 1982) whether or not oncogenes do indeed have any functions other than to kill organisms is irrelevant to the development of, and the validity of, this theory.

Recent findings by Simon, Kornberg & Bishop (personal communication, 1983) indicating that the *src* oncogene is present in the genome of *Drosophila Melanogaster*, and the Shilo & Weinberg (1981) report of *Caenorhabditis elegans* nematode DNA hybridizing to oncogenes suggest that oncogenes are present in all Bilaterian invertebrates. As for vertebrates, as noted by Bishop (1982), "Of 17 retrovirus oncogenes identified to date, 16 are known to have close relatives in the normal genomes of vertebrate species". Perhaps of equal significance to these molecular findings is Harshbarger's (1980) report of "...the strongest candidate neoplasm yet seen in *Platyhelminthes*, a phylum at the primitive level of only two germ levels". Viewed in conjunction with Gateff & Schneiderman's (1968) report of lethal and transplantable

neoplasia in *Drosophila Melanogaster*, this pathological finding suggests support for the conclusion that all Bilaterian invertebrates, as well as all vertebrates, have the potential to die of cancer.

Although the reports of DeFeo, Papageorge, Stokes, Temeles & Scolnick (personal communication, 1983) and of Hammond & Bishop (personal communication, 1983) indicate that DNA homologous to *ras* and *fps* oncogenes, respectively, is present in yeast, these are not oncogenes as defined since it is assumed that single-celled organisms cannot die of cancer.

Anti-oncogenes are defined as those which were originally selected because they helped to reduce genetic losses to cancer. Because the process leading to such genetic deaths is believed to begin with imprecise replication of the genetic program in a single cell, I conclude that all anti-oncogenes also function as enhancers of precise replication. The report by Yunis (1983) that "High resolution banding techniques...have revealed that malignant cells of most tumors analyzed have characteristic chromosome defects", seems to lend support to the idea that oncogenes are activated in response to mutational events, and therefore, that selected anti-oncogenes would tend to minimize the incidence of these potentially lethal occurrences.

Adaptive pro-oncogenes are those that imparted some survival benefit to the germ line in spite of a likely increase in juvenile deaths from cancer following their selection. Increased somatic complexity, greater body size, extended pre-reproductive life and migration to more mutagenic habitats occurred in so many Bilaterian lineages that they can be confidently judged to have been adaptive. It is, however, most probable that selection of such characters was followed by increases in the incidence of somatic mutational events in juveniles and resulted in increased losses of genetic material to cancer.

The concept of genes that were both adaptive and pro-oncogenic would explain what Mayr (1982) calls transformational, or vertical, evolution in the Bilateria; and it would account for the persistence, at least in some species, of juvenile cancer 700-800 million years after its presumed origin (Graham, 1983). Selection of adaptive pro-oncogenes would have increased the pressure for

more effective anti-oncogenes, which, because of their inherent replication enhancive properties, would have enabled the surviving gene pools to create the more complex (or larger or more exposed) animals whose development was by then imbedded in the genetic program. The relative volume of adaptive pro-oncogenes (and anti-oncogenes) selected over time would explain the existence in modern Bilateria of both relatively simple animals and those that are very complex. Those germ lines that created the most complex animals endured the most genetic losses to cancer and *vice versa*.

This idea is supported by the relative lack of complexity in Bilaterian animals whose ancestors seem not to have ventured from shelters that afford good protection from sunlight and other carcinogenic radiation: earthworms are not as complex as insects, and all bivalves are simpler than the octopus. This pattern would seem to require a mechanistic explanation that is exclusive to the Bilateria, for, although there are no extant or extinct species of large-bodied, relatively simple Bilateria in exposed habitats, the combination of large bodies, relative simplicity and exposure to sunlight is observable in many plants and *Coelenterates*.

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