Reply to the comment of Dr H.I. Hadler

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The hypothesis that DNA fragments may become liberated from mitochondria and incorporated into the nuclear genome, thereby contributing to the development of cancer, has been formulated as early as 1971 by Hadler et al. [1]. In recent years it has become increasingly apparent that oxidative DNA damage by endogenously produced oxygen radicals is far more common than covalent DNA modification by chemical carcinogens. Being unaware of Hadler's proposal, which restricts itself to chemical carcinogenesis, I recently put forward the hypothesis [2] that mitochondrial DNA fragments, caused by *normal oxygen metabolism,* after integration into the nuclear genome may be the *natural* cause of aging and some forms of cancer. This idea is based mainly on the finding that: (i) mitochondria produce large amounts of oxygen radicals; (ii) in mitochondria the steady-state level of DNA damage including strand breaks is very high; (iii) cells can contain several thousand mitochondrial DNA copies; (iv) there is an inverse relationship between basal metabolic rate (oxygen consumption per unit weight) and longevity; and (v) cumulative cancer risk increases with approximately the fourth power of age. We are now attempting to verify our hypothesis with the powerful techniques of molecular biology.

Hadler's hypothesis on chemical carcinogenesis and my hypothesis on natural aging and carcinogenesis may merge because many natural and man-made carcinogens induce the formation of oxygen radicals in the body [3]. Good examples are hydrazines or quinoid compounds like menadione (vitamin K). Menadione is redox-cycled in mitochondria [4] and has properties very similar to the carcinogen 4-nitroquinoline-1-oxide and its metabolite 4-hydroxyaminoquinoline-1-oxide [5].

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