Vitamin A: Potential Protection from Carcinogens

The primary thrust of cancer therapy has been the destruction of malignant cells after they have been formed. A somewhat smaller effort has been made to prevent cancer by halting contact between environmental carcinogens and susceptible tissues. Almost no effort, however, has been made to discover what might be done during the period between exposure of a cell to a carcinogen and that cell's transformation to malignancy. Some recent work presented in Bethesda last month at a workshop on vitamin A, sponsored by the National Cancer Institute (NCI) and Hoffmann–La Roche, Inc., however, suggests that it might be possible to interfere with the progression of an exposed cell to transformation and to mediate a return to normalcy. The potential mediators of the interference are derivatives of a common substance: vitamin A.

The onset of a tumor has been considered to occur in three distinct phases —initiation, preneoplasia, and transformation. During initiation, a carcinogen effects some relatively permanent change in one or more cells (such as a change in a gene) that may lead to malignancy. In transformation, the cells rather abruptly show the properties characteristic of tumors and begin proliferating. Preneoplasia encompasses the cellular events occurring in the long period between initiation and transformation—often 20 years or more in humans.

Almost nothing is known about cellular changes in preneoplasia; but it is clear that in many cases, perhaps even a majority, the preneoplastic cells are repaired and "spontaneously" revert to health. A method to increase the frequency of such reversions could prove quite useful, particularly in cases where there has been prolonged exposure to carcinogens (as in smokers and asbestos workers), but there has previously been little evidence to support such a possibility.

Vitamin A (retinol) is known to play a role, among other things, in the differentiation of epithelial cells into specialized tissues, although the nature of the role is unclear. It is thus not surprising that it might also play a role in the development of epithelial tumors, since tumorigenesis generally involves a loss of differentiation. Perhaps the most crucial finding in terms of cancer prevention, as some scientists at the workshop suggested, is that many carcinogens are much more potent in animals that have a long-term deficiency in vitamin A.

Michael Sporn and David Kaufman (NCI), for example, have shown that various carcinogens bind much more tightly to DNA in cultured tracheas isolated from vitamin A–deficient hamsters than to DNA in tracheas from healthy animals. The available evidence suggests that there should be a corresponding increase in the incidence of tumor formation. Paul Newberne and Adrianne Rogers (Massachusetts Institute of Technology, Cambridge) have shown that there is a marked increase in the incidence of colon tumors caused by the carcinogen aflatoxin B_1 in rats that are deficient in vitamin A. While these results are still very preliminary, they are potentially of great import. According to Barbara A. Underwood (Pennsylvania State University, University Park), as many as 30 percent of the population show below-average concentrations of vitamin A in the liver. Some scientists think this is indicative of long-term vitamin A deficiency.

Even in animals or organs from animals that are not deficient in vitamin A, additional quantities of retinol or its derivatives can exert a protective effect. Kaufman, for instance, has shown that simultaneous administration of retinyl acetate and benzo[*a*]pyrene can inhibit the binding of the carcinogen to DNA in cultured hamster tracheas. Dharam Chopra (Southern Research Institute, Birmingham, Alabama) has shown that retinoic acid and its analogs can inhibit the activity of certain carcinogens on cultured prostates from mice and can reverse the effects of carcinogens applied prior to its administration. Donald Hill (Southern Research Institute) has shown that retinol inhibits the oxidation of benzo[*a*]pyrene to its presumed carcinogenic form in mouse and hamster liver and lungs. Paul Nettesheim (Oak Ridge National Laboratory) has shown that retinyl acetate can reduce the incidence of lung tumors produced in rats by methylcholanthrene. And Curtis Port (Illinois Institute of Technology, Chicago) has shown that the administration of 13-*cis*-retinoic acid after hamsters have been exposed to the carcinogen can inhibit the formation of lung tumors by benzo[*a*]pyrene.

In certain cases, retinol derivatives or analogs can even have an effect on cells that have been transformed. Richard Swarm (Hoffmann–La Roche, Nutley, New Jersey) has shown that 13-*cis*-retinoic acid can inhibit the growth of transplanted chondrosarcomas in rats. Werner Bollag (Hoffmann–La Roche, Basel, Switzerland) has demonstrated that retinoic acid can cause a marked reduction in the size of dimethylbenzanthracene-induced papillomas in mice. Bollag has also shown that retinoic acid analogs can produce regressions in squamous cell and basal cell carcinomas in mice and humans.

There is, unfortunately, little theoretical support for these observations, primarily because so little is known about the role of vitamin A in normal differentiation. Part of the effect, as suggested by Hill's work, may result from the inhibition of enzymes that activate certain chemicals to their carcinogenic form. But Chopra has shown that retinoic acid can inhibit the effects of some carcinogens that do not require activation.

An alternative possibility, suggests Monte Meltzer (NCI) is that the vitamin A compounds somehow stimulate the immune system to be more effective in countering malignancy. Meltzer has thus found that retinyl palmitate can produce a hundredfold potentiation of the antitumor effects of BCG, another stimulant of immune response. But a determination of whether either of these mechanisms or perhaps some unexpected one is operative will require more experimentation.

Although these results are very encouraging, they are also somewhat distressing for they hold the potential to provoke a new nutritional fad that could far outstrip those associated with vitamins C and E. Unlike C and E, vitamin A is highly toxic at doses only slightly higher than the minimum daily requirement. It produces effects that include pathological changes in the skin, generalized itching, loss of hair, blurring of vision, and headaches. Many of the scientists are thus screening synthetic analogs of retinol for new compounds that do not exhibit these side effects. But until such analogs are found, any self-medication or increased consumption of vitamin A could prove extremely hazardous.

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