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EDITORIAL

THE FLUORIDE-CANCER CONTROVERSY

Identification of a suspected carcinogenic and mutagenic substance is often extremely difficult. The great number of such agents involved, their interaction with each other, the slow onset of the disease, and the fact that experimental animals and humans differ in their response to cancer-producing agents are but a few of the many roadblocks in cancer research. Nevertheless, through animal experimentation and large-scale statistical surveys of human populations, certain chemicals have now been linked with the production of malignant diseases and congenital abnormalities, two conditions which seem to be interrelated. It has been shown recently that about 90% of organic compounds that were found to be mutagenic are also carcinogenic, i. e. are cancer-producing (1).

Among inorganic substances, compounds of nickel, chromium, and arsenic have been definitely identified as carcinogens or at least as contributing factors (2). It is logical to ask, therefore, if such an agent as fluoride, with its tendency to remain in many organs of the body for long periods of time, might also produce cellular abnormalities as well. Indeed, there is circumstantial, experimental, and clinical evidence linking long-term intake of minute amounts of fluoride with the production of cancer.

Circumstantial Evidence: In areas where fluorspar is mined, the incidence of lung cancer is usually quite high. For instance, in a mining community of St. Lawrence, Newfoundland, 21.8% of all employees, and 36.2% of underground miners, died of lung cancer during the years 1933 to 1961. The dust from this mine contained 62% fluorspar and 19% quartz. Unfortunately, it is not clear to what extent fluoride contributed to this condition because considerable radioactivity was also present in this mine; the role of fluoride was not investigated (3).

Similarly, in the vicinity of two aluminum factories Russian scientists (4) encountered a higher cancer mortality than in a "control" area seven kilometers distant where the air was less contaminated. Compared with the cancer death rate in Moscow, there was a substantially higher rate in both factory areas. The investigators attributed the major part of the carcinogenic activity to atmospheric 3, 4-dimethylbenzanthracene but also recorded that the contaminated air contained hydrogen fluoride. Fluorides are generally recognized as the principal air pollutants near aluminum factories and, therefore, are likely to have considerable bearing on these findings.

Additional circumstantial evidence of the carcinogenicity of fluoride is provided by V.A. Cecilioni, a physician in Hamilton, Ontario, who ob-

served an incidence of 65 deaths from lung cancer per 100,000 inhabitants close to the steel mills in that city compared with only 12 in the section of the city most distant from the factories and 23 for the Province of Ontario and for Canada as a whole. Whereas here, too, other toxic substances were emitted into the air, Cecilioni's environmental data showed a marked prevalence of fluoride in vegetation in the areas of higher cancer mortality (5).

Experimental Evidence: Experimental data also suggest, but do not prove, that fluoride is involved in the production of malignancies. Beryllium fluoride was found to be one of the most potent causes of lung tumors of all beryllium compounds tested when inhaled by rats in extremely small doses in long-term experiments (6). For instance, as little as 1.368 $\mu g/ft^3$ of beryllium fluoride was carcinogenic compared with 128 $\mu g/ft^3$ for beryllium sulfate and 1008 $\mu g/ft^3$ for beryllium phosphate.

Even more suggestive are experiments on rats by Czechoslovakian researchers who incorporated fluorine into dimethylaminoazobenzene, a powerful carcinogen, and observed that the tumor-producing ability of this compound was seven times greater than when other halogens were incorporated into the molecule (7). This was true even in the 4-position in which the other substituents such as bromine and iodine reduced or even eliminated the carcinogenicity.

These studies have considerable bearing on the significance of experiments reported in 1954 from the Clayton Foundation Biochemical Institute, University of Texas at Austin, by Alfred Taylor. Dr. Taylor had been testing various chemicals added to drinking water of cancer-prone mice in order to determine whether these agents might delay or prevent the onset of cancer. In other words, his work was not intended to study the toxicity of fluorides. Surprisingly, the mice drinking water containing sodium fluoride at the 1 ppm concentration developed cancer at an earlier age than the control animals maintained on fluoride-free water.

Taylor's preliminary work was challenged because the fluoride content of the mice's ration contained from 20-38 ppm, thus supposedly precluding a proper control. In subsequent studies, covering 12 experiments on 645 mice, Taylor eliminated this factor altogether by using a low fluoride (< 2 ppm) grain diet (8) and confirmed that as little as 1 ppm of fluoride in the drinking water shortened the life span of cancer-prone mice by an average of 9%, regardless of whether they died of cancer or of some other disease.

In an investigation that seemed to contradict Taylor's findings, H.S. Fleming of Yale University reported that 20 ppm fluoride (as sodium fluoride) in drinking water of mice bearing implants of a sarcoma inhibited, rath-

er than accelerated, the growth of the tumors (9). These experiments however covered a period of only a few weeks, not the full lifespan of the mice, and details of this work have never been published. Taylor was well aware of the retarding action of large dosages of sodium fluoride on cancer implants because most agents at a dosage toxic to animals also tend to interfere with cell growth.

In another study by J.J. Bittner and W.D. Armstrong, 36 mice received 5 ppm in their water, 34 mice 10 ppm fluoride, and 31 served as controls (10). No significant difference was observed in the age at which cancer developed. Referring to this apparent contradiction to his findings, Taylor stated: "Since our data indicate that fluoridated water does not affect every mouse in a group but only certain susceptible individuals, it becomes necessary to have large numbers of animals in order to obtain results which are not due to chance segregation. Accordingly, a control of 31 mice is entirely inadequate" (11).

Indeed, Taylor's later experiments in 1964 (12) and in 1965 (13), substantiated his earlier findings. They demonstrated that fluoride stimulated the growth of cancer more than bromide and iodide. At dosages which ranged from 1 to 1000 ppm sodium bromide in drinking water, cancer growth was accelerated, whereas in the fluoride studies concentrations of only 1 to 55 ppm sufficed to produce the same effect (11). Both halides promoted the growth of cancer tissue whether given in the drinking water to cancer-bearing mice or by subcutaneous injection, but sodium fluoride was more effective at lower concentrations. Taylor's 1965 experiments were carried out on 991 mice, bearing transplanted tumors, and on 1,817 eggs, which contained implanted mouse cancer tissue. In both cases, sodium fluoride hastened the growth of cancer tissue regardless of whether the halogen was added to the drinking water of the mice, injected into the skin, or added to a suspension of cancer tissue before its introduction into the animals. In the eggs, the growth of cancer was accelerated when sodium fluoride was added to the cancer suspension before it was inoculated into the yolk sac and also when fluoride was introduced over the membranes in the chick embryo in which cancer tissue was already growing. Thus, Taylor's work agrees with the above-quoted work of Marhold, who also found fluoride more carcinogenic than bromide. In spite of these carefully executed investigations, no further experimental studies on the possible carcinogenicity of fluoride have appeared in scientific literature.

Clinical Evidence: Certain observations on humans also strongly suggest that fluorides may, under certain conditions, contribute to the development of malignancies. Three Arizona clinicians detected giant monocytoid cells in the bone marrow, "suggestive of a reticulo-endothelial malignancy", in patients who received 16 to 150 mg fluoride per day for one to

thirty-six months in treatment of osteoporosis (14). Whereas these amounts are larger than those encountered from fluoridated water, it has recently been established that in experimental animals bone marrow-cells are subject to significant alterations in the chromosome integrity at the "optimal" fluoride concentration in drinking water.

Statistical Evidence: A different approach to the problem has been followed by J. Yiamouyiannis and Dean Burk. These scientists compared the official US mortality figures for cancer in the 10 largest fluoridated US cities with those of the 10 largest non-fluoridated cities having the same cancer death rates during the decade before fluoridation (15). Because of many variables involved in death from cancer, a study of this kind to be meaningful, requires comparison of extraordinarily large numbers of deaths. This requirement was fulfilled since, altogether, 11 million people (fluoridated) were compared with 7 million (nonfluoridated). In 1969 the overall cancer death rate was approximately 18% higher or about 3000 more per 10 million persons in the fluoridated than in nonfluoridated cities. During the prefluoridation period 1940-1950 cancer deaths increased in both groups at a practically identical rate. The average mortality from cancer increased faster in the fluoridated cities immediately after fluoridation in 1952-1956 and continued to increase for at least 10 more years.

These results differ from those obtained from a study by P.N. Sheppard, R. Doll and L.J. Kinlen (16) based on a much smaller population total (1,300,000). They found no difference in cancer mortality in British communities where water contained fluoride naturally at 1 ppm and above compared to others with 0.1 to 0.2 ppm. Unfortunately, this investigation did not take into account the British tea-drinking habit, which precludes an accurate statistical evaluation, because in England tea adds about as much fluoride to the daily diet as fluoridated water (17).

The validity of the Yiamouyiannis-Burk findings has been further challenged in a general press release by the US National Cancer Institute which urged that at least eight other conceivable factors - including age, sex, and distribution of cancer according to organs involved - be examined. A formal study by R.N. Hoover and colleagues of the National Cancer Institute discussed cancer mortality during the years 1950 to 1969 but did not deal with the same cities as those of Yiamouyiannis and Burk (18). These investigators considered the following variables: age, sex, and site of cancer at 5 year intervals in selected non-fluoridated, artificially fluoridated, and natural fluoride counties. They could not ascribe any trend of cancer mortality to the consumption of artificially fluoridated water or to water containing fluoride naturally. These scientists, however, acknowledge the many pitfalls in statistics of this kind:

> Since demographic factors such as urbanization, socio-economic class, and ethnicity affect cancer rate, we attempted to control for them by various multivariate techniques, including cross-classification and regression analyses. In addition, we made comparisons involving the same area before and after fluoridation. These methodologies cannot exclude the influence of all variables affecting cancer risk, particularly when one is dealing with heterogeneous and dynamic populations. For example, when the same area before and after fluoridation is compared to a control area, changes in other potential risk factors may have occurred differentially over time in these areas also. However, the ratios of urbanization, socio-economic, and ethnic variables in the group fluoridated in 1950-54 to those in the control group varied by 8% or less between the 1950 and 1970 censuses.

The task of relating community fluoridation measures to total county populations is complicated by the varying definitions of "community", the small size of many water districts, and the fact that some communities purchase their water from others, making it difficult to identify "exposed" and "unexposed" counties throughout the entire country (18). Indeed, the selection for comparison of two cities Birmingham, Alabama, (nonfluoridated but highly industrialized) and Denver, Colorado, (fluoridated since March 1954) both of which have had an unusually steep population growth during the study period, constitutes a major shortcoming in the Hoover statistics. Other variables having a considerable effect on mortality data that were not taken into account by either survey are the hardness of water (its mineral content other than fluoride), the increased consumption of fluoride from food and inhalation of polluted air, and the intercity and interstate transfer of fluoride-containing food and beverages.

Concerning the Yiamouyiannis-Burk findings Taves has concluded from a study of standardized mortality ratios (SMR) in the 20 largest US fluoridated and nonfluoridated cities, that the rise in cancer mortality was limited to a particular set of fluoridated cities and that their rates were higher prior to fluoridation (19). He noted that only one of the fluoridated cities has gained in population from 1950-1970, in contrast to seven of the nonfluoridated cities.

In rebuttal, Yiamouyiannis et al. have shown that the SMRs can be misleading and that actual age-group data are needed to make reliable comparisons. They extended their analysis of cancer mortality to allow for differences in age, sex, and race (20). In this further study the cancer death rates for persons up to age 45 in the ten largest fluoridated and ten largest nonfluoridated US cities differed only slightly. For the age groups

45-64 and 65 and over, however, the cancer death rates were significantly higher in the fluoridated than in the nonfluoridated cities. No significant sex ratio differences were found in any of the age groups of the two sets of cities, and in the fluoridated cities the increases in nonwhite populations did not correlate with the increased cancer death rate in the older age groups.

In assessing the possible carcinogenicity of fluoride, it is well established that certain fluoride-containing agents, such as fluorouracil, have been used successfully to treat cancer and do indeed slow down the growth of cancer. Such paradoxical behavior of the halogen is not unexpected because in organic compounds the covalently bound fluorine atom merely reinforces the action of the parent molecule in contrast to its own specific properties when fluoride is in an inorganic (ionic) form. But even by itself, especially in large doses, fluoride is known to interfere with cell growth (21) and is, therefore, likely to be inhibitory toward cancer.

The above data suggest that fluoride warrants a high priority for study as an environmental carcinogen. Its potential as a cancer-producing agent has not been recognized because it has only recently emerged as a significant industrial pollutant. Its ubiquity in air, food and water, the high physiological reactivity, and its tendency to accumulate in the body, make it a prime candidate for the induction of malignant diseases. Its potential as a carcinogen, however, has been obscured because scientists and scientific organizations regard fluoride as a harmless agent. To date, the clinical evidence concerning the carcinogenicity of fluoride is sparse, and the available statistics do not permit a final conclusion. On the other hand, Taylor's findings leave no doubt that 1 ppm fluoride in water accelerates cancer growth in mice and the findings of Yiamouyiannis and Burk greatly increase the likelihood that fluoridated water does indeed promote cancer.

Bibliography

1. Ames, B.N., McCann, J. and Sawyer, C.: Mutagens and Carcinogens. Science, 194:132-133, 1976. 2. Waldbott, G.L.: Health Effects of Environmental Pollutants. C.V. Mosby Co., St. Louis, 1973. 3. deVilliers, A.J. and Windish, J.P.: Lung Cancer in the Fluorspar Mining Community. Radiation, Dust, and Mortality Experience. Brit. J. Ind. Med., 21:94-109, 1964. 4. Litvinov, N.N., Goldberg, M.S., Kimina, S.N.: Morbidity and Mortality in Man Caused by Pulmonary Cancer and Its Relation to the Pollution of the Atmosphere in the Areas of Aluminum Plants. Acta Unionis Internationalis Contra Cancrum, 19:742-745, 1963. 5. Cecilioni, V.A.: Further Observations on Cancer in a Steel City. Fluoride, 7:153-165, 1974. 6. Schepers, G.W.H.: Neoplasia Experimentally Induced in Beryllium Compounds. Progr. Exp. Tumor Res., 2:203-244, Karger, Basel, New York, 1961. 7. Marhold,

J. and Matrka, M.: Carcinogenicity and Oxidation of Fluoro-Derivatives of Dimethylaminoazobenzene. Fluoride, 2:85-90, April 1969. 8. Taylor, A.: Sodium Fluoride in Drinking Water of Mice. Dent. Digest, 60:170-172, 1954. 9. Fleming, H.S.: Effect of Fluorides on the Tumors 37 After Transplantation to Selected Locations in Mice and Guinea Pigs. (Abstract) J. Dent. Res., 32:646, 1953. 10. Bittner, J.J. and Armstrong, W.D.: Lack of Effects of Fluoride Ingestion on Longevity of Mice. (Abstract) J. Dent. Res., 31:495, 1952. 11. Taylor, A.: Letter to the Science Editor, Fluoride and Cancer. Saturday Rev. Oct. 2, 1965, p. 73. 12. Taylor, A.: Effect of Sodium Bromide on Cancer Growth. Cancer Res., 24:751-3, May 1964. 13. Taylor, A.: Effect of Sodium Fluoride on Tumor Growth. Proc. Soc. Exp. Biol. Med., 119:252-5, 1965. 14. Duffey, P.H., Tretbar, H.C. and Jarkowski, T.L.: Giant Cells in Bone Marrows of Patients on High-Dose Fluoride Treatment. Ann. Int. Med., 75:745-47, 1971. 15. Yiamouyiannis, J. and Burk, Dean: Fluoridation of Public Water Systems and Cancer Death Rates (CDRS) in Humans. Federation Proc., Abst. 67th Ann. Meeting Amer. Soc. Biol. Chemists, San Francisco, 35:1707, 1976. 16. Sheppard, P.N., Doll, R., and Kinlen, L.J.: Fluoridation. New Scientist, 69:304, Feb. 5, 1976. 17. Cook, H.A.: Fluoride Intake Through Tea in British Children. Fluoride, 3:12-18, 1970. 18. Hoover, R.N., McKay, F.W. and Fraumeni, J.F.: Fluoridated Drinking Water and the Occurrence of Cancer. J. Natl. Cancer Institute, 57:757-68, 1976. 19. Taves, D.R.: Fluoridation and Cancer Mortality. Unpublished paper, University of Rochester, N.Y., supported by the U.S. Publ. Hlth. Serv., Grant No. GM 15190. 20. Yiamouyiannis, J. and Burk, Dean: Fluoridation and Cancer. Age-Dependence of Cancer Mortality Related to Artificial Fluoridation. Fluoride, 10:102-125, 1977. 21. Berry, R.J. and Trillwood, W.: Sodium Fluoride and Cell Growth. Brit. Med. J., 2:1064, Oct. 1963.

G.L.W.

FLUORIDATION AND CANCER
AGE-DEPENDENCE OF CANCER MORTALITY RELATED TO ARTIFICIAL FLUORIDATION

by

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Delaware, Ohio and Washington, D.C.

SUMMARY: Data indicating a more rapid increase in cancer death rate in fluoridated than in nonfluoridated cities were analyzed to determine to what extent the net increase observed in fluoridated cities could be attributed to age, race, or sex. Between 1952 and 1969, no significant fluoridation-linked increase in cancer death rate could be observed in populations 0-24 and 25-44 years of age. In populations 45-64 years of age, a fluoridation-linked increase in cancer death rate of 15/100,000 population was observed ($P < .02$); in populations 65+ years of age, an increase of 35/100,000 was observed ($P < .05$). The fluoridation-linked increase in cancer death rate could not be ascribed to changes in the racial or sex compositions of the fluoridated and nonfluoridated populations.

Tumorigenic effects of low levels of fluoride have been reported by Herskowitz and Norton (1) who were able to induce tumors in 5-90% of the fruit flies exposed to 20 to 50 ppm fluoride with a dose-dependent effect. Taylor and Taylor (2) observed a 13-17% increase in tumor growth rate in cancer-prone mice fed 1 ppm fluoride in the drinking water.

A number of other papers have demonstrated mutagenic effects of fluoride (3-15). Most recently, reports that low levels of fluoride added to the drinking water of mice can cause chromosomal damage have aroused more concern (16). As little as 1 to 5 ppm fluoride given to mice fed low-fluoride diets produced a significant dose-dependent increase in the rate of chromosomal aberrations in the testes and bone marrow of mice within 3 to 6 weeks (17). It is generally agreed that the mutagenic activity of a substance in such systems could be a warning of its possible cancer-causing activity.

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Presented at the 8th Conference of the International Society for Fluoride Research, Oxford, England, May 29-31, 1977.

The purpose of this paper is to present a detailed analysis of the cancer death rates of residents of fluoridated and nonfluoridated cities to see if the implications and observations concerning the carcinogenicity of fluoride observed under controlled laboratory conditions with animals could be confirmed epidemiologically in humans.

Methods

The ten largest fluoridated cities* in the United States were taken as the experimental group. In 1953, the year closest to the initiation of fluoridation for which cancer death rate data from the National Center for Health Statistics are available, the cancer death rate of each of these cities was above 155 cancer deaths per 100,000 inhabitants. The ten largest cities in the United States not fluoridated as of 1969 but with a 1953 cancer death rate greater than 155 per 100,000 per year were taken as the control group (Table 1).

Total cancer deaths for each of the cities for 1940-50 and 1953-69 were obtained from **Vital Statistics of the U.S.** for those years. City data were not reported in **Vital Statistics** for 1951 and 1952. Total cancer deaths for Boston were not reported for 1953-4 and 1956-8. These figures were estimated by linear interpolation.

Annual resident cancer deaths from 1952 to 1969 by age (0-24, 25-44, 45-64, and 65+) for Philadelphia, Cleveland, Pittsburgh, New Orleans, Seattle, Cincinnati, Atlanta, Columbus, Newark, and Portland were provided by the respective state health departments. Similar data for Baltimore, Milwaukee, and Boston were provided through the respective city health departments or their annual reports. Data for Washington, D.C. were obtained through **Vital Statistics** and data for St. Louis, Kansas City, San Francisco, Los Angeles, and Chicago** were obtained through the respective state health departments or their annual reports and in part through their city health departments. Buffalo data were supplied by the Erie County Health Department. Similar data for race and sex (where available) were obtained through the same sources. Missing data for Philadelphia and Pittsburgh in 1952 and Buffalo in 1968 were supplied by means of linear extrapolation and interpolation. Cancer death rates by site were obtained from **Vital Statistics of the U.S.** published by the National Center for Health Statistics. Age-, race-, sex-specific population estimates for these cities were obtained by linear interpolation of census figures.

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*According to the 1960 census, "cities" as used in this manuscript refers to central cities.
**For Chicago, occurrence cancer deaths for 1952-8 for each age group were normalized to resident cancer deaths; for Kansas City, residence-occurrence deaths for 1952-9 for each age group were normalized to residence cancer deaths.

Table 1

Selection of Cities

	Fluoridated Before 1960	CDR Greater Than 155/100,000 in 1953	Date Fluoridated
1 Chicago	x	x	1956
2 Philadelphia	x	x	1954
3 Baltimore	x	x	1952
4 Cleveland	x	x	1956
5 Washington	x	x	1952
6 Milwaukee	x	x	1953
7 St. Louis	x	x	1955
8 San Francisco	x	x	1952
9 Pittsburgh	x	x	1952-3
10 Buffalo	x	x	1955

	Not Fluoridated as of 1969	CDR Greater Than 155/100,000 in 1953	Date Fluoridated
New York		x	1965
1 Los Angeles	x	x	—
Detroit		x	1967
Houston	x		—
2 Boston	x	x	—
Dallas			1966
3 New Orleans	x	x	*
San Antonio	x		—
San Diego	x		—
4 Seattle	x	x	*
5 Cincinnati	x	x	*
Memphis	x		—
6 Atlanta	x	x	*
7 Kansas City (Mo.)	x	x	—
8 Columbus (O.)	x	x	*
Phoenix	x		—
9 Newark	x	x	—
10 Portland	x	x	

*December 1969 or thereafter

To study the effects of artificial fluoridation, calculations of the total cancer death rate were made year-by-year prior to fluoridation of the experimental group, 1940 to 1950, and after fluoridation of the experimental group but before any fluoridation of the control group, 1953-1969. In addition, linear regression analysis of cancer death rates of each of the age groupings 0-24, 25-44, 45-64, and 65+ were made from 1952 to 1969. All averages of cancer death rates are unweighted averages. Age-adjusted cancer death rates were also computed by the direct method using a reference population with an age distribution intermediate between the control and experimental groups.

Census figures were obtained from **Census of the U.S. Population** 1940, 1950, 1960, and 1970 and from Special Report PC (3) 1D, published by the U.S. Bureau of the Census.

Data regarding fluoridation status of experimental and control cities were obtained from **Fluoridation Census 1969**, published by the Division of Dental Health, U.S. Public Health Service.

Results

The crude cancer death rates of both groups of cities had a strikingly similar trend between 1940 and 1950 (Figure 1). Subsequent to fluoridation however, an equally striking divergence could be observed that was maintained through 1969, the last year of study. This increase in crude cancer death rate could be observed in virtually all of the fluoridated cities when compared to the control cities, indicating that the difference in averages was not due to the sharp increase in cancer death rate of only one or two of the fluoridated cities (Table 2). Figure 2 indicates the increase in deaths due to cancers of various tissues.

Since cancer death rates are dependent on the age distribution of a population, the age distributions of both groups of cities were compared for 1950, 1960, and 1970 (Table 3). The trends in age distribution for the two groups of cities are similar; however, a slightly more rapid increase in the age of the population of the fluoridated cities as compared to that of the nonfluoridated cities was observed.

To determine whether this slight age differential might account for the divergence in crude cancer deaths following fluoridation, year-by-year cancer death rates were computed for each of the age groups 0-24, 25-44, 45-64, and 65+ for both the fluoridated (Table 4) and nonfluoridated (Table 5) groups of cities; year-by-year averages of cancer death rates for both groups were also computed. Linear regression analysis of the year-by-year averages (Table 6a) indicates a significant decrease in the cancer death rates in both groups of cities in the 0-24 age group and a less significant decrease in the 25-44 year age group.

In populations 45 and over, an increase in cancer death rate was observed in

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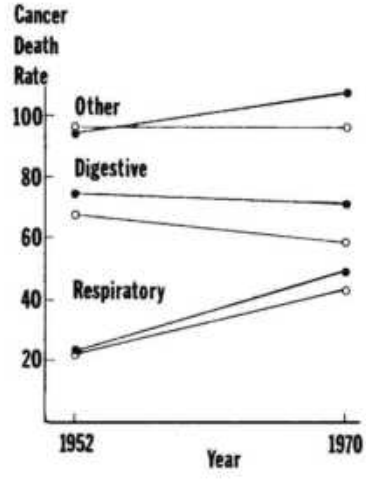
Figure 1

Vertical lines at 1952 and 1956 contain the period during which fluoridation of the experimental group began. All figures represent crude cancer death rates.

Figure 2



Lines represent a linear regression of year-by-year deaths due to cancers as listed above.

Table 2

Cancer Death Rates (CDRs) Before and After Fluoridation

	Average 5-Year CDR Before Fluoridation	Average 5-Year CDR After Fluoridation	
Cities Fluoridated in 1952			
Baltimore	171	195	+24
Washington	157	178	+21
San Francisco	193	214	+21
10 Control Cities	177*	188	+11
Cities Fluoridated in 1953			
Milwaukee	176*	187	+11
Pittsburgh	177*	219	+42
10 Control Cities	178*	188	+10
Cities Fluoridated in 1954			
Philadelphia	187	205	+18
10 Control Cities	182*	190	+08
Cities Fluoridated in 1955			
St. Louis	201	223	+22
Buffalo	193*	212	+19
10 Control Cities	184*	190	+06
Cities Fluoridated in 1956			
Chicago	188*	196	+08
Cleveland	188*	199	+11
10 Control Cities	188*	190	+02

*1951 and/or 1952 data missing from **Vital Statistics.**

Table 3

Age Distribution (as %) of Fluoridated & Nonfluoridated Populations

	Fluoridated	Nonfluoridated
	0-24	
1950	35.71	36.15
1960	39.78	41.03
1970	42.94	44.80
	25-44	
1950	32.83	32.17
1960	26.40	26.20
1970	22.74	23.19
	45-64	
1950	23.30	22.73
1960	23.27	22.14
1970	22.42	20.82
	65+	
1950	8.18	8.94
1960	10.54	10.63
1970	11.91	11.17

Table 4 Year-by-Year Cancer Death Rates by Age Group — Fluoridated Cities

	Under Age 25									Age 25 To 44									Age 45 To 64								
	Chicago	Philadelphia	Baltimore	Cleveland	Washington	Milwaukee	St. Louis	San Francisco	Pittsburgh	Buffalo	Average	Chicago	Philadelphia	Baltimore	Cleveland	Washington	Milwaukee	St. Louis	San Francisco	Pittsburgh	Buffalo	Average	Chicago	Philadelphia	Baltimore	Cleveland	Washington	Milwaukee	St. Louis	San Francisco	Pittsburgh	Buffalo	Average
1952	15	9	9	8	8	8	10	8	9	9	9	346	350	380	357	326	309	313	315	351	350	340											
1953	12	9	10	7	11	12	8	9	12	6	10	345	353	362	355	342	311	318	316	391	333	343											
1954	11	9	9	7	10	8	7	11	8	12	9	334	358	352	361	343	338	344	306	372	355	346											
1955	15	8	7	10	9	8	10	7	12	11	10	341	339	359	348	309	320	327	339	389	345	342											
1956	11	8	8	8	11	9	6	12	6	12	9	360	372	395	357	344	317	358	326	380	357	357											
1957	12	9	9	8	10	11	6	11	8	9	9	353	374	403	354	382	302	337	337	372	354	357											
1958	12	8	9	6	10	9	9	10	8	11	9	338	346	371	364	382	317	351	321	334	357	348											
1959	9	8	7	6	9	8	5	11	7	11	8	331	351	373	360	370	285	386	327	369	351	350											
1960	10	8	5	10	7	8	6	9	5	10	8	349	374	380	357	369	277	379	321	348	305	346											
1961	9	8	7	12	9	4	8	7	10	9	8	335	361	360	350	364	268	361	328	388	366	348											
1962	8	9	6	7	7	7	8	9	9	7	8	336	366	364	368	364	290	364	340	374	323	349											
1963	9	8	7	7	8	9	8	8	9	8	8	353	342	386	359	368	290	376	320	388	361	354											
1964	8	7	8	8	8	6	9	8	7	9	8	345	362	375	341	369	316	357	337	413	365	358											
1965	9	9	8	7	7	6	6	11	10	8	8	348	359	413	339	406	316	364	361	404	344	365											
1966	8	8	7	9	9	9	7	7	9	4	8	348	367	403	374	383	272	399	322	413	406	369											
1967	9	8	6	5	10	9	5	9	8	6	8	361	369	404	402	375	309	396	327	430	351	372											
1968	8	7	8	10	7	6	8	9	8	7	8	365	378	392	425	413	323	416	362	436	374	388											
1969	7	7	6	8	4	6	7	10	6	11	7	369	393	406	373	390	328	402	356	459	360	384											
1952	48	51	56	49	51	51	37	46	53	48	49	1043	1056	1022	1084	Age 65 & Over 973	1192	905	1067	1094	1018	1045											
1953	46	52	49	43	48	57	39	46	60	47	49	1030	1057	992	1044	923	1086	947	990	1061	1042	1017											
1954	51	48	46	41	60	52	51	44	51	52	50	1034	1046	1082	1047	932	1129	923	989	1094	1053	1033											
1955	54	47	55	53	48	37	45	42	53	42	48	999	1044	1079	1094	987	1108	944	981	1167	1079	1048											
1956	53	51	52	53	51	38	52	35	59	49	49	1007	1090	1077	1060	1088	1169	980	1033	1119	1010	1063											
1957	53	52	49	47	47	41	58	42	48	49	49	1028	1101	1044	1089	1090	1092	1029	1075	1158	1027	1073											
1958	55	50	56	49	51	41	55	43	53	44	50	997	1012	1049	1107	960	1051	1000	953	1092	1135	1036											
1959	48	48	54	46	55	46	54	39	40	65	50	1006	1051	1079	1048	1010	920	1003	874	1050	1081	1012											
1960	49	48	68	50	58	40	54	44	43	54	51	1049	1037	1056	1069	921	1063	1025	1027	1058	1011	1032											
1961	50	47	52	50	48	30	46	39	47	51	46	1045	1062	1097	1145	916	867	1017	1035	1070	1140	1039											
1962	50	50	56	51	45	41	60	44	45	52	49	1015	1034	1009	1200	963	1019	961	1012	1045	1068	1033											
1963	45	51	58	46	55	37	61	38	41	41	47	1047	1090	1032	1194	945	1058	974	1056	1069	1110	1058											
1964	50	48	55	46	51	42	51	33	46	39	46	1033	1068	1098	1171	1026	1010	983	1034	1068	1028	1052											
1965	50	49	56	48	54	35	54	45	63	52	51	1069	1073	1137	1186	956	1034	942	1101	1045	1251	1079											
1966	51	48	55	39	47	45	60	39	59	60	50	1066	1117	1096	1204	1062	1064	1086	1025	1155	1107	1098											
1967	47	48	46	46	62	38	54	37	46	59	48	1052	1049	1092	1200	1047	1068	983	1076	1161	1117	1085											
1968	49	48	55	39	46	33	55	34	52	51	46	1064	1036	1138	1128	1016	1074	984	1061	1155	1103	1076											
1969	46	43	47	49	54	46	58	31	36	44	45	1033	1053	1108	1114	1005	999	976	1016	1063	1029	1040											

Table 5 Year-by-Year Cancer Death Rates by Age Group — Nonfluoridated Cities

Under Age 25

	Los Angeles	Boston	New Orleans	Seattle	Cincinnati	Atlanta	Kansas City	Columbus	Newark	Portland	Average
1952	10	9	9	9	8	16	6	11	12	10	10
1953	9	6	11	9	8	14	9	12	7	9	9
1954	8	12	8	10	9	15	8	8	9	12	10
1955	10	6	17	7	9	7	12	7	11	11	10
1956	10	7	9	14	9	9	10	4	9	8	9
1957	8	5	8	12	8	7	7	7	10	9	8
1958	9	6	10	8	11	8	9	6	10	5	8
1959	8	7	17	8	7	8	7	7	7	12	9
1960	8	9	14	6	6	8	8	8	9	14	9
1961	8	9	10	10	6	9	9	8	11	9	9
1962	9	9	13	7	5	9	6	7	5	6	8
1963	9	8	13	11	7	6	8	7	5	7	8
1964	8	8	7	9	9	5	7	9	11	8	8
1965	6	8	11	7	7	8	5	6	7	7	7
1966	9	8	8	8	9	5	11	4	7	5	7
1967	9	7	7	7	8	5	6	8	10	6	7
1968	9	6	8	7	6	6	9	9	7	14	8
1969	8	7	5	6	9	9	5	8	10	11	8

Age 25 To 44

	Los Angeles	Boston	New Orleans	Seattle	Cincinnati	Atlanta	Kansas City	Columbus	Newark	Portland	Average
1952	39	39	47	46	44	70	45	36	46	34	45
1953	44	38	55	36	52	65	47	53	49	35	47
1954	42	46	43	48	44	61	49	44	47	44	47
1955	43	47	42	42	49	70	38	46	62	44	48
1956	44	39	55	44	50	65	33	46	46	47	47
1957	38	44	48	36	45	63	33	36	48	38	43
1958	45	45	47	42	63	62	51	39	59	39	49
1959	42	43	51	47	59	53	43	42	51	50	48
1960	38	45	53	36	67	50	46	42	43	41	46
1961	39	54	55	40	59	68	44	29	49	50	49
1962	44	46	61	49	49	43	39	38	43	37	45
1963	43	43	51	34	44	41	45	41	53	49	44
1964	42	43	58	40	56	51	44	46	61	38	48
1965	38	53	50	34	49	49	54	38	50	28	44
1966	44	53	50	37	55	58	45	44	45	24	46
1967	36	41	59	36	56	45	44	37	53	44	45
1968	37	27	52	49	54	49	46	46	49	38	45
1969	38	38	55	30	50	45	29	33	55	44	42

Age 45 To 64

	Los Angeles	Boston	New Orleans	Seattle	Cincinnati	Atlanta	Kansas City	Columbus	Newark	Portland	Average
1952	274	345	394	275	332	383	276	259	391	265	319
1953	281	328	359	274	355	370	313	288	405	322	330
1954	285	354	367	276	358	431	289	344	386	258	335
1955	291	298	392	341	358	379	302	312	385	261	332
1956	295	349	402	296	336	378	297	305	397	277	333
1957	277	344	364	286	336	338	304	317	392	285	324
1958	290	347	410	306	348	378	317	348	392	258	339
1959	308	347	342	304	351	342	309	326	415	273	332
1960	279	396	387	278	365	318	314	335	381	319	337
1961	296	358	371	310	352	321	316	321	383	261	329
1962	289	358	341	284	373	315	277	315	379	306	324
1963	296	368	392	269	365	384	339	327	388	288	342
1964	300	365	388	296	379	345	308	315	359	291	335
1965	292	378	361	304	346	377	311	304	424	283	338
1966	284	365	383	296	361	383	311	330	433	291	344
1967	287	370	405	300	409	368	341	299	427	326	353
1968	304	341	402	274	416	369	349	343	346	340	348
1969	300	347	409	318	435	363	349	343	355	300	352

Ages 65 & Over

	Los Angeles	Boston	New Orleans	Seattle	Cincinnati	Atlanta	Kansas City	Columbus	Newark	Portland	Average
1952	900	1113	998	911	1040	1048	969	942	1156	832	991
1953	895	1088	1013	968	972	902	968	1028	1174	825	983
1954	844	1249	679	969	1008	877	935	969	1171	874	978
1955	859	1219	1004	1010	1066	961	898	937	1038	837	983
1956	914	1075	1018	1026	1050	855	876	866	1052	806	954
1957	939	1198	1055	974	1039	872	858	959	1148	878	992
1958	863	1106	1089	986	996	746	909	1067	1038	889	969
1959	904	1030	984	1000	1035	913	876	1030	1123	815	971
1960	900	1092	952	964	1032	788	948	927	926	846	938
1961	896	1108	991	969	996	834	852	960	1178	845	963
1962	865	1218	905	920	1059	827	931	1023	1167	959	987
1963	914	1185	959	869	951	881	874	991	1078	913	962
1964	895	1104	1008	905	1053	903	905	985	1074	920	975
1965	898	1127	1092	964	1091	934	879	1014	1093	901	999
1966	947	1084	1008	947	1007	871	961	1006	1040	828	970
1967	931	1016	940	916	1062	899	1038	962	1106	920	979
1968	940	1017	1016	1032	1134	808	1004	932	1155	833	987
1969	937	1135	978	931	1168	803	899	982	1123	918	987

Table 6a

Linear Regression of Year-By-Year Average Cancer Death Rates (N=18)

Age Group	Cities	Sample Size	Correlation Coefficient	Slope	Cancer Death Rate-1952	Cancer Death Rate-1969	CDR Increase 1952-1969	P
0-24	Fluoridated	18	-0.8802	-0.1414	9.70	7.30	-2.40	$< 10^{-5}$
	Nonfluoridated	18	-0.7954	-0.1465	9.69	7.20	-2.49	$< 10^{-4}$
25-44	Fluoridated	18	-0.4754	-0.1651	49.96	47.15	-2.81	< .05
	Nonfluoridated	18	-0.4127	-0.1569	47.33	44.67	-2.66	< .10
45-64	Fluoridated	18	0.8375	2.165	338.3	375.1	36.8	$< 10^{-5}$
	Nonfluoridated	18	0.7826	1.395	323.5	347.2	23.7	$< 10^{-4}$
65+	Fluoridated	18	0.4901	2.186	1032.8	1069.9	37.1	< .05
	Nonfluoridated	18	0.0678	0.1920	974.4	977.6	3.2	NS

P value tests $r \neq 0$ with 100 (1-P)% certainty NS - not significant

all cases with the exception of the nonfluoridated 65+ age group. Linear regression analysis of year-by-year cancer death rates from individual city data (Table 6b) confirms these findings.

In addition, the increases in cancer death rates for both 45-64 and 65+ age groups are greater for the fluoridated group of cities than for the nonfluoridated group of cities, whereas no significant differential in cancer death rate trends in the 0-24 and 25-44 year age groups are evident. To test the significance of these differences, a linear regression analysis of year-by-year differences of the average cancer death rates of the fluoridated group of cities minus the average cancer death rates of the nonfluoridated group of cities was performed (Table 7). No significant difference in the cancer death rate of either the 0-24 or 25-44 year age group could be observed; however significant increases were observed in fluoridated cities in populations 45 and over: an increase of 15.2 cancer deaths per 100,000 population ($P < .02$) in the 45-64 year age group and an increase of 35.4 cancer deaths per 100,000 population ($P \leq .05$) in the 65+ age group. The differences observed are quite similar to the differences that would be computed from Tables 6a and 6b (Table 8).

Whereas the cancer death rate in the fluoridated cities is clearly increasing faster than in the nonfluoridated cities, it might still be argued that the age intervals chosen were too large and that the 45-64 year age group in the fluoridated cities is growing older faster than the same age group in the nonfluoridated cities, and similarly for the 65+ age group. Table 9 shows that the age distribution trends within these age groups are virtually identical and dispels such an objection.

Age-corrected cancer death rates were calculated by using a reference population with an age distribution intermediate between those of the fluoridated and nonfluoridated populations of 1952 and 1969 (Table 3 and Table 10).

The age-corrected cancer death rates appear on Table 11 and reflect 8-9 more cancer deaths per 100,000 population per year in the fluoridated cities than in the nonfluoridated cities.

There is a greater increase in the percentage of nonwhites in the fluoridated group of cities than in the nonfluoridated group. Most of this increase occurs in the 0-24 and 25-44 year age groups, with smaller increases observed in the 45-64 and 65+ age groups (Table 12). To determine whether this relative increase in nonwhite population could account for the increase in cancer death rate observed in fluoridated cities, a regression analysis of increase in age-adjusted cancer death rate against increase in % nonwhite population was performed for each city. No significant correlation could be obtained. Similarly, since the most significant increase in cancer death rate of fluoridated cities in excess of that of nonfluoridated cities occurred in the 45-64 age group, a linear regression of increase in cancer death rate of cities for this group as a function of increase in % nonwhite population was performed. Again no significant correlation could be observed.

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Table 6b

Linear Regression of Year-By-Year Cancer Death Rates for Each City (N=180)

Age Group	Cities	Sample Size	Correlation Coefficient	Slope	Cancer Death Rate-1952	Cancer Death Rate-1969	CDR Increase 1952-1969	P
0-24	Fluoridated	180	-0.3792	-0.1388	9.57	7.08	-2.49	≤ 10
	Nonfluoridated	180	-0.3097	-0.1416	9.67	7.12	-2.55	$<10^{-4}$
25-44	Fluoridated	180	-0.0857	-0.1123	49.42	47.40	-2.02	NS
	Nonfluoridated	180	-0.1026	-0.1673	47.39	44.38	-3.01	<.20
45-64	Fluoridated	180	0.3722	2.257	337.2	377.9	40.7	$<10^{-5}$
	Nonfluoridated	180	0.1603	1.341	324.5	348.6	24.1	<.05
65+	Fluoridated	180	0.1790	2.246	1031.9	1072.4	40.5	<.02
	Nonfluoridated	180	0.0109	0.2100	974.2	978.0	3.8	NS

P value tests $r \neq 0$ with 100 (1-P)% certainty
NS - not significant

Table 7

Linear Regression of Year-by-Year Differences in Average Cancer Death Rates

Age Group	Sample Size	Correlation Coefficient	Slope	Difference* in CDR F-NF 1952	Difference in CDR F-NF 1969	Increase in Difference in CDR F-NF from 1952 - 1969	P
0-24	18	0.1443	0.0227	-0.1929	+0.2157	+0.41	NS
25-44	18	0.0196	0.0093	+2.212	+2.370	+0.16	NS
45-64	18	0.5294	0.8916	+12.98	+28.13	+15.2	<.02
65+	18	0.4338	2.0815	+57.36	+92.75	+35.4	<.05

P value tests $r > 0$ with 100 (1-P)% certainty.

*The difference in cancer death rate obtained by linear regression of the year-by-year differences in the average cancer death rate of the ten fluoridated cities minus the ten nonfluoridated cites. NS - not significant

Table 8

Increase in the Difference in Cancer Death Rate (per 100,000) of Fluoridated Cities and Nonfluoridated Cities by Age from 1952 to 1969

	Age Group			
Method*	0-24	25-44	45-64	65+
6a	+0.09	-0.15	+13.1	+33.9
6b	+0.06	+0.99	+16.4	+36.7
7	+0.41	+0.16	+15.2	+35.4
	(NS)	(NS)	(P <.02)	(P <.05)

Table 9

Age Distribution Within Age Groups 45-64 and 65+ for Fluoridated (F) and Nonfluoridated (NF) Cities

	1950	1960	1970
F (55-64/45-64)	.43	.45	.48
NF (55-64/45-64)	.43	.45	.47
F (75+/65+)	.29	.31	.37
NF (75+/65+)	.29	.34	.38

Table 10

Age Distribution of Reference Population

	0-24	25-44	45-64	65+
1952	36.72	31.55	22.88	8.86
1969	43.47	23.45	21.69	11.39

This table was obtained by taking an average of the values for 1950 and 1970 on Table 3 and interpolating to obtain an age distribution exactly between the fluoridated and nonfluoridated cities for 1952 and 1969.

Table 11

Age-Adjusted Cancer Death Rates (per 100,000) of Fluoridated and Nonfluoridated Cities

	1952	1969	Increase*
Fluoridated Cities			
6a	188.25	217.46	29.21
6b	187.69	218.31	30.63
Nonfluoridated Cities			
6a	178.83	200.26	21.43
6b	179.08	200.50	21.43
Difference			
6a	9.42	17.20	7.78
6b	8.61	17.81	9.20
7	8.68	17.32	8.64

*As calculated by the methods described in Tables 6a, 6b, and 7.

Table 12

% Nonwhite in Fluoridated and Nonfluoridated Cities for 1950, 1960 & 1970

	Total	0.24	25-44	45-64	65+
1950					
Fluoridated	15.9	18.36	17.50	12.56	8.07
Nonfluoridated	15.3	17.27	18.61	12.64	9.28
Difference	0.6	1.09	-1.11	-0.08	-1.21
1960					
Fluoridated	25.7	31.50	27.81	18.92	11.95
Nonfluoridated	20.7	24.59	22.45	16.27	11.29
Difference	5.0	6.91	5.36	2.65	0.66
1970					
Fluoridated	35.4	42.79	37.39	27.13	18.72
Nonfluoridated	28.6	34.17	29.02	22.76	16.29
Difference	6.8	8.62	8.37	4.37	2.43
Net Increase in F-NF from 1950 to 1970	6.2%	7.53%	9.48%	4.45%	3.64%

While nationally the cancer death rate of nonwhites is increasing faster than the cancer death rate of whites, we have been unable to observe such a trend in central cities. When the cancer death rate of nonwhites was plotted as a function of the proportion of nonwhites living in central cities to total nonwhites living in the U.S. ($NW_{cc}/NW_{u.s.}$) for 1920, 1930, 1940, 1950, 1960, and 1970, correlation coefficients of .902, .952, and .982 were observed for age groups 45-54, 55-64, and 65-74, respectively. When the same data were tabulated for whites, it was found that whites and nonwhites at similar degrees of urbanization experience similar cancer death rates.

From 1952 to 1969, the proportion of males 45-64 and 65+ decreased faster in the fluoridated group of cities than in the nonfluoridated group of cities (Table 13).

Table 13

Sex Composition of Fluoridated and Nonfluoridated Populations

		Males per Total Population		
	Population	1950	1960	1970
Total	Fluoridated	.486	.482	.471
	Nonfluoridated	.482	.478	.471
0-24	Fluoridated	.481	.480	.491
	Nonfluoridated	.493	.494	.492
25-44	Fluoridated	.481	.475	.483
	Nonfluoridated	.481	.489	.491
45-64	Fluoridated	.495	.469	.461
	Nonfluoridated	.482	.472	.463
65+	Fluoridated	.473	.431	.403
	Nonfluoridated	.429	.418	.406

Discussion

According to the National Cancer Institute, the total U.S. age-adjusted cancer mortality rate (per 100,000) for white males has increased from 165.3 in 1950-4 to 182.5

in 1965-9. Similarly, the cancer death rate of highly urbanized counties has increased accordingly during the same period (18). Thus, during this period, there has been a real increase in cancer death rate that cannot be explained by either age or urbanization.

It has been strongly suggested that the addition of chemical carcinogens to the environment is a major cause of this increase in cancer (19).

> " . . . the U.S. population . . . is being continually exposed to a wide range of known and identified chemical carcinogens in their air, water, and food, besides, in all likelihood, to a greater range still of unknown or untested carcinogens."

Furthermore, the inability to detect the carcinogenicity of a substance epidemiologically does not demonstrate that that substance is not carcinogenic:

> " . . . it is generally considered that epidemiological techniques are unlikely to detect weak carcinogens unless there are sharp differentials in exposure of the general population, as with cigarette smoking; even with smoking, the single largest cause of cancer deaths, several decades of investigation were required before causality could be established. For widely dispersed agents . . . , human experience is unlikely to provide any meaningful indication of safety or hazard" (19).

In this context, it is not surprising that both negative and positive findings concerning a link between fluoridation and cancer have been reported. In most of these reports (20, 21, 22, 23), no study of cancer death rates before and after fluoridation was made.

Only recently have before-and-after studies been performed.

In November 1975 the NCI released a report (24), later published in its Journal (25), indicating no excessive increase in cancer death rate after fluoridation as compared to before fluoridation. The shortcomings of this study have already been described elsewhere (26).

Yiamouyiannis and Burk earlier reported a substantial increase in crude cancer death rate following fluoridation (26) and subsequently reported preliminary findings indicating that this increase occurred in white as well as nonwhite and occurred exclusively within 45-64 and 65+ age groups (27).

The present study shows that the increase in cancer death rates in fluoridated cities is significantly higher in people aged 45 and over than in nonfluoridated cities.

Age-corrected cancer death rate figures confirm earlier indications using crude cancer death rates that the cancer death rate in fluoridated cities is increasing at a faster rate than the cancer death rate of nonfluoridated cities.

Within central cities, the cancer death rate of nonwhites is not increasing faster than the cancer death rate of whites. The disagreement of these findings with national figures is due to the greater urbanization trends of nonwhites. Since this study considered central cities only, the urbanization-related increase in cancer death rate among nonwhites was eliminated.

In fact, looking at increases in age-adjusted cancer death rates of the 20 cities as a function of increase in the % population nonwhite, no significant correlation could be observed.

All other things being equal, there is no reason to expect that "nonwhite" cancer death rate should be increasing at a faster rate than "white" cancer death rate. In the deep south states where urbanization among whites and nonwhites is comparable (about 50%), there is no significant difference in cancer death rates between the two groups. Only in northern states, where 70% of the whites and 95% of the nonwhites live in urban areas, is the cancer death rate among nonwhites greater than the cancer death rate among whites.

Nationally, the cancer death rate of males is higher than that of females in populations 45+ years of age (28). Age-sex corrected cancer death rates indicate 9-10 more cancer deaths per 100,000 per year in the fluoridated group of cities than in the nonfluoridated group of cities.

The unreliability of the SMR (Standardized Mortality Ratio) used in a number of studies of the fluoridation-cancer link has been discussed elsewhere (29) but also deserves mention here. Consider Table 14 of two hypothetical populations in which one population serves as a control and the other population is fluoridated at the end of 1950. The increase in the crude cancer death rate for the fluoridated population (279 - 204 = 75) exceeds the increase in the crude cancer death rate for the nonfluoridated population (258 - 204 = 54); however the increase in SMR for the fluoridated population (1.24 - 1.00 = 0.24) is less than the increase in SMR for the nonfluoridated population (1.26 - 1.00 = 0.26). Comparison of the two populations in Table 14 shows that the fluoridated population has, in every age group, a cancer death rate increase equal to or greater than that of the nonfluoridated population.

In this illustrative case, the crude death rate indicated (in part) a true (greater) increase in cancer death rate in the fluoridated population relative to the nonfluoridated population, whereas the SMRs indicated an untrue (lesser) increase in cancer death rate in the fluoridated population relative to the nonfluoridated population.

Table 14

Age Group (years)	Nonfluoridated — 1950 Population	Cancer Deaths	Cancer Deaths per 100,000	Prefluoridated — 1950 Population	Deaths	Cancer Deaths per 100,000	Reference Population Cancer Deaths per 100,000
0-	300,000	24	8	300,000	24	8	8
25-	300,000	120	40	300,000	120	40	40
45-	300,000	900	300	300,000	900	300	300
65+	100,000	1000	1000	100,000	1000	1000	1000
All ages	1,000,000	2044	204	1,000,000	2044	204	
Expected		2044			2044		
SMR		1.00			1.00		

Age Group (years)	Nonfluoridated — 1970 Population	Cancer Deaths	Cancer Deaths per 100,000	Fluoridated — 1970 Population	Deaths	Cancer Deaths per 100,00	Reference Population Cancer Deaths per 100,000
0-	300,000	24	8	350,000	28	8	8
25-	300,000	210	70	300,000	210	70	40
45-	300,000	1350	450	200,000	900	450	300
65+	100,000	1000	1000	150,000	1650	1100	1000
All ages	1,000,000	2584	258	1,000,000	2788	279	
Expected		2044			2248		
SMR		1.26			1.24		

The unreliability of the SMR is further evident from the findings of Taves (30) who reported a mere 2% increase in cancer death rates in large cities from 1950 to 1970 as compared to the NCI figure of approximately 13% (18) and our figure of approximately 14% during the same period of time. Using the same data, Taves was also able to observe that by using different reference populations, he could get results indicating a positive or negative relationship which depended only upon the reference population he was using, clearly indicating that his results were artefacts of the method itself.

Considering other demographic variables, only one remained that might indicate an alternative explanation for the increased cancer death rate observed in the fluoridated group of cities. In the fluoridated group, most of the cities experienced a decrease in population, whereas among the nonfluoridated cities, most experienced an increase in population. Comparison of the cancer death rate of fluoridated cities whose population decreased with the cancer death rate of nonfluoridated cities whose population decreased still indicated a higher cancer death rate in the fluoridated group of the same magnitude, 8 per 100,000 per year.

This study was confined to large cities for the following reasons: 1) Fluoridated water comprises only part of the fluoride intake. Food products and beverages such as infant formulas, soft drinks, beer, spaghetti, salad dressings, jellies, etc. that are made with water will contain more or less fluoride depending on whether or not the water in that area is fluoridated. People living in large cities are more likely to consume products made in that area than are people living in smaller cities. This means that in larger cities fluoride intake will be more directly related to water fluoride content than in smaller cities. 2) Each city provides a large enough sample size to justify the use of unweighted averages. 3) Highly urbanized areas are compared to highly urbanized areas. 4) Data for large cities in the detail necessary for the present study are more readily available. 5) Using city rather than county or SMSA (Standard Metropolitan Statistical Area) data allows a study involving areas that are either completely fluoridated or completely nonfluoridated.

In a preliminary survey, the 1970 cancer death rates of all cities east of the Mississippi with population 10,000 and over were compared, state by state, for fluoridated and nonfluoridated cities. For each state, the percent difference in the cancer death rate of the fluoridated cities and the nonfluoridated cities was determined, weighted by the square root of the product of the state's population in cities 10,000 and over that were fluoridated and the state's population in cities 10,000 and over that were not fluoridated ($\sqrt{P(F) \times P(NF)}$); these values were added for all states east of the Mississippi. Again an excess in cancer death rate similar to that reported herein was found.

Animal Studies: The increase in the incidence in melanotic tumors in fruit flies exposed to low levels of fluoride originally reported by I. Rapaport (31) was

confirmed by Herskowitz and Norton who showed a dose-dependent increase in tumor incidence with increasing levels of fluoride (1).

Taylor and Taylor (2) reported that 1 ppm fluoride in the drinking water of DBA strain mice implanted inguinally with RC mammary adenocarcinoma experienced a 13-17% increase in tumor growth rate, although a dose-dependent relation in this case was not observed. Both control (n=203) and experimental (n=184) groups of mice were fed a mixed grain diet containing negligible amounts of fluoride. An increase in the incidence of mammary cancer has been reported in C3H and DBA female mice fed 1 ppm fluoride in their drinking water (32), but no significant difference was found in CD-1 strain mice fed "10 ug/ml fluorine as sodium-fluoride" in their drinking water (33).

From our results, it is not possible to determine whether the fluoridation-linked increases in cancer death rate were due to increased incidence, or increased mortality of persons who already had cancer.

Studies of the relationship of nonwater-borne fluorides and cancer have reported positive correlations between food fluoride levels and stomach cancer (34) and a possible correlation between air-borne fluorides and lung cancer (35 and 36).

In addition, in vivo and in vitro experiments indicating that 1 ppm fluoride interferes with DNA repair (37) and that low levels of fluoride can alter the G/C ratio of RNA (38) provide one explanation of how the carcinogenic and mutagenic effects of fluoride may be mediated.

Conclusions

In view of animal studies showing that low levels of fluoride are tumorigenic and that 1 ppm fluoride increases tumor growth rate, interferes with DNA repair in vitro and in vivo, and is mutagenic, it is not surprising that this study has found an increase in human cancer death rate in fluoridated areas. Furthermore, it perhaps would not have been surprising to have found that the carcinogenic effects of fluoride would be swamped out by the variation in cancer death rates of individual cities due to other variables. According to current dogma, 20-30 years must pass before a substance will begin to affect cancer death rate. In this context, the two most powerful results of this paper are 1) that a large part of the increase in cancer death rate occurred in a relatively short time (5 years) and 2) that is increase plus additional increases were sustained during the entire period of study. Another premise of the current dogma is that all carcinogens exhibit a dose-dependent relationship. In the case of fluoride, it appears that a chronic low-level exposure to fluoride would be optimal for producing metabolic aberrations conducive to producing a cancerous cell (1) or selectively stimulating the growth rate of cancerous cells (2) and that higher concentrations do not enhance these effects and may, in fact, lead to cell stasis or death.

We expect that the value of the fluoridation-linked increase reported herein is low since we do not believe that the increase in cancer death rate in fluoridated vs. nonfluoridated cities is a linear function of time. Thus fitting our data to a straight line would tend to minimize the increase. Also, because of the movement of people and fluoride-containing food products in and out of the cities studied, we believe the effects observed were diluted and that, had the populations and food products been confined to their areas, a larger fluoridation-linked increase in cancer would have been observed.

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Bibliography

1. Herskowitz, I.H. and Norton, I.L.: Increased Incidence of Melanotic Tumors in Two Strains of Drosophila Melanogaster Following Treatment with Sodium Fluoride. Genetics, 48: 307-10, Feb. 1963.
2. Taylor, A. and Taylor, N.C.: Effect of Sodium Fluoride on Tumor Growth. Proc. Soc. Exp. Biol. Med., 119:252-55, 1965.
3. Bale, S.S. and Hart, G.E.: Cytogenetic and Genetic Effects of Fluoride on Barley. I. Comparative Study of the Effects of Sodium Fluoride and Hydrofluoric Acid on Seedling Root Tips. Can. J. Genetics and Cytol., 15:695-702, 1973.
4. Bale, S.S. and Hart, G.E.. Cytogenetic and Genetic Effects of Fluoride on Barley. II. Effects of Treatments of Seedling Coleoptiles with Sodium Fluoride. Can. J. Gen. and Cytol., 15:703-12, 1973.
5. Mohamed, A.H., Applegate, H.G. and Smith, J.D.: Cytological Reactions Induced by Sodium Fluoride in Allium Cepa Root-Tip Chromosomes. Can. J. Gen. Cytol., 8:241-4, 1966.
6. Mohamed, A.H., Smith, J.D. and Applegate, H.G.: Cytological Effects of Hydrogen Fluoride on Tomato Chromosomes. Can. J. Gen. and Cytol., 8:575-83, 1966.
7. Mohamed, A.H.: Cytogenetic Effects of Hydrogen Fluoride Treatment in Tomato Plants. J. Air Poll. Control Ass., 18:395-8, June 1968.

8. Mohamed, A.H.: Chromosomal Changes in Maize Induced by Hydrogen Fluoride Gas. Can. J. Gen. and Cytol., 12:614-20, Sept. 1970.
9. Mitchell, B. and Gerdes, R.A.: Mutagenic Effects of NaF and SnF_2 on Drosophila Melanogaster. Fluoride, 6:113-7, 1973.
10. Mukherjee, R.N. and Sobels, F.H.: The Effects of Sodium Fluoride and Iodoacetamide on Mutation Induction by X-irradiation in Mature Spermatazoa of Drosophila. Mutation Res., 6:217-25, Sept.-Oct. 1968.
11. Gerdes, R.A., Smith, J.D. and Applegate, H.G.: The Effects of Atmospheric Hydrogen Fluoride upon Drosophila Melanogaster. Atmospheric Envir., 5:113-22, March 1971.
12. Mohamed, A.H.: Induced Recessive Lethals in Second Chromosomes of Drosophila Melanogaster by Hydrogen Fluoride. Proc. 2nd International Clean Air Congress of the International Union of Air Pollution Prevention Associations, December 1970, 26.
13. Plotko, E.G. Kostlyuchenka, V.A. and Panycheva, E.N.: Toxicity of Weakly Soluble F^- Introduced by Inhalation. Gig. I Sanit., 4:14-16, 1973.
14. Voroshilin, S.I., Plotka, E.G., Gatiyatullina, E.Z. and Gileva, E.A.: Cytogenic Effect of Inorganic Fluorine Compounds on Human and Animal Cells In Vivo and In Vitro. Genetika, 9:115-20, 1973.
15. Jagiello, G. and Lin, J.: Sodium Fluoride as Potential Mutagen in Mammalian Eggs. Arch. of Env. Hlth., 29:230-35, 1974.
16. Mohamed, A.H.: Fluorides in Water may be Genetic Hazard. Chem. and Eng. News, 54:30, 1976.
17. Mohamed, A.H.: Personal communications, March 1977.
18. Peters, J.A.: Personal communication from the Nat. Cancer Inst., Aug. 19, 1975.
19. Epstein, S.S.: Environmental Determinants of Human Cancer. Cancer Res., 34:2425-35, 1974.
20. Hagan, T.L., Pasternack, M. and Scholz, G.C.: Water-borne Fluorides and Mortality. Publ. Hlth. Rep., 69: 450-4, May 1954.
21. Kinlen, L.: Cancer Incidence in Relation to Fluoride Level in Water Supplies. Community Hlth., 6:69-74, 1974.
22. Heasman, M.A. and Martin, A.E.: Mortality in Areas Containing Natural Fluoride in their Water Supplies. Monthly Bull. of the Ministry of Hlth., London, 150-61, 1964.
23. Delaney, J.J., Burk, D. and Yiamouyiannis, J.A.: Fluoridation and Cancer. Congr. Rec., July 21, 1975, H7172-6.
24. Hoover, R.N., McKay, F.W. and Fraumeni, J.F.: Fluoridated Drinking Water and the Occurrence of Cancer. Epidemiology Branch, Nat. Cancer Inst., Nov. 14, 1975.
25. Hoover, R.N., McKay, F.W. and Fraumeni, J.F.: Fluoridated Drinking Water and the Occurrence of Cancer. J. Natl. Cancer Inst., 57:757-68,

Oct. 1976.

26. Delaney, J.J., Yiamouyiannis, J.A. and Burk, D.: Cancer from our Drinking Water? Congr. Rec., Dec. 16, 1975:H12731-4; Nat. Hlth. Fed. Bull., 22:5-10, Feb. 1976.
27. Yiamouyiannis, J.A. and Burk, D.: Fluoridation of Public Water Systems and Cancer Death Rates in Humans. Paper presented at the 67th Annual Meeting, Amer. Soc. Biol. Chemists, Fed. Amer. Soc. Exp. Biol., June 1976.
28. Mason, T.J., McKay, F.W., Hoover, R., Blot, W.J. and Fraumeni, J.F.: Atlas of Cancer Mortality for U.S. Counties: 1950-1969, DHEW Publ. No. (NIH) 75-780, 1975.
29. Yiamouyiannis, J.A.: Fluoridation and Cancer. Presented at the symposium on "Continuing Evaluation of the Use of Fluorides", 143rd Nat. Meeting, Amer. Ass. Advancement Sci., Feb. 1977.
30. Taves, D.R.: Fluoridation and Cancer. Presented at the symposium on "Continuing Evaluation of the Use of Fluorides", 143rd Nat. Meeting, Amer. Ass. Advancement Sci., Feb. 1977.
31. Rapaport, I.: Infantile Mongolism. A deviation of Tryptophan Metabolism Induced by Fluorine in Drosophila. Bull. Acad. Nat. Med. (Paris), 145:450-3, June-July, 1961.
32. Taylor, A.: Sodium Fluoride in the Drinking Water of Mice. Dent. Digest, 60:170-2, April 1954.
33. Kanisawa, M. and Schroeder, H.A.: Life Term Studies on the Effect of Trace Elements on Spontaneous Tumors in Mice and Rats. Cancer Res., 29:892-5, April 1969: see also, Fleming, H.S.: Effect of Fluorides on the Tumor S 37 after Transplantation to Selected Locations in Mice and Guinea Pigs. J. Dent. Res., 32:646, Oct. 1953; Finerty, J.C. and Grace, J.D.: Effect of Fluoride on Tumor Growth. Texas Rep. Biol. Med., 10:501-3, 1952.
34. Okamura, T. and Matsuhisa, T.: Studies on Fluoride and other Related Material in Rice. I. The Fluoride Content of Lowland Nonglutinous Unpolished Rice and its Geographical Correlation with Mortality from Gastric Cancer. Nippon Sakumotsu Gakkai Kiji, 32:132-8, 1963.
35. Litvinov, N.N., Goldberg, M.S. and Kimina, S.M.: Morbidity and Mortality in Man caused by Pulmonary Cancer and its Relation to the Pollution of the Atmosphere in the Areas of Aluminum Plants. Acta Unionis Internationalis Contra Cancrum, 19:742-5, 1963.
36. Cecilioni, V.A.: Observations on Cancer in a Steel City. Fluoride, 7:153-65, July 1974.
37. Klein, W., Kocsis, F. and Wottawa, A.: DNA Repair and Environmental Substances. Report of the Austrian Society of Atomic Energy, Seibersdorf Research Center, 1-8, May 1976.
38. Chang, C.W.: Effect of Fluoride on Nucleotides and Ribonucleic Acid in Germinating Corn Seedling Roots. Plant Physiol., 43:669-74, May 1968.

Discussion

Prof. Burgstahler: From your unadjusted curves it almost seems that something ceased to occur in the cities that did not fluoridate after 1950. I realize, of course, that the pre-1950 increases in cancer death rates might have tapered off without something ceasing to occur, but I wonder what comment you might care to make on this.

Dr. Burk: The way I like to draw the curves is as differences in cancer death rates plotted against time. In this way one can see clearly that the effect showed up right after the start of fluoridation and that the differences have continued to grow even to the present. Although corrections for small differences in age and race between the two sets of cities make the rate differences less than the unadjusted ones, adjustment for the "mixing" factor arising from the use of fluoridated foods and beverages in nonfluoridated cities would doubtless show that the true differences are much larger. In England, because tea drinking is so widespread, it would probably be impossible to detect differences such as we have found.

Dr. Moolenburgh: Can you explain why the standard mortality ratio (SMR) approach seems to show no increase in cancer death rate with fluoridation (or even some "protection" from it), while your data show just the opposite?

Dr. Burk: That is because SMR calculations are arbitrary, fictitious, and hypothetical; they depend strictly on what figures are used as a standard. SMR calculations are useful in certain types of statistical analyses but not here. Even the National Cancer Institute SMR figures for fluoridated versus nonfluoridated cities differ significantly from those calculated by Dr. Taves.

Dr. Oelschlager: How do your data compare with those of other countries such as India and England? Do they have any bearing on specific cancer sites, such as the 7-fold higher esophageal cancer rate in England?

Dr. Burk: Direct comparison of these cancer death rates with those of other countries is not possible. There are too many demographic, climatological, environmental, dietary, and other differences. Only by comparing an extremely large number of people in comparable circumstances, as in our ten largest fluoridated and nonfluoridated U.S. cities, can such a comparison be meaningful.

Dr. Teotia: This paper is very exciting, but I believe other factors such as increasing air pollution, growth in industrialization, and differences in smoking habits must be considered and ruled out before the differences which you report can be attributed to fluoridation.

Dr. Burk: What you say is true, but by taking the ten largest cities in each group throughout the United States, these factors tend to be equalized. With such large numbers of people involved it is highly unlikely that there would be appreciable differences in such factors as smoking habits or even the amount and effects of air pollution.

FLUORIDE-INDUCED CHANGES IN 60 RETIRED ALUMINUM WORKERS

by

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SUMMARY: Orthopedic, radiological and analytical examinations were performed in a group of 60 retired disabled workers of an aluminum factory. Occupational disease had previously been recognized in this group because of disturbances in the respiratory and circulatory systems. The age of those examined averaged 49.6 years; the duration of exposure averaged 16.9 years; 88.3% had worked in the electrolysis department.

In the majority of cases orthopedic examination showed changes of a generalized character in locomotion, differing in the degree of intensity. Exostoses and ossification of the interosseous membranes and muscle attachments were the most frequently detected radiological changes. Generalized sclerosis and periosteal reactions occurred less frequently. No major variations from the norm were noted in the levels of serum calcium, phosphorus, acid and alkaline phosphatase.

Expansion of the industrial uses of fluoride compounds accounts for an ever-increasing pollution of the environment. The halogen emanates into the environment during industrial exploitation of minerals containing fluoride (cryolites, apatites, phosphorites) in aluminum and fertilizer factor-

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ies. Fluoride compounds, emitted during electrolysis and other processes using the above-mentioned minerals, are absorbed by the lungs and by the digestive tract whence they are promptly transported to the circulatory system (1-3). About 60% of a given dose is excreted with the urine, but almost 90% of what remains accumulates in bones (3-5) due to the affinity of fluoride for hydroxyapatite, the basic mineral substance of bone. Fluoride exchanges the hydroxyl ion of hydroxyapatite to fluoroapatite, which is much less soluble than hydroxyapatite (6, 7). At the same time fluoride affects the activity of parathormone, calcitonin, and the acid and alkaline phosphatases. Reduction in the solubility of the bone apatite crystals together with the hormone changes leads to a positive calcium balance and to the predominance of osteogenesis (6-11).

The morbid changes of chronic, excessive fluoride intake are known as fluorosis which occurs either in the form of industrial fluorosis in workers exposed to fluoride compounds or as endemic fluorosis in regions with a high fluoride content naturally in drinking water (1-2, 12-18). The clinical picture of industrial fluorosis consists of changes in the respiratory, circulatory and digestive systems, in dental and neurological abnormalities and in changes in bones and joints (2, 12, 14, 19-24). Locomotor changes due to great variations in temperature, humidity and mechanical stress during work hours often occur in foundry workers, especially in aluminum smelters where exposure to fluoride may be a health hazard.

This study will evaluate fluorotic changes in a group of 60 retired disabled workers of an aluminum factory.

Method and Material

In the 60 retired workers occupational disease had previously been diagnosed on the basis of changes in the respiratory-circulatory system. Their ages ranged from 37 to 69 (average 49.6). They had been working in in the aluminum factory from 10 to 29 years (average 16.9). Fifty-three had previously worked in the electrolysis department, including 32 electrolysis operators, 7 anode operators, 14 at other jobs in the same department; 7 subjects had been employed in other departments.

All retired disabled workers underwent orthopedic check-ups and x-rays of the lumbar spine, pelvis and forearms. Radiograms of other parts of the skeleton were taken in selected cases. Levels of serum calcium, phosphorus, acid and alkaline phosphatase were determined, as well as the fluoride levels in the urine. In one case the fluoride content of a bone sample was estimated.

Results

I. Clinical Changes in Bones and Joints: In the majority of cases orthopedic examination showed generalized changes in locomotion of various degrees of intensity. Most often the patients complained of back pain. Pains in the shoulders, elbows, forearms and lower legs were common. These pains differed in intensity and occurred constantly or periodically with no clear relationship to effort. Upon examination, we found limited mobility in the joints of the spine and extremities, ranging from a trivial to a marked decrease in the range of movements.

In the spine, we most frequently found limitation of movements in the lumbar and thoracic region, but rarely in the cervical spine. In a few cases the spine was ankylosed. In 15 patients we found disturbances in the spinal column in the form of dorsal kyphosis and lumbar scoliosis. Marked restriction of the respiratory movements of the chest was also encountered. The average difference in chest circumference at maximal inspiration and expiration was 2.5 cm.

In the extremities, limitation in the rotatory movements of the forearms, shoulders and hip joints occurred most frequently, while limitation of movements on the sagittal plane was noted less often. In about

Table 1
Clinical Changes in Bones and Joints

Symptoms	Frequency of Occurrence
Pain in joints	90%
back	78%
shoulder	63%
knee	43%
hip	38%
elbow	31%
Limitation in range of movements	68%
rotation of forearms	67%
movements of spine	63%
movements of hip	43%
movements of shoulder	36%
movements of elbow	27%
movements of knee	25%
Crepitation during movement	42%

half the cases we observed crepitation in the joints during movements, especially in the knee joints.

The painful symptoms reported did not always correspond to the limitation in the joint mobility, since we also found limitation of movement in joints without pain. The clinical changes in locomotion are summarized in Table 1.

II. Radiological Changes in the Skeleton: An evaluation of radiograms of the lumbar spine, pelvis, forearms and lower legs is presented in Table 2. A common finding in the radiogram was marginal exostoses of the

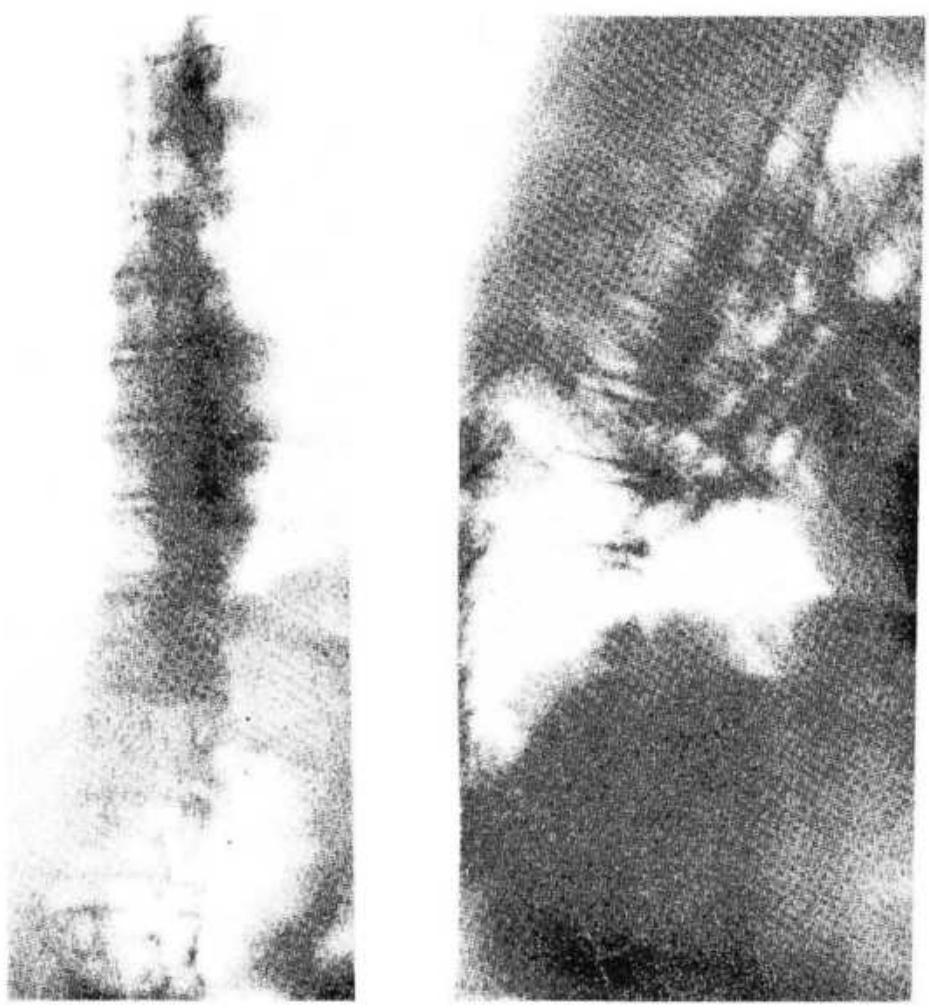
Table 2
Radiological Changes in the Skeleton

Symptoms		Frequency	
Ossification of ligaments and muscle attachments, and exostoses		97%	
	spine		95%
	pelvis		93%
	forearms		58%
	lower legs		57%
Lumbar scoliosis		45%	
Congenital spinal defects		28%	
Ossification of joint capsules		65%	
	hip		55%
	knee		25%
	elbow		15%
Free intra-articular bodies		48%	
Ossification of pubic symphysis		54%	
Blurring of outline of sacro-iliac joints		32%	
Ossification of interosseous membranes		97%	
	forearms		97%
	lower legs		57%
Periosteal bone appositions		68%	
	forearms		68%
	lower legs		53%
Thickening of cortical bone		87%	
	forearms		73%
	lower legs		67%
Thickening of acetebulum bottom			54%
Alteration of bone structure			
Osteo-		66%	
sclerosis	pelvis		47%
	spine		41%
Resorption		8%	
	forearms		6%
	spine		4%
	pelvis		2%

vertebral corpora and ossifications of the longitudinal ligaments and annular fibrosis, leading to the formation of osseous bridges between adjoining vertebrae (Figure 1). In the patients with lumbar scoliosis the changes described were more advanced (Figure 2). Congenital defects of the sacro-lumbar area such as spina bifida, sacralization of L_5 and lumbarization of S_1 were found in 15 patients.

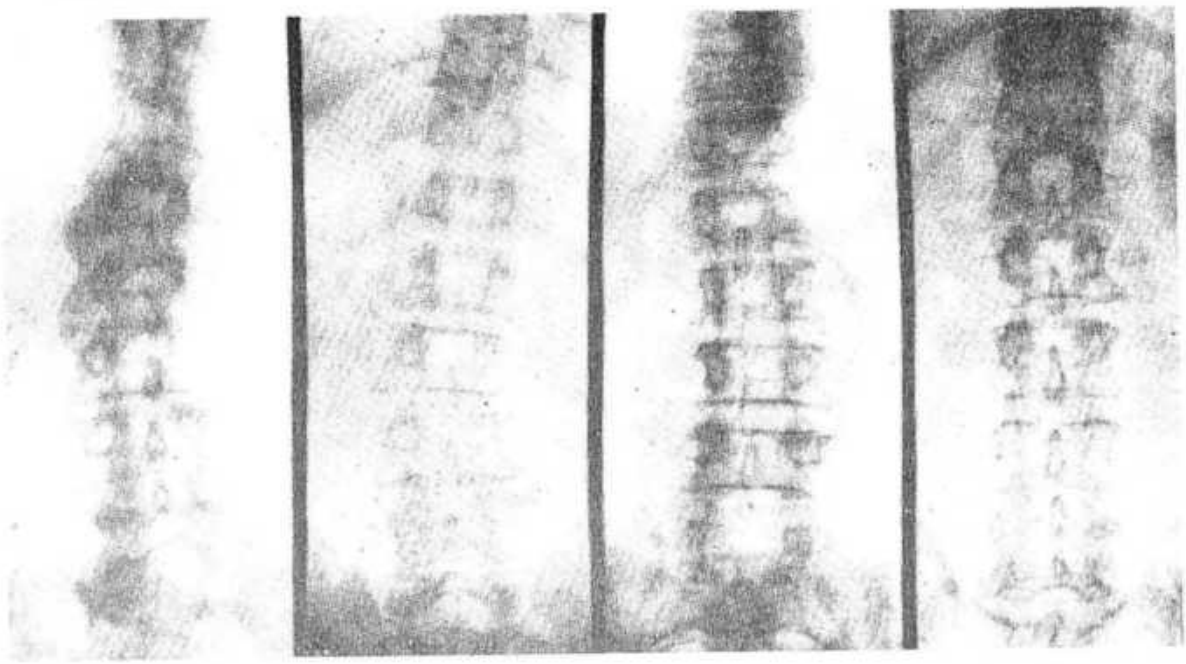
The radiological changes in the pelvis included ossification of the muscle attachments of the iliac bone, the ramus of the ischiac bone and the pelvic ligaments. In the radiogram of the pelvis ossification of joint capsules, free intra-articular bodies, and obliteration of the sacro-iliac joint spaces were found.

Figure 1
Fluorotic Change in the Spine of an Aluminum Worker Aged 42



Marginal exostoses on the anterior and posterior surfaces of the vertebral bodies, slight osteosclerosis, thoracic kyposis and lumbar scoliosis.

Figure 2
Different Degrees of Osteosclerosis of the Lumbar Spine



Advanced degenerative changes and disturbances in the lumbar spinal statics.

In all cases the radiograms of the forearm and lower leg showed ossification of the interosseous membranes. Ossification of the capsules of the elbow and knee joint and free intra-articular bodies occurred more rarely. Thickening of the cortical bone at the diaphysis was noted frequently and ranged from a small degree up to complete closure of the medullary cavity.

Bone Structure: In the x-ray evaluation, special attention was paid to a marked increase in the patterns of the bone structure. Half the cases examined showed a distinctive and marked density of the bone shadow together with a thickening of the trabeculation to the point of complete disappearance of the latter. It should be pointed out that we diagnosed osteosclerosis on the basis of visual comparison of the radiogram with the picture normally encountered and accepted its existence only in cases which were free of any doubt. More precise evaluation would be possible only after performing densimetric analysis.

A few cases showed disturbances in the trabecular structure besides osteosclerosis in the form of dispersion and in addition mottled osteosclerosis of the substantia spongiosa as well as endosteal bone resorption.

III. Other Changes : In all patients respiratory-circulatory symptoms occurred which were the main cause qualifying them for a disability pension. Only a few cases were qualified for a disability pension due to other diseases. Thirty of those examined suffered from diseases of the alimentary tract, such as dyspepsia or gastritis. Gastric or duodenal ulcers occurred in 7 (or 12%) of those examined, 5 of whom (8%) had undergone gastric resection.

The majority of cases exhibited dental changes such as a tendency to abrasion, fragility, etc. Cholelithiasis and urolithiasis occurred in 13% of cases. As many as 23% suffered from psychiatric disturbances such as depression, mental sluggishness, or memory disturbances. The frequency of non-locomotor changes is presented in Table 3.

Table 3
Non-skeletal Changes

Manifestations	Frequency of Occurrence
Respiratory and circulatory system	97%
Digestive system	51%
Gastric ulcer	12%
Status after stomach resection	8%
Urolithiasis and cholelithiasis	13%
Dental changes	74%
Psychiatric disturbances	23%

IV. Additional Tests: The fluoride levels in the urine were markedly elevated in all cases. No appreciable abnormal variations were noted in the serum calcium, phosphorus or alkaline and acid phosphatase levels. A detailed analysis of the additional tests will be presented separately. The fluoride level in a bone sample from the iliac crest in one case was 120 mg% in the fat-free bone ash (25).

A comparison of the frequency of occurrence of changes in bones and joints in workers with various degrees of exposure to fluoride compounds (electrolyser operators and others from the same and other departments) is presented in Table 4 and the frequency of changes in both groups as related to the length of employment (10-15 years or 16-20 years) in Table 5.

Table 6 shows the relationship of the changes to the age of those examined in the age-groups under 50, 51-60, and above 60. The frequency of changes in retired workers does not depend on the place of work or the position, but on the length of employment. Those who had worked longer and the older age groups showed greater changes in locomotion.

Table 4
Relation of Changes in Bones and Joints to the Jobs

Symptoms	Electrolysis Department			Other Departments	Total
	electrol. operator	anode operator	others		
	32	7	14	7	60 cases
Joint pains	97%	71%	86%	86%	90%
Limitation of movements	75%	57%	57%	71%	68%
Disturbances in spinal column (clinical and radiological)	56%	71%	50%	43%	55%
Ossification of muscle attachments, exostoses	97%	86%	100%	100%	97%
Ossification of interosseoesus membranes	97%	86%	100%	100%	97%
Periosteal bone appositions	63%	71%	86%	57%	68%

Table 5
Changes in Bones and Joints Related to Duration of Exposure

Symptoms	10-15 years	16-20 years	Total
	14 cases	46 cases	60 cases
Joint pains	71%	96%	90%
Limitation of movements	57%	72%	68%
Disturbances of spinal column (clinical and radiological)	57%	54%	55%
Ossification of muscle attachments, exostoses	86%	100%	97%
Ossification of interosseous membranes	100%	93%	97%
Periosteal bone appositions	57%	72%	68%

Table 6
Relation of Changes to Age

Symptoms	under 50 years	51-60 years	over 60 years	Total
	28 cases	20 cases	12 cases	60 cases
Joint pains	90%	86%	100%	90%
Limitation of movements	46%	86%	75%	68%
Disturbances of spinal column (clinical and radiological)	50%	55%	67%	55%
Ossification of muscle attachments, exostoses	96%	95%	100%	97%
Ossification of interosseous membranes	96%	95%	100%	97%
Periosteal bone appositions	58%	75%	83%	68%

Discussion

The clinical and radiological findings in the group investigated correspond to the picture of industrial fluorosis described by others (1-2, 12-14, 17, 19, 21-24, 26). Complaints of pain and limitations in joint movements are less characteristic features than the changes shown in radiograms.

Typical fluorotic changes in the radiogram are generalized osteosclerosis, periosteal reactions, and ossification of the interosseous membranes and muscle attachments (1-2, 12, 14, 17, 19-20, 24). Less characteristic but commonly occurring in the radiogram of the lumbar spine are exostoses and ossification of ligaments, presenting the radiological picture of spondyloarthrosis or spondylitis ankylopoetica (19, 21-22, 27-28).

The part played by fluoride in degenerative changes in the spine and joints has not yet been elucidated. Fradà, Vischer and Andreyeva reported the frequent occurrence of degenerative changes in subjects exposed to fluoride compounds, but Zipkin and Steinberg found no relation between the action of fluoride and degenerative changes (7, 15, 21, 29-30).

In our material we noted degnerative changes in the lumbar spine in 95% of cases, which suggests that fluoride accelerates these changes. In addition to pain in the lower spine which is associated with radiological changes, patients with negative x-ray findings also complain of pain in the lumbar-sacral area, an indication that symptoms precede changes demonstrable by x-ray (2, 31-33). In our subjects radiological changes, especially ossification of the interosseous membrane, were found in patients who had not reported any painful symptoms.

In the group studied, radiological findings were present in 96% of cases. Such a high incidence of changes is undoubtedly the result of selection of the group examined. Occupational disease was diagnosed in all cases; all were employed for over 10 years. According to Roholm (17) initial bone changes occur after 2.5 - 4 years but according to Andreyeva they are rare before 9 - 10 years of work (12). The frequency of appearance of radiological changes in aluminum workers has been evaluated by different authors: Andreyeva noted 33%, Fradà 10%, Gotlib 9.5% (12, 14, 21). In a selected group of workers with long employment Vischer reported changes in 86% of cases (2).

We have not found that elbow joints, especially the right ones are more often affected than others as reported by Fradà and Vischer (2, 14) nor have we seen any essential differences in the radiograms of a group of workers periodically using percussion tools as compared with other groups.

Respiratory-circulatory and digestive symptoms, dental and neuromuscular changes in locomotion found in the cases show that chronic fluoride intoxication involves the entire human body and is not confined to teeth and bones as pointed out by Waldbott (34).

Conclusions

1. Pathological changes in locomotion were found in all sixty retired aluminum workers.

2. These changes were of a generalized character manifesting pains in joints and limitation in movements of differing intensity.

3. Radiograms showed most frequently ossification of the interosseous membranes and muscle attachments, as well as exostoses. Ossification of the joint capsules, free intra-articular bodies or generalized osteosclerosis were found less often.

4. Changes in the bones and joints occurred more frequently in workers who had retired after a long period of employment and in the elderly. The position held did not affect the frequency of occurrence of changes.

5. Bone changes in the radiogram are a valuable criterion in the diagnosis of fluorosis.

6. Workers in aluminum factories should undergo regular prophylactic x-ray examinations.

Acknowledgements

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Bibliography

1. Martin, A.E.: Industrial Fluoride Hazards. Fluoride and Human Hlth., 310-316, WHO, Geneva, 1970.
2. Vischer, T.L., Bernhein, C., Gudjikoff, C., Wettstein, P.P., and Largier, R.: Industrial Fluorosis. Fluoride in Medicine, 96-105, Hans Huber Publishers, Bern, 1970.

3. Wallace – Durbin, P.: The Metabolism of Fluoride in the Rat using F-18 as a Tracer. J. Dent. Res., 11:789-800, 1954.
4. Ahrens, G.: The Excretion of Fluoride by Osteoporotic Patients Under Sodium Fluoride Therapy. Fluoride in Medicine, 175-177, Hans Huber Publishers, Bern, 1970.
5. Hein, J.W.: Distribution in the Soft Tissue of the Rat of Radioactive Fluoride Administered as Sodium Fluoride. Nature, 178:1295-1298, 1956.
6. Baylink, D.: Effect of Fluoride on Bone Formation, Mineralization and Resorption in the Rat. Fluoride in Medicine, 37-69, Hans Huber Publishers, Bern, 1970.
7. Gedalia, I., Zipkin, I.: The Role of Fluoride in Bone Structure. Israel J. of Medical Science, No. 72-878224, Jerusalem, 1973.
8. Messer, H.H., Armstrong, W.D., Singer, L.: Fluoride, Parathyroid Hormone and Calcitonin: Effects on Metabolic Processes Involved in Bone Resorption. Calc. Tissue Res., 13:227-233, 1973.
9. Messer, H.H., Armstrong, W.D., Singer, L.: Fluoride, Parathyroid Hormone and Calcitonin: Inter-relationship in Bone Calcium Metabolism. Calc. Tiss. Res., 13:217-225, 1973.
10. Reutter, W.F., Siebenman, R.: Fluoride in Osteoporosis. In Fluoride in Medicine. Vischer, T.L., Ed., Hans Huber, Bern, 1970, pp. 143-152.
11. Teotia, S.P.S., Teotia, M.: Hyperactivity of Parathyroid Glands in Endemic Osteofluorosis. Fluoride, 3:115-125, 1972.
12. Andreyeva, T.D., Girskaya, E.Y.: Radiological Diagnosis of Bone Changes in Workers with Fluorosis from Cryolite and Aluminum Plants. Voprosy Gigieny i Profiessyonalnoy Patologii v Tsvietnoy i Chernoy Metallurgii, Sverdlovsk, 1971, pp. 52-54.
13. Bhussry, B.R., Demole, V., Hodge, H.L., Jolly, S.S., Singh, A. and Taves, P.R.: Toxic Effects of Larger Doses of Fluoride. Fluorides and Human Health, W.H.O., Geneva, 1970, pp. 225-265.
14. Fradà, G. and Mentesana, G.: The Clinical Features of Hydrofluorosis. Pan minerva Medica, 8:50-57, 1966.
15. Johnson, C.L., Smith, F.A.: Fluoride Chemistry. vol. IV, Academic Press, New York and London, 1965.
16. Jolly, S.S.: Hydric Fluorosis in Punjab. Fluoride in Medicine, 106-21, Hans Huber Publishers, Bern, 1970.
17. Roholm, K.: Fluoride Intoxication. H.K. Lewis, London, 1937.
18. Teotia, M. and Teotia, S.P.S.: Further Observations on Endemic Fluoride-Induced Osteopathies in Children. Fluoride, 3:143-151, 1973.
19. Franke, J.: Die Knochenfluorose. Therapie Woche, 23-43, 3954, 1973.
20. Gorzkowski, E., Domański, Z., Jelonek, W., Neuman, Z. and Szymkowitz, M.: Ogólny stan zdrowia pracowników zakladów nawozów fosforowych. Wybrane zagadnienia toksykologii przemyslowej zwiazków fluoru.,

23-26. Poznańskie Towarzystwo Naukowe, Szczecin-Poznań, 1871.
21. Gotlib, E.V., Simahina, P.G., Miller, S.V., Zislin, D.N., Girskaya, E.Y. and Andreyeva, T.D.: Occupational Pathology in Workers from Electrolysis Departments of Aluminum Plants. In no. 12, pp. 33-37.
22. Grinberg, A.V., Orlovska, T.V., Ornican, E.Y. and Sagotov, I.S.: The Early X-Ray Diagnosis of Fluorosis. In no. 12, pp. 49-51.
23. Gubanov, E.N.: Dental Changes in Workers from Electrolysis Departments of Aluminum Plants. In no. 12, pp. 44-46.
24. Tzonchev, V., Seidel, K., Dimitrov, M.: The Radiology of Joint Diseases. Butterworth and Co., 1973.
25. Klewska, A.: Application of Microdiffusion Technique to the Determination of Fluoride in Biological Material. Arch. Med. Sad. i Krym., 13:279-283, 1973.
26. Waldbott, G.L. and Cecilioni, V.A.: "Neighborhood" Fluorosis. Fluoride, 2:287-396, 1969.
27. Borejko, M., Dziak, A.: Radiological Examination in Orthopaedics. PZWL, Warsow, 1973, pp. 1-11 and 221-230.
28. Bruhl, W.: The Disease of the Locomotor System. PZWL Warsow, 1969, pp. 413-433.
29. Steinberg, C.L., Gardner, D.E., Smith, F.A. and Hodge, H.C.: Comparison of Rheumatoid (ankylosing) Spondylitis and Crippling Fluorosis. Ann. Rheum. Dis., 14:378, 1955.
30. Zipkin, I., Sokoloff, L., Frazier, P.D.: A Study of the Effect of Fluoride on Bone and Osteoarthritis in Mice. Isr. J. Med. Science, 3: 719, 1967.
31. Cook, H.A.: Crippling Arthritis Related to Fluoride Intake. Fluoride, 4:209-213, 1972.
32. Steinberg, C.L., Gardner, D.E., Smith, F.A. and Hodge, H.C.: Fluoridation of Public Water Supplies and its Relation to Musculoskeletal Diseases. N. Engl. J. Med., 258-322, 1958.
33. Waldbott, G.L.: Incipient Chronic Fluoride Intoxication from Drinking Water I. Report on 52 Cases. Acta Medica Scand., 156:157-168, 1956.
34. Waldbott, G.L.: Introduction, Symposium on the Non-Skeletal Phase of Chronic Fluorosis. Fluoride, 9:5-8, 1976.

Discussion

Dr. Waldbott: I consider Dr. Czerwinski's paper very important, as he has described the same symptoms in industrial fluorosis that I have observed in incipient poisoning from fluoridated water. Thus my observations on preskeletal fluorosis are being confirmed.

POTENTIAL FLUORIDE INTAKE OF NORTHERN CANADIAN INDIANS

by

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SUMMARY: In Cree Indians of Northwest Quebec, Canada, fluoride in tea, soft drinks and baking powder was found to constitute a major constituent of the diet. Consumption of tea may begin at an early age, as it is fed to infants in bottles.

Introduction

Tea has been well documented as representing an important contribution to dietary fluoride intake (1-5).

Most foods are poor sources of fluoride, even when grown in soil rich in fluoride. In soil, fluoride becomes converted to insoluble calcium salt, and is often unavailable to vegetation. Tea and some other plants in the Theaceae family, which require relatively acidic soil, are exceptional in their facility to concentrate fluoride (1).

A recent analysis of 16 varieties of China (C. sinensis) and Indian (C. assamica) tea, unfermented (green), partly fermented (oolong) and fermented (black) shows that the dry weight fluoride concentration of leaves is in the range of 40-120 ppm (6). In this study the observation was made that the fluoride content of tea leaves increases with the age of the leaves (6). Green tea, which comprises young foliage, shows fluoride values lower than the mature leaves used for black teas. Most American brands were identified as black tea, and consequently the fluoride values are in the higher range (73-114 ppm). Cook (7) has reviewed data on the fluoride content of tea leaves and reported a range of 121-260 ppm. An average of 186 ppm fluoride or 0.32 mg is contained in a cup in a 1% infusion, and 0.52 mg if the infusion shows 1.65 % (one tea bag per two cups water yields approximately a 1.6% infusion).

Potential adverse effects of fluoride from tea have been discussed by Cook (8), Webb-Peploe (9), Fand (4), and Jolly (10).

A study of caffeine intake by Cree Indians in Rupert House, an Indian settlement in Northwest Quebec, suggested that tea consumption was

substantial, exceeding that reported for any other part of Canada (4). For this reason a survey of the potential fluoride intake in this community in relationship to tea consumption was undertaken.

Tea was introduced to the Indians of Northern Canada in the late 1600s with the establishment of the Hudson Bay Company trading posts. However, it most likely did not become a staple in the Northern Indian diet until the early 1900s when dog teams were used to carry provisions from the settlement areas into the bush.

Although reference is often made to the consumption of tea in the anthropological, historical, and medical literature, little specific information is given regarding the amount and frequency of tea intake (12 14).

Canada's Department of Health and Welfare, in its 1974 Indian and Eskimo survey, collected data on the intake of caffeine beverages for the general Canadian population but little or none for this segment of the population.

Tea Consumption and Preparation in Rupert House: A typical per capita intake of tea in Rupert House was found to be 6 to 8 cups of "strong" tea per day. The capacity of a cup ranges from mugs holding 8 ounces (240 ml) to very large containers exceeding 10 ounces (300 ml). It was observed that the tea was strong and steeped for many hours. A large pot of water is put on to boil early in the morning, and bags of tea are added to the pot. The pot usually remains on the fire all day, being kept warm, not hot (11). Other informants have confirmed these observations regarding the preparation of tea in Indian communities. It is not unusual for small children to drink tea with sugar and a small amount of milk in bottles.

Fluoride Content of Tea as Prepared in Rupert House—an Estimate: This obviously lengthy contact between the tea leaves and water in the tea infusions prepared in Rupert House maximizes the extraction of tannin, caffeine, and fluoride. With increased infusion time there is a consistent but slight increase in fluoride extraction; up to 75% of the fluoride is extracted from the leaves by boiling water (15, 7).

Although no analysis was made of the fluoride content of tea as prepared in Rupert House, an estimate can be made by the use of data supplied by Cook (7). His data show that a 1.6% infusion made with fluoride-free water and tea leaves at 186 ppm fluoride will yield 0.52 mg fluoride per cup.

Water in Rupert House is believed to contain low levels of fluoride (16). Consumption of 6 to 8 cups of tea per day could thus provide a daily in-

take of 3.12 to 4.00 mg fluoride. This amount is a low estimate because of the unknown number of tea bags added to the water and because of the unknown effect of day-long steeping on the concentration of fluoride. The tea of preference in Northern Indian communities is India tea (Red Rose brand). As mentioned previously, American brand black tea has a higher fluoride concentration than less fermented teas (6).

Other Sources of Fluoride

Carbonated Beverages: Consumption of carbonated beverages among Northern Canadian Indians living in settlements is high (17), but intake levels have not been recorded. Because today many food items are processed with fluoridated water, carbonated beverages could contribute importantly to the total fluoride intake. Marier (18) observed that carbonated beverages prepared with fluoridated water contain 0.77 ppm fluoride whereas beverages prepared with unfluoridated water contain only 0.02 ppm. A 12 ounce bottle of carbonated beverage prepared with fluoridated water contributes 0.27 mg fluoride to the total dietary intake. Some individuals consume several bottles or cans daily.

No information is available regarding the location of processing plants where the carbonated beverages are bottled, which can be purchased by the Rupert House population at the local Hudson Bay Company store. However, as shown elsewhere (19), 50% of Quebec's carbonated beverages are processed at a plant in Laval, Quebec, where fluoridated city water is used.

Canned Fruits and Beverages: Whereas canned fruits and vegetables, processed with fluoridated water, are also potential sources of fluoride in the diet, intake of these canned goods is not high in the Rupert House community.

Baking Powder: Baking powder is used extensively by Northern Canadian Indians to make a scone-like pancake bread called bannock and contributes to the total daily fluoride intake according to the amount of baking powder used and the size of the portion of bannock consumed. It is not unusual to use 2 to 4 teaspoons (8 to 16 gms) of baking powder per bannock and many individuals consume a whole one. The fluoride content in baking powder is limited to 10 ppm by Canada's food and drug regulations (20).

Potential Health Effects from Fluoride Intake

As shown, fluoride intake, especially from tea consumption in Northern Canadian Indian settlements is potentially high. Yet little or no information has been collected regarding mottling of teeth in this population. Nor

are data on the incidence of arthritic symptoms readily available. According to several local physicians and dentists, tooth decay due to high carbohydrate intake appears to be a major problem in the Canadian North (17).

Malnutrition: Several authors have indicated that malnutrition contributes to the toxicity of fluoride (21, 1), particularly when associated with high fat and alcohol consumption and low intake of vitamin C, calcium, and magnesium as found in the diet of the Northern Canadian Indian (22-26). The concentration of magnesium and calcium in ground water in the region of Northern Canada under study is low (16).

Besides high dietary intake of fluoride through tea and baking powder in certain areas of Northwest Ontario and Northwest Quebec, Indians depend upon fish contaminated by mercury as a major protein source for 4 to 5 months of the year. The population of Rupert House is located in one of these high risk areas. No data are available on the possible synergistic action of mercury and fluoride, particularly with reference to their effect on enzyme systems and interference with thiamin metabolism.

Bibliography

1. Fluoride and Human Health. World Hlth. Organization, Geneva, 1970. 2. Waldbott, G.L.: Fluoride in Food. Am. J. Clin. Nutr., 12:455-62, 13:393, 1963. 3. Jackson, D. and Weidman, S.M.: Fluorine in Human Bone Related to Age and Water Supply of Different Regions. J. Path. Bact., 76:451-59, 1958. 4. Fand, R.: Medical Aspects of Fluoride and Fluorosis. Intern. J. Env. Stud., 5:87, 1973. 5. Underwood, E.: Fluorine, in Trace Elements in Human and Animal Nutrition. Academic Press, London, 1971. 6. Ma, T.S. and Gwirtsman, J.: Determination of Fluorine in Tea. Intern. J. Env. Analyt. Chem., 2:133, 1972. 7. Cook, H.A.: Fluoride Intake through Tea in British Children. Fluoride, 3:12-18, 1970. 8. Cook, H.A.: Crippling Arthritis Related to Fluoride Intake (Case Report). Fluoride, 5:209-213, 1972. 9. Webb-Peploe, M.M. and Bradley, W.G.: Endemic Fluorosis with Neurological Complications in a Hampshire Man. J. Neurol. Neurosurg. Psych., 29:577-585, 1966. 10. Jolly, S.S.: Fluoride Balance Studies in Endemic Fluorosis. Fluoride, 9:138-147, 1976. 11. Farkas, C.S. and Beckett, D.: Non-Alcoholic Beverage Consumption in a Northern Indian Settlement and Potential Health Effects. J. Canad. Diet. Ass., 38:57, 1977. 12. Kerr, A.J.: Anthropological Report on the Rupert House Indians. unpubl. manuscript, 1950, pp. 235, 241. 13. Rogers, E.: The Quest for Food and Furs, Mistassini Cree 1953-54. Natl. Museum of Canada, Publications in Ethnology #5 Ottawa, 1973, p. 75. 14. Lang, M.G.: Nutrition in Indians and Northern Health Services. Nutrition Notes, Cnd. Dept. Hlth. and Welfare, 16, 1960. 15. Sinclair, H.M. and Hollingsworth, D.: Hutchinson's Food and the Principles of Nutrition. 12 ed. Edw. Arnold, Lon-

don, 1969, p. 481. 16. Phaneuf, R.; Consultant, Mercury Studies Program, National Indian Brotherhood, Ottawa, July, 1976. 17. Mayhall, J.T.: Dental Caries and Nutrition. Nutrition of Indian and Eskimo Children, Ross Laboratory, Montreal, 1975, p. 155. 18. Marier, J. and Rose, D.: The Fluoride Content of some Foods and Beverages-a Brief Survey Using a Modified Zr - SPADNS Method. J. Food Science, 31:941-6, 1966. 19. Farkas, C.S.: Water Fluoridation, the Human Diet and the Environment. Society to Overcome Pollution, Montreal, 1973. 20. Government of Canada, Food and Drug Regulations 1970 #B 150001, p. 65. 21. Suttie, J. and Phillips, P.: Fluoride Ingestion and Vitamin Metabolism. In Fluorine and Dental Health: The Pharma - cology and Toxicology of Fluorine, Muhler, J.C.; Indiana Press, 1959, p. 70. 22. Pass, C.: Report of Preliminary Diet Survey of Cree Population. Medical Services, Health and Welfare, Canada, Jan. 1976. 23. Nutrition Canada, Health and Welfare, Ottawa Indian Survey, 1975. 24. Farkas, C.S.: Consideration of Potential Magnesium Deficiency Among Northern Indians of Eastern Canada. J. Cnd. Diet. Ass., 38:57, 1977. 25. Lee, M., Reyburn, R., Carrow, A.: Nutritional Status of British Columbia Indians. Cnd. J. Publ. Hlth., 62:285-296, 1971. 26. Manning, P.J.: The Nutritional Basis of Otitis Media. Op. Cit., Ross Labs, 1975, p. 151. 27. Farkas, C.S.: Components of Northern Canadian Indian Diet and Mercury Toxicity; with Special Attention Paid to Thiamin, Magnesium, and Fluoride. Manuscript, National Indian Brotherhood, June, 1976.

SPECIAL REPORT

AAAS FLUORIDE SYMPOSIUM IN DENVER

by

G. L. Waldbott and J. Yiamouyiannis
Warren, Michigan and Delaware, Ohio.

At its annual Conference on February 25, 1977, the American Association for the Advancement of Science held a symposium in Denver, Colorado, entitled, "Continuing Evaluation of the Use of Fluoride". The morning session was devoted to the metabolic and dental aspects of fluoride. In the afternoon the question of safety was examined which, as expressed in the program, "has received considerable attention by the academic community over the years, but has often not entered adequately into the considerations of the clinician". This part of the session was intended to consider "some special cases which represent potential risks if the problems are not recognized by the clinician or investigator involved".

R. F. Sognnaes, Professor of Oral Biology at the University of California, Los Angeles, introduced the morning session with an historical review of fluoridation of drinking water. He reminded the audience that 1977 was the 60th anniversary of the reports of mottled enamel by F.S. McKay which subsequently, in 1931, was shown to be caused by fluoride in drinking water. As a result of the discovery of the cariostatic property of fluoride, it is estimated that some 105,800,000 people in the United States are now drinking fluoridated water. Sognnaes pointed to the advantages of fluoridating water in schools, a measure first introduced in the city of Elkwood, Pennsylvania, which may serve as a substitute for municipal water fluoridation. He also suggested that, in non-fluoridated communities, tea with added lemon juice might be a suitable source of fluoride intake. He considers fish, "the richest source of fluoride in food", which can provide an increase in fluoride uptake.

The paper by D.R. Taves of Rochester, New York, concentrated on two subjects namely, the uptake of fluoride through food and homeostasis of fluoride in the bloodstream. He stated that fluoride assays by the ion specific electrode which he used for fluoride analysis did not yield as high fluoride levels as the direct colormetric method used by Spencer for the kind of foods which she analyzed. He confirmed her observation that chicken contains a relatively high amount of fluoride (of the order of 5 ppm) but for most other common foods his values were significantly lower than those she obtained. On the question of homeostasis of fluoride in the blood stream, Taves' conclusions disagreed with those of Singer and Armstrong. His results indicated a passive diffusion of fluoride rather than homeostasis.

W.S. Guy of Children's Hospital, Cincinnati, Ohio, stressed the need for differentiating between inorganic and organic fluoride in human plasma. In conjunction with Taves, he had isolated in 1976 by spectroscopic analysis, perfluorooctanoic acid, a major component in pooled plasma which accounts for at least 1/3 of the total organic fluoride content. This compound reaches the blood stream from the use of such products as floor waxes, wax paper, Scotch Guard, and other items. Along with Taves, Guy suggested that fluoride determinations by methods of Armstrong and Singer are inaccurate and that the blood levels of fluoride correlate much more closely with fluoride levels in drinking water than has been previously reported. The levels of organic fluoride, however, were not related to the content of inorganic fluoride in drinking water. He suggested that in infants fluoride supplements amounting to 1/2 mg daily are excessive. He also discussed the fetoplacental barrier for fluorides.

T.M. Marthaler of the University of Zurich, Switzerland, reviewed the fluoridation studies carried out in the USA during the 40's and 50's in Kingston-Newburgh, Grand Rapids, Brantford-Sarnia, and Evanston-Oak Park in support of the hypothesis that fluoridation reduces tooth decay by 2/3. He

pointed out that regular intake of fluoride tablets accounts for fluoride uptake in the tooth which is comparable to that from fluoridation of water. In dentin, considerably more fluoride accumulates than in deep enamel.

E. Johansen of the University of Rochester, N.Y., School of Medicine and Dentistry, presented a paper on the effect of dental hygiene combined with local application of a fluoride-containing dentifrice in patients who had been treated for cancer by irradiation to the point that their salivary glands were no longer functional. As a result of the lack of saliva flow (plus other possible unknown factors) the teeth would normally undergo severe degradation. He treated these patients with intensive dental care, a mineral mouthwash, removal of food debris, topical self-application of fluoride at 20,000 ppm, and special fluoride-containing chewing gum. This treatment retarded the deterioration of teeth. In individuals aged 6 to 80 years he virtually eliminated caries by these measures. He pointed out that caries develops at the interior layer of the enamel and that much fluoride applied topically is lost after 24 hours.

In the discussion, H.C. Hodge of the University of California School of Medicine, San Francisco, emphasized that the consumption of fluoridated water by newborn infants is potentially harmful because they might develop dental fluorosis. Furthermore, in fluoridated communities no supplementary fluoride (tablets or drops) should be administered because of the narrow margin of safety of fluoride. In the discussion, the following possible sources of an overdose were noted: 1) infant formulas made with fluoridated water; 2) baby food, especially those containing chicken; 3) infant formulas reconstituted with fluoridated water; 4) swallowing of fluoridated toothpaste and 5) excessively high doses of fluoride (5 to 7 ppm) which are supplied in drinking fountains in schools. One participant suggested that the Dental Section of the AAAS should alert the American Medical Association and American Association of Pediatrics to the concern of the Section, but no action to this effect was taken.

The afternoon session opened with an outstanding paper by J.O. Jowsey of the Mayo Clinic, Rochester, Minnesota. She pointed out that osteoporosis is becoming more and more prevalent and is attacking people at a young age. Adequate exercise and adequate calcium intake in the diet can prevent osteoporosis but after the disease begins it is difficult to cure. Osteoporotic patients cannot exercise—one of the means of preventing osteoporosis—and the more severe the disease the less beneficial are calcium supplements. At this stage, administration of fluoride alone worsens the condition of the osteoporotic patient but when taken together with large amounts of calcium, Jowsey reported a therapeutically ameliorative effect on the osteoporotic patient. Calcium carbonate-sodium fluoride tablets, according to Jowsey, have not been approved by the Food and Drug Administration; because

they are not patentable drug manufacturers have not requested FDA's approval for them.

G.M. Whitford of the Medical College of Georgia showed that, in anesthetized rats, renal clearance of fluoride is determined by the urinary pH, not by the flow rate of the urine nor by the amount of potassium excreted, as formerly believed. Reabsorption of urine in the renal tubules is inversely related to the pH of the tubular fluid. Whitford also found that fluoride is absorbed by the bladder, probably as HF. This process too is inversely related to the pH of the urine. At pH 1.85, 70% of radioactive fluoride was absorbed but only 5% at pH 5.5.

W.J. Johnson of the Mayo Clinic discussed the effect of fluoridated water in hemodialysis. In 7 nephritic patients with skeletal changes (5 of whom had dental fluorosis as well) from natural fluoride areas in the USA, hemodialysis with fluoridated water aggravated the kidney disease and led to spontaneous fractures. Fluoride-containing water increased the fluoride concentration in the blood by 10 to 20 micromoles/liter, or by 0.19 to 0.38 ppm. Johnson also showed that patients with renal failure retain more fluoride.

R.A. VanDyke of the Mayo Clinic discussed the biotransformation of fluoride-containing anesthetics in the body. In the complete absence of oxygen, halothane is known to cause renal failure. The loss of fluoride ions from these anesthetics accounts for the damage to kidneys.

The final paper by Suttie of the University of Wisconsin at Madison dealt with the effect of fluoride on cultured cells. Fluoride at 10 ppm inhibited growth of cell cultures (L Cells). By selection and cloning, Suttie was able to increase cell resistance to fluoride after previous exposure. He theorized that fluoride-resistant cells may be able to pump out the fluoride which has entered into them. He was also able to show metabolic distortions in cells at fluoride levels which did not affect the growth rate of his cells, the most significant of which was the depletion of DPN (or NAD), the biologically active form of niacinamide.

The discussion that followed the afternoon program revolved around the current controversy concerning the possible relationship between fluoridated water and cancer. This subject receives further attention on page 102 in this issue.

FLUORIDE ABSORPTION FROM THE RAT URINARY BLADDER: A pH-DEPENDENT EVENT

by

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Augusta, Georgia

(Abstracted from Am. J. Physiol., 232:F10-F15, 1977)

In previous studies the authors showed that the pH of the renal tubular fluid is the major determinant of the renal clearance rate of fluoride. They now focus attention to the possibility that HF may diffuse from the low pH bladder content across the bladder epithelium and thus be re-absorbed. Fluoride absorption from the urinary bladder by the non-ionic diffusion of HF can be extensive and is related to the pH of the urine.

The ureters of female Wistar rats were ligated near their midpoint and, by means of a polyethylene catheter, buffered solutions were introduced into the bladder in the range of 1.85 to 7.90 mM of stable fluoride and 0.012 to 8.81 mM, respectively. (The minimal pH of mammalian urine is approximately 3.95.) ^{14}C inulin served as a marker for dilutional changes in buffer fluoride concentrations and ^{18}F was employed to confirm systemic absorption. In preliminary experiments the authors studied 1) the influence of volume on intravesicular pressure and on fluoride absorption; 2) the extent of systemic absorption of ^{14}C inulin; and 3) the immediate changes in fluoride and ^{14}C inulin concentrations.

Results: The experiments revealed that the fluoride absorption from the bladder is inversely related to pH over the 1.85-5.50 range. Mean, 15-min radiofluoride absorption values were 70% at pH 1.85, 37% at pH 3.95, and 5% at pH 5.50. These fractional absorption values were not significantly influenced by the concentrations of carrier fluoride, by the buffers used, or by the presence of urine. Above pH 5.50, pH-independent absorption occurs to a slight extent. The results are consistent with a first-order absorptive process by the non-ionic diffusion of hydrogen fluoride.

This research has important clinical implications, especially in the treatment of acute fluoride intoxication and in diseases where respiration is markedly depressed. In such cases, catheterization of the bladder could reduce fluoride recycling. The findings also point to a similar mechanism of gastric absorption of fluoride in the presence of an acid stomach content. The intracellular and extracellular partitions of fluoride may also be related to pH gradients.

The variability in results from experiments designed to assess the anticaries effects of fluoride can also be explained, in part, by group variations in fluoride excretion due to changes in urinary pH. Relatively minor decreases in urinary pH can dramatically influence the degree of renal reabsorption of fluoride.

SERUM IONIC FLUORIDE: NORMAL RANGE AND RELATIONSHIP TO AGE AND SEX

by

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(Abstracted from Clin. Chem., 22:1884-1888, 1976)

By means of the Orion fluoride electrode the authors determined the normal range of serum ionic fluoride concentrations, particularly their relationship to sex and age. Determinations were made in 87 men aged 18-92 (mean, 46 years) and 49 women aged 19-64 (mean, 38). None had any clinical condition related to bone or kidney disease and all had normal values for serum creatinine and alkaline phosphatase. None were on medication which could have influenced the serum ionic fluoride concentrations.

In the group of 51 men below age 35 the mean serum ionic fluoride was 0.876 ± 0.275 μmol/l (0.017 ppm) whereas in the 36 men aged 46 to 92 the mean serum ionic fluoride value, 1.183 ± 0.350 (0.022 ppm), was significantly higher. In normal women, however, serum ionic fluoride concentrations correlated in simple linear regression with age. The minimum and maximum values were 0.022 - 0.315 and 0.022 ± 1.065 μmol/l. The authors found no differences in the mean concentration of fasting serum and plasma ionic fluorides derived from the blood specimens. Whole blood showed a mean of 1.50 μmol/l (0.028 ppm) in five fasting subjects.

Factors which account for higher fluoride values at higher ages are consumption of tea and other food-related sources of fluoride, exacerbated

impairment of renal function in older people and increased release of previously deposited bone fluoride. Enhanced release of fluoride from bone observed in females following menopause might be another factor.

FLUORIDE UPTAKE IN RATS GIVEN TEA WITH MILK

by

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(Abstracted from J. Dent. Res., 55:916, Sept.-Oct. 1976)

Seventy-five male rats were divided into five groups of 15 each. Group 1 received tea prepared by adding 15 tea bags (2 gms) to 1 liter of boiling water (fluoride concentration of the tea was 4.3 ppm); group 2, tea diluted with milk; group 3, distilled water containing no fluoride; group 4, distilled water diluted with milk containing 0.034 ppm total fluoride; and group 5, distilled water diluted with sodium fluoride at a 1:3 ratio that contained 2.9 ppm fluoride. Each rat consumed about the same amount of fluid (30 ml daily) and received a standard diet of up to 5 ppm fluoride ad libitum.

After 40 days the animals were sacrificed. Their femurs and mandibular and maxillary bone segments, and their molar teeth, were removed and analyzed for fluoride.

The various fluids, containing 2.9 ppm fluoride, resulted in significant increases in the fluoride levels of the femur ash. It suggested that fluoride was absorbed almost as completely from milk as from water with high fluoride concentrations. Rats given tea diluted with distilled water or milk showed higher concentrations of fluoride in the molar surfaces than those given distilled water diluted with milk. This increased availability of fluoride from tea was attributed to chelating properties of the organic acids present in tea. The rats given tea diluted with milk showed lower concentrations of fluoride in their molar surfaces than rats given tea diluted with water, probably due to the attenuating effect of milk in the tea.

THE FLUORIDE CONTENT OF SOME VARIETIES OF TEA OBTAINED AT THE BELGIAN MARKETS AND IN THEIR INFUSIONS

by

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(Abstracted from Arch. Belges de Med. Soc. Hyg., Med. du Travail et Med. Leg., 33:551-556, Nov.-Dec., 1975)

The authors determined the fluoride content of some 60 different kinds of tea which are available at the Belgian market using the method of Verloo and Cottenie for the analysis. The amounts of fluoride in tea ranged from 50 to 125 mg/kg and the infusions (about 1 gm/ml water) contained from 0.06 to 0.15 mg per cup. When two grams were added to 100 ml of water, 0.19 to 0.36 mg per cup was consumed. In the dry leaves of mint, camomile, eglantine, orange blossoms, lemon with spices, verbena, lime tree, fluoride values of the order of 0.5 to 4 mg/kg were found which would provide a minimum of approximately 0.0012 mg per cup of solution.

The authors state that "the quantity of fluoride ingested in a tea drinker is not negligible". If to this value fluoride is added from other nutrients, especially that from drinking water in some areas, fluoride in tea could eventually induce toxicity, particularly among people with kidney disease.

CORRECTION: The title of the article by Miller, G.W. et al. in 10:76-82, April 1977, should have read, "Alkaline Phosphatase Activity, Fluoride, Citric Acid, Calcium, and Phosphorus Content in Bones of Cows with Osteofluorosis".

On page 79, Table 3, under rib, osteofluorotic, the value should read, 15997.5 ppm.

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