Some of the most effective anti-cancer drugs are fluoride containing compounds, such as fluorouracil; others, especially certain inorganic salts, tend to stimulate the growth of a neoplasm.

This paradoxical action of fluoride is well established in other phases of fluoride research. It is illustrated by Berman on page 1530f this issue with respect to fluoride's inotropic effect on the heart muscle.

When the fluoride ion is incorporated into the molecule of dimethylaminoazobenzene, a powerful carcinogen, the cancer-producing ability of this compound is enhanced seven times as much as by substitution with other halogens(1). This occurs even in the 4-position in which all other substituents reduce or eliminate the carcinogenicity.

Among inorganic fluoride compounds, beryllium fluoride and cerium fluoride have produced experimental tumors. In these compounds the role of the fluoride ion is not clear.

Beryllium fluoride is one of the most potent neoplastogenic of all beryllium compounds when inhaled in long-term experiments in extremely small doses (2). According to Cember (3) radioactive cerium fluoride produces cancer in rats by intratracheal insufflation. The radioactivity of this compound rather than the fluoride component appears to be primarily responsible for this action. Whether or not the fluoride ion acts as a synergist was not explored by the authors.

In a Canadian fluorospar mining community, St. Lawrence, Newfoundland, during a 10 year period, 23 of 51 deaths were due to lung cancer among employees with one or more years of underground mining experience (4). The dust in the mine contained, on an average, 62% fluor spar (CaF$_2$) and 19% quartz. The investigators de Villers and Windish (4) attributed the cancer to radiation with an average alpha energy between 2.5 and 10 times the previous suggested working level of 1.3 x 10$^{-5}$ Mev per liter of air. However, in 9 of 60 locations of the mine, where tests for fluoride were made, the average concentration exceeded the official threshold limit values of 2.5 mg of F$^-$/m$^3$. Here too, the role of the fluoride ion was not investigated.

In the environs of two aluminum factories a Russian team, Litvinov et al. (this issue, p. 189) encountered a higher incidence of cancer mortality than in a control area seven kilometers distant where the air was less contaminated. Compared with the cancer mortality in Moscow, there was a substantially higher incidence in both factory areas. The authors were mainly concerned with studying the action of 3, 4-dimethylbenzanthracene. They
attributed the major part of the carcinogenic activity of the flydust to this compound. They also named HF as one of the contaminants. Since fluoride is generally recognized as one of the major air pollutants near aluminum plants, it could have considerable bearing on the findings of the Russian investigators. This question was not investigated by the authors.

More specifically, fluoride was implicated as a carcinogen in experiments by Taylor at the Clayton Foundation Biochemical Institute, University of Texas. He had been testing various chemicals added to drinking water of cancer-prone mice in order to determine whether they might delay or prevent the onset of cancer. The mice which were given a sodium fluoride solution at a concentration of 1 ppm in their drinking water developed cancer at an earlier age than the control animals maintained on fluoride-free water.

Taylor's preliminary work was challenged on the basis that the bone meal content of the mice's ration contained a relatively high concentration of fluoride. In subsequent experiments, Taylor eliminated this factor altogether. He carried out a total of 12 experiments involving 645 mice (5). The data indicated that drinking water containing as little as 1 ppm of fluoride shortened the life span of cancer-prone mice by an average of 9%, regardless of whether they died of cancer or another disease.

Research by two other investigating teams seems to contradict Taylor's findings:

In 1953, Fleming (6) of the Yale University School of Medicine, transplanted a tumor known as sarcoma 37 into young adult mice and guinea pigs. To one group, he administered NaF in concentrations of 20 ppm in drinking water. He injected 1,000 ppm of NaF intraperitoneally into another group. A control group bearing tumor transplants received no injections of fluoride. The daily dose was approximately 0.05 cc of the fluoride solution for the mice; a larger dose, namely 0.5 cc, for the guinea pigs because the latter are larger in size. The fluoride-treated animals bearing the tumor transplants lived longer and lost less weight than the control animals. Growth of the tumors was inhibited by fluoride.

Fleming's animals were subjected to the drug for a few weeks only. Therefore, his work does not precisely parallel that of Taylor whose mice received minute amounts of fluoride daily for a lifetime. Moreover, it is generally recognized that high doses of NaF tend to inhibit the growth of cancer implants as do many other compounds at a dosage toxic to the animal.

In the other experiments Bittner and Armstrong (7), used 36 mice that were given 5 ppm fluoride in their drinking water; a second group of 34 mice received 10 ppm. Thirty-one mice served as controls. The authors reported no significant differences in the age at which cancer developed. Only an abstract of this work was published and the full details are unavailable. The authors concluded that fluoride has no effect on longevity.
of mice. The abstract shows that the experimental animals were young; their initial weights were 18 to 25 grams; the tests were continued for less than 10 months (294 days). In order to test the effect of a compound on longevity, it is obviously necessary to keep the experiment going until the animals die of disease or of old age and to keep records of weekly or monthly deaths for each group. Moreover the number of mice, included in each group as reported in the abstract, was far too small to reveal a significant effect of fluoridated drinking water on the entire life span.

In 1964 Taylor reported studies on the effect of sodium bromide upon cancer tissue (8). He observed that sodium bromide in low concentrations stimulated the growth of cancer tissue which was cultivated in eggs as well as that transplanted into mice. Upon comparing the action of sodium bromide with that of two other halides, sodium iodide and sodium fluoride, he found that fluoride's carcinogenic effect was even more pronounced than that of the other two. Sodium fluoride stimulated cancer growth at even lower concentrations than sodium bromide (9).

These observations (9) were based on 54 experiments with 991 mice bearing transplanted tumors and 58 experiments with 1817 eggs implanted with mouse cancer tissue. The statistical significance of the results would appear to be beyond question. At very low concentrations sodium fluoride accelerated the growth of mouse cancer tissue regardless of whether it was cultivated in mice or in embryonated eggs. Stimulation of cancer growth occurred regardless of whether the mice received sodium fluoride in their drinking water, whether they received it by subdermal injection or whether it was added to a cancer tissue suspension before inoculation. Likewise in eggs, the growth-stimulating effect occurred when sodium fluoride was added to the cancer suspension before inoculation into the yolk sac and when sodium fluoride was introduced over the chick membranes of eggs containing an established growth of cancer tissue.

As an interesting sidelight, Taylor noted that when the mouse cancer tissue was cultivated in egg, the cancer grew as an independent body in the yolk sac but shared the circulatory system of the supporting chick embryo. The introduction of fluoride stimulated the growth, not only of the cancer but, of the associated chick embryo as well. This result was uniform and occurred reproducibly in hundreds of tests. On the other hand, fluoride failed to affect growth of the chick embryo when the eggs were not inoculated with cancer. In other words, the acceleration of the growth of these embryos was mediated through the effect of the fluoride on the cancer tissue.

Some of the contradictory results reported above are undoubtedly due to fluoride's well-known paradoxical biological action: In a highly dilute solution fluoride appears to stimulate tumor growth, when more concentrated to inhibit it. The concentration of fluoride added to a suspension of cancer cells before they are inoculated into eggs or mice is much higher than when present in blood plasma where there is a constant tendency toward homeostasis.
The same is true when cancer cells are cultivated in vitro. Addition of fluoride to the suspension has been shown to inhibit the growth of cells. Berry and Trillwood, as reviewed in this issue page 157, observed growth retardation of HeLa cells in a fluoride medium at a concentration of 1/10 ppm (10), DeJong at 4.5 ppm (11), Armstrong and Singer at 10 ppm (12). No research is available on whether or not fluoride in more minute amounts than those mentioned above will stimulate growth of cancer cells in vitro.

Other reasons for divergent results concerning the action of fluoride on cancer cells cultured outside of the body are outlined by Berry in this issue page 157. Some of the individual tumor cells undergo adaptive changes and acquire greater resistance to the drug. Furthermore, there is always the possibility of infection of the cells which inhibits cancer growth. In association with fluoride, infected cancer transplants grow much more slowly than the same transplants in control animals. Likewise, minor modifications of the culture medium as well as the strain of cancer cells may affect the results.

It thus appears that the question of the carcinogenic action of fluoride is far from being solved. The matter of its paradoxical action has not received adequate attention. The subject constitutes a fruitful area for further research.

Bibliography


LIVER DAMAGE IN CHRONIC FLUORIDE INTOXICATION

Cases of chronic fluoride intoxication due to industrial hazards are rarely reported in the medical literature. The following brief case report of chronic fluoride poisoning is of special interest because of liver involvement, a rarely described feature of the disease. It was presented to the editor in a letter by D. M. Gumprecht, M. D. of Coeur d'Alene, Idaho.

On October 7, 1952, J. R. S., age 32, consulted Dr. Gumprecht because of vague pain and abdominal distress, of a few days' duration, in the region of the liver and gallbladder. It had been preceded for approximately three months by episodes of "indigestion", flatulence, loss of appetite and general malaise.

The patient had previously been in perfect health. On examination he was slightly icteric. Tenderness was elicited in the right upper quadrant, in the liver and gallbladder region. The teeth exhibited a distinctly brownish discoloration. The gallbladder X-ray showed poor concentration of the dye without evidence of stones. The patient was given a diet low in fat, bile salts and a high potency vitamin B preparation.

The patient, a waterworks employee, had been adding sodium fluoride to the water supply of a pipeline during the summer months. He had to sift out the powder before adding it to the machine because of contamination by stones and other gross impurities. His health improved after a new shipment of the chemical arrived and it was no longer necessary to sift it.

However, the vague abdominal pains and general malaise persisted. Additional X-rays of the stomach, taken in April 1953, revealed a slightly enlarged duodenal loop above the head of the pancreas. The gallbladder X-ray showed improvement in the concentration of the dye. Again there was no evidence of stones. The "indigestion" and marked general malaise continued.

On November 10th, the patient experienced another episode of severe pain in the liver area with slight fever and night sweats, jaundice, anorexia, "staining of teeth" and marked general fatigue. The white blood count was slightly elevated. The symptoms subsided gradually. A consultant W. Myhre, M. D., of Spokane concurred with the diagnosis of fluoride poisoning. With increasing water demands during the summer months, the patient had to handle more fluoride which aggravated the condition.