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Dept. of Nuclear Medicine
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Dr Jorg Spitz
Dept. of Nuclear Medicine
Wiesbaden, Germany

Prof S P S Teotia
LLRM Medical College
Meerut, India

Dr Sally Wheeler, Hawkesbury
Agricultural Research Unit
Richmond NSW, Australia

Prof Y Yoshida
Osaka Medical College
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IN MEMORIAM
Edith M Waldbott
October 5, 1903 - January 14, 1997

It is with a deep and heartfelt sense of loss that we report the passing of Edith M Waldbott, widow of George L Waldbott MD, the founder of our Society and long-time editor of our Journal. During the decade following Dr Waldbott’s death in July 1982, Mrs Waldbott very ably and unstintingly edited and published Fluoride until 1992, when the present editor assumed this responsibility.

Born and raised in Cincinnati, Ohio, as Edith Marks, daughter of a noted shoe manufacturing family, she was the middle child of four brothers. In 1921 she entered Vassar College in Poughkeepsie, New York, as a scholarship student, where she received her BA degree in psychology and zoology in 1925. She then did post-baccalaureate research in embryology at Woods Hole, Massachusetts, and later studied medical illustrating at Johns Hopkins University in Baltimore, Maryland.

During these years she met Dr Waldbott, who had recently begun his medical practice in Michigan, and they were married on June 18, 1927. They had two daughters, Edith, who lives in Michigan, and Betsy, who lives in Israel where she teaches English and writing.

With her special talent for architectural planning, Mrs Waldbott designed three of their own homes plus a charming rustic summer cottage. Among her other artistic interests were jewelry-making in enamel and silver.

Even as a housewife and mother, Mrs Waldbott put her training in science to good use. According to Dr Waldbott, “she assisted me in preparing my manuscripts ever since we were married. Her main interests had been in science, fine arts, antiques and of course the education of our two daughters.”

In the early 1950s, Mrs Waldbott began looking into reports on biological effects of fluoride, especially in humans. She drew some of this information to the attention of Dr Waldbott, who became increasingly interested in it and soon undertook further study on his own. In 1954, much to his surprise, he encountered cases of serious reversible illness from fluoride in drinking water in his allergy practice that provided clear and unequivocal proof that Mrs Waldbott’s concerns about the supposed safety of water fluoridation were indeed justified.

In 1955 Mrs Waldbott inaugurated National Fluoridation News as a bi-monthly source of documented information about research and events concerning water fluoridation. Writing most of it herself, she edited and published NFN for seven years before relinquishing it to Ethel Day in Hempstead, New York, who, with the assistance of her well-known illustrator husband, Robert Day, continued it from 1963 to 1985. Publication of NFN was then continued by Shirley Graves in San Anselmo, California, but it ceased publication, unfortunately, in 1988.

After Dr Waldbott began our journal Fluoride in 1968, Mrs Waldbott devoted increasing amounts of her time to revising and editing manuscripts submitted for publication. This challenging task she continued untiringly for ten years after Dr Waldbott’s death, under her modest self-imposed title of “Interim Editor”.

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Intensely devoted to a genuine practice of her Christian faith, Mrs Waldbott was a constant source of inspiration and trust to all who knew her. Her keen mind was that of an inquiring scholar anchored in courage and persistence. But, perhaps most of all, she will be remembered for her warmth and kindness toward everyone she met as well as for her love of truth, beauty, justice, goodness, and integrity.

Mrs Waldbott lived a very uplifting and fulfilling life. She was looking toward her eternal reward when she died peacefully in her sleep at her home in Rochester Hills, Michigan, at age 93. Besides her two daughters, she is survived by four grandchildren and four great grandchildren.

For much of the foregoing information the writer is indebted to Dr and Mrs Waldbott's grandson, Arne Wadenstierna, and to their daughter, Betsy Ramsay, who helped with the transition period of this journal in 1991.

Dr and Mrs Waldbott on their 50th wedding anniversary

This issue of Fluoride contains an expanded Discussion Section, because of the very welcome response by members and readers to our invitation to them, in the November 1996 number, to comment on the varying views expressed in our past editorials and in letters to the editor, on controversial subjects related to fluoride research. We believe such discussion can be a valuable contribution to the scientific process.

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NUTRITION SURVEY IN DENTAL FLUOROSIS-AFFLICTED AREAS

Y X Chen, M Q Lin, Y D Xiao, W M Gan, D Min and C Chen
Nanchang, Jiangxi, China.

SUMMARY: The fluoride (F) intake, diet, and health status of children in two dental fluorosis-afflicted areas in the Province of Jiangxi, China were studied in an attempt to correlate nutritional status with dental fluorosis. The relationship between milk consumption and the incidence of dental fluorosis among the children was stressed in this study. Average body weight of the children approximated that of the national standard. Protein intake was above the national standard of 0.75 g/kg body weight/day, but the protein was derived mainly from plant sources. Calcium intake was found to be insufficient. Based on the diet and fluoride intake of the studied groups, the areas with a better nutritional status were found to have a lower incidence of dental fluorosis. The incidence among milk-consuming children was lower than that of non-milk-consuming children.

Key words: Calcium; Dental fluorosis; Milk consumption; Nutrition survey.

INTRODUCTION

Several fluorosis-afflicted areas exist in Pingxiang District within the province of Jiangxi, China. Overall incidence rate of dental fluorosis in the district was reported to be above 50%.1,2 Fluoride content of drinking water has been analyzed for every village in the region, and the average is lower than 0.3 mg/L. Although the daily fluoride (F) intake by the residents in the disease area was higher than that in non-disease (reference) area, it was no more than 3.5 mg/person.3 Except for exposure to high levels of environmental F (air pollution, mainly from coal-burning in residents' homes, affecting food),1-4 little is known about other factors contributing to the high incidence of dental fluorosis among the residents. In this study we carried out a nutrition survey of residents in two villages within the district, in an attempt to correlate nutritional status of the residents with the incidence rate of dental fluorosis.

MATERIALS AND METHODS

Study areas: Two villages whose dental fluorosis incidence rate was similar to each other but whose economic conditions markedly differ from each other were selected for this study. One of the villages, located in a suburban area with a higher living standard, had 30% incidence of dental fluorosis. The other village, located in a rural area with poor economic conditions, had 34% incidence of dental fluorosis.

Fluoride intake: Fluoride intake was assessed by analyses of fluoride levels in the air, water, and several kinds of foods including rice, and vegetables.

Nutrient intake: Using questionnaires, the annual food consumption by 150 households in each village was studied. Based on food composition tables, daily dietary intake by the adult residents were calculated.

Health examination: 120 male residents and an equal number of female residents, aged 40-50, were selected from each village for health examination. The residents had been living in the district all their lives and were free from...
chronic diseases except for dental fluorosis. Physical examination and biochemical tests, including blood and urine tests, were performed.

**Dental fluorosis among children:** A dental fluorosis survey among school children, both boys and girls, age 8-14, was carried out using questionnaires and a follow-up study in several schools. The children were divided into groups based on whether or not they consumed milk from four years of age. Incidence of dental fluorosis in the two groups was studied based on Dean’s classification.

**RESULTS**

Total fluoride intake by residents living in the suburban area was more than 20% higher than that in the rural area, and more than 90% of the total F intake was derived from consumed food (Table 1).

**TABLE 1. Daily fluoride intake**

<table>
<thead>
<tr>
<th>Area</th>
<th>Total fluoride intake (mg/day/person)</th>
<th>Percent of total intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X ± SD</td>
<td>Water</td>
</tr>
<tr>
<td>Suburban</td>
<td>3.20 ± 0.07</td>
<td>5.0</td>
</tr>
<tr>
<td>Rural</td>
<td>2.44 ± 0.33</td>
<td>7.0</td>
</tr>
</tbody>
</table>

The protein intake among the residents in the disease areas was found to be close to the recommended standard, i.e. 0.75 g/kg body weight (Table 2). But in the rural areas, more than 80% of the protein was supplied from plant sources. Consumption of calcium was found to be very low. Furthermore, most of the calcium ingested was obtained from plant sources. The protein and calcium intakes by the suburban residents were higher than those by the rural residents.

**TABLE 2. Daily protein, calcium and phosphorus intake by adults**

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Daily Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Suburban</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>78.4 ± 3.2</td>
</tr>
<tr>
<td>Plant source</td>
<td>45.3 ± 6.5</td>
</tr>
<tr>
<td>Animal source</td>
<td>33.1 ± 0.8</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>432 ± 12.1</td>
</tr>
<tr>
<td>Plant source</td>
<td>274 ± 14.2</td>
</tr>
<tr>
<td>Animal source</td>
<td>158 ± 8.3</td>
</tr>
<tr>
<td>Phosphorus (mg)</td>
<td>1740 ± 27.4</td>
</tr>
</tbody>
</table>

The average body weight of the residents under study, calculated by a modified Broca's method, was found to be close to the standard value. No significant differences in body weight were observed between suburban and rural residents (Table 3). Results of blood chemistry tests showed normal values for blood composition, reflecting normal functioning of the liver and kidneys.
The incidence rates of dental fluorosis among 1,100 children from the study areas were found to differ markedly, depending on whether or not the children consumed milk. The rate of dental fluorosis of the milk-drinking group was 7.2%, whereas that of the non-milk-drinking group was 37.5% (Table 4).

**Table 3. Comparison of height and weight of adults (mean ± SD)**

<table>
<thead>
<tr>
<th>Area</th>
<th>Sex</th>
<th>N</th>
<th>Height (cm)</th>
<th>Body weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suburban</td>
<td>Male</td>
<td>42</td>
<td>159.8 ± 5.0</td>
<td>58.1 ± 7.8</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>52</td>
<td>150.2 ± 6.0</td>
<td>51.5 ± 7.1</td>
</tr>
<tr>
<td>Rural</td>
<td>Male</td>
<td>52</td>
<td>158.5 ± 6.0</td>
<td>55.3 ± 7.1</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>68</td>
<td>149.3 ± 5.0</td>
<td>49.9 ± 5.7</td>
</tr>
</tbody>
</table>

**Table 4. Incidence of dental fluorosis among children**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Cases</th>
<th>Incidence rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk-drinking</td>
<td>181</td>
<td>13</td>
<td>7.1</td>
</tr>
<tr>
<td>Non-milk-drinking</td>
<td>929</td>
<td>348</td>
<td>37.4</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Results of physical and nutrition examinations indicated that the average adult body weight of the two areas under study was in accord with the standard values. However, while the average protein intake by the residents in the disease areas was close to the recommended standard, i.e., 0.75g/kg body weight, the intakes by the suburban residents were 37% higher than those by the rural residents. Furthermore, most (83%) of the protein consumed by the rural residents was found to be derived from plant sources. By contrast, in the suburban areas, the residents' protein derived from plant sources accounted for only 58%.

More strikingly, the average daily calcium intake by the rural residents was only about one-third of the level recommended by the Chinese Society of Nutrition Science, i.e. 800 mg/day/person. Although calcium intake of the suburban residents was higher than that of the rural residents, it was still below the standard. In the digestive tract, calcium mixes with proteins, amino acids, and sugars to form soluble complexes, enhancing its absorption. In Pingxiang district, especially in rural areas, most of the calcium was derived from plant foods. The levels of oxalate, phytate, and phosphate in such foods are, therefore, high. As is widely known, these chemical substances will react with calcium ions, forming insoluble salts and thus reducing calcium absorption. Also, the ratio of calcium to phosphorus between 2:1 and 1:1 in food is considered favourable to calcium absorption. Results of the nutrition survey indicated that the average Ca:P ratio of the residents diet was far below this ratio. Such low Ca:P ratio may lead to reduced calcium absorption, also. Moreover, an insufficient supply of calcium in the diet would result in lowered CaF₂ formation, thus increasing the absorption of fluoride.
In summary, although the daily fluoride intake by the rural residents was 2.44 mg/person, compared with 3.20 mg/person by the suburban residents, the rural residents had more than 30% higher incidence of dental fluorosis. Furthermore, dental fluorosis incidence rate in milk-consuming children was shown to be only one-fifth that in non-milk-consuming children. These results strongly suggest that inadequate intakes of protein and calcium are important factors contributing to fluorosis, and that an increase in the intakes of both calcium and protein while decreasing the intake of fluoride appears to be an important preventive medicine for the residents under study.

Acknowledgment: We are indebted to Professor Ming-Ho Yu for his meticulous review and continuous support for our research work.

REFERENCES
TOXICITY FROM WATER CONTAINING ARSENIC AND FLUORIDE IN XINJIANG

G Q Wang, Y Z Huang, B Y Xiao, X C Qian, H Yao,
Y Hu, Y L Gu, C Zhang and K T Liu
Urumqi, Xinjiang, China

SUMMARY: Further study was made of the estimated population of 50,760 using well water high in arsenic and fluoride in the area of Kuitun, in China, by examining, for arsenism and fluorosis, over 3,500 residents using water from seven wells. Arsenic and fluoride were seen to be able to exert toxic effects independently when present in well water at levels of 0.12 mg/L or more of arsenic and 0.2 mg/L or more of fluoride. As the level of arsenic increased from 0.12 to 0.6 mg/L the incubation period for arsenism decreased from 10 to 0.5 years and the prevalence at 10 years increased from 1.4 to 47%. Improvement occurred in 82% and the development of new cases was prevented one year after the quality of the water was improved.

Key words: Arsenic; Arsenism; China; Epidemiology; Fluorosis; Toxicity; Water.

INTRODUCTION

Chronic toxicity from arsenic, arsenism, and fluoride, fluorosis, in a large area near Kuitun (Kuytun) was described by Wang in 1985. By fuzzy cluster analysis and investigation of the arsenic and fluoride content of drinking water, food, air, hair, and urine in areas of endemic disease and a control area it was determined that main source of arsenic and fluoride was well water. Detailed clinical studies of patients from affected and control areas were made including investigation with limb radiography, skin biopsy, electrocardiography, nail fold microcirculation observation, nerve conduction studies, and fiberoptic gastroscopy. A study of the birth weight of 1153 babies, four of whom had congenital defects, born in the high arsenic and fluoride area from 1984 to 1988, found this to be lighter than that for a control area. The present study describes an epidemiological survey of the area and interventions for prevention and treatment.

MATERIALS AND METHODS

A preliminary survey in 1982 of the water from 619 wells in the Kuitun area showed 102 to contain water with a high content of arsenic and fluoride. Further analysis of these 102 wells in 1989 showed similar findings (Table 1).

<table>
<thead>
<tr>
<th>Arsenic mg/L</th>
<th>F- 1.0-1.9 mg/L</th>
<th>F- 2.0-3.9 mg/L</th>
<th>F- &gt;4.0 mg/L*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05-0.09</td>
<td>26</td>
<td>11</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>0.10-0.19</td>
<td>5</td>
<td>13</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>0.20-0.29</td>
<td>1</td>
<td>8</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>0.30-0.39</td>
<td>0</td>
<td>5</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>0.40-0.49</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>0.50-0.59</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>&gt;0.60**</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Number of wells</td>
<td>32</td>
<td>39</td>
<td>31</td>
<td>102</td>
</tr>
</tbody>
</table>

* Highest level of fluoride was 21.5 mg/L
** Highest level of arsenic was 0.88 mg/L

Xinjiang Medical College, Urumqi 830054, China.
The varying amounts of arsenic in the well water were related to varying sulphate concentrations resulting in the formation of insoluble arsenic sulphate.\(^7\) The wells containing high arsenic and fluoride levels were found over an area of 1,200 km\(^2\) near the southwest part of the low-lying land of Zhuiger Basin, north of the Tian Shan mountains in the lower reaches of the Kuitun River (Kuyuting He). The arsenic and fluoride content of the well water increased progressively as the elevation above sea level decreased from the highest point at Kuitun City, at 455 m above sea level, to the lowest area in the north of the Zhuiger Basin. The wells had been created in the 1960s and subsequently, with the residents using surface water prior to that time.

The population using water from the wells containing high levels of arsenic and fluoride was calculated to be 50,760. Many were farm workers who had immigrated from Henan Province.

The residents using water from seven wells, with a variety of arsenic and fluoride levels, created between 1969 and 1979 were examined for the presence of toxicity from arsenic (3,621 examined) and fluoride (1,178 examined). Some patients with arsenism and fluorosis were further examined by electrocardiography (ECG, 61 examined), peripheral microcirculation investigation (124 examined), electromyography (EMG, 47 examined), and biopsy (6 examined).

One year after improvements to part of the water supply had been made, at a cost of 17,000,000 yuan, the severity of illness was reassessed in 458 patients, who had previously been affected, and the occurrence of new cases of illness looked for.

The diagnostic criteria for the presence of arsenism were a) a history of drinking water with a high arsenic level and b) the presence of at least one of the two main symptom/sign complexes of chronic arsenism involving abnormal cutaneous pigmentation, due to arsenic, or keratoderma\(^8\) or c) a secondary diagnostic feature such as a raised arsenic level, in the urine or hair, or other manifestations of arsenism such as peripheral neuropathy or multiple skin carcinomas.\(^9\) The diagnostic criteria for the presence of fluorosis were a) a history of drinking water with a high fluoride level and b) the presence of at least one of the two main symptom/sign complexes of chronic fluorosis involving, clinically or on radiography, dental fluorosis or osteofluorosis\(^8\) or c) a secondary diagnostic feature such as a raised fluoride level, in urine or hair, or other manifestations of fluorosis.\(^10\)

**RESULTS**

The relationship between health status and the use of water from the seven wells, with a range of arsenic and fluoride levels, is shown in Table 2.

The development of dental fluorosis was not affected by the level of arsenic in the water. When the fluoride concentration in the well water was 3.5 mg/L or more, over 90% of children, aged 8-15 years, developed dental fluorosis, irrespective of whether the arsenic level in the water was 0.034 mg/L or 18 times greater at 0.600 mg/L. All children aged 5 years or more with dental fluorosis had coarse stripes of bone on pelvis radiographs with the radiographic features of adult osteofluorosis appearing at ages 10 or more.\(^11\)
When the water fluoride level was 3.5 mg/L or more, increasing levels of arsenic in the water were associated with a higher prevalence of arsenism and a shorter incubation period. When the water arsenic level was 0.12 mg/L the prevalence of arsenism, in residents who had drunk the water for more than 10 years, was 1.4%, while among those using water with a level of 0.6 mg/L the prevalence was 47.2%. Similarly, the incubation period for the development of arsenism among residents using water with an arsenic level of 0.12 mg/L was 10 years while among those using water with 0.06 mg/L arsenism began to appear after 6 months. More severe degrees of arsenism were associated with a shorter incubation period.

The degrees of severity of arsenism and fluorosis were compared in 56 adult patients with both arsenism and fluorosis who used water from the well produced by productive team 8 on farm A and found not to be significantly related (Table 3).

### Table 2. Well water content of arsenic and fluoride and health status

<table>
<thead>
<tr>
<th>Well</th>
<th>Year</th>
<th>Fluoride mg/L</th>
<th>Nc</th>
<th>Fluorosis (%) (dental)</th>
<th>Arsenic mg/L</th>
<th>Nd</th>
<th>Arsenism (%) (cutaneous)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5T, BF</td>
<td>1979</td>
<td>0.2</td>
<td>283</td>
<td>41 (14)</td>
<td>0.009</td>
<td>235</td>
<td>0 (0)</td>
</tr>
<tr>
<td>14T, AF</td>
<td>1972</td>
<td>9.4</td>
<td>243</td>
<td>231 (95)</td>
<td>0.020</td>
<td>585</td>
<td>0 (0)</td>
</tr>
<tr>
<td>17T, AF</td>
<td>1972</td>
<td>3.5</td>
<td>89</td>
<td>81 (91)</td>
<td>0.034</td>
<td>395</td>
<td>0 (0)</td>
</tr>
<tr>
<td>7T, AF</td>
<td>1973</td>
<td>3.4</td>
<td>97</td>
<td>89 (92)</td>
<td>0.120</td>
<td>419</td>
<td>6 (1)</td>
</tr>
<tr>
<td>5T, AF</td>
<td>1969</td>
<td>5.1</td>
<td>126</td>
<td>119 (94)</td>
<td>0.452</td>
<td>394</td>
<td>61 (15)</td>
</tr>
<tr>
<td>8T, AF</td>
<td>1972</td>
<td>3.5</td>
<td>224</td>
<td>212 (95)</td>
<td>0.578</td>
<td>652</td>
<td>191 (29)</td>
</tr>
<tr>
<td>8T, CF</td>
<td>1969</td>
<td>3.5</td>
<td>116</td>
<td>110 (95)</td>
<td>0.600</td>
<td>941</td>
<td>444 (47)</td>
</tr>
</tbody>
</table>

a Well identification: T = productive team, F = farm.
Example: 5T, BF = a well produced by productive team number 5 on farm B.
b The year in which the well was dug.
c Number of persons examined for the presence of dental fluorosis. Total = 1178.
d Number of persons examined for the presence of cutaneous manifestations of arsenism (arsenic dermatosis). Total = 3621.

### Table 3. Degrees of severity of osteofluorosis and arsenism in 56 adults

<table>
<thead>
<tr>
<th>Degree of severity of osteofluorosis</th>
<th>Degree of severity of arsenism (arsenic dermatosis)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>slight</td>
<td>moderate</td>
<td>severe</td>
</tr>
<tr>
<td>II</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>23</td>
</tr>
</tbody>
</table>

Chi-square = 2.75  Degrees of freedom = 2  p > 0.25  Not significant

The ECG was found to be abnormal in 48 out of 61 patients (79%) with the lesions affecting the myocardial muscle and conducting system. A peripheral microcirculatory disturbance involving Raynaud's syndrome was found in 43 out of 124 patients (35%) and confirmed by observation of the microcirculation. Peripheral neuropathy was found by EMG in 28 of 47 patients (60%) with others having subclinical peripheral neuropathy. Carcinoma was confirmed by biopsy in the skin of five patients and in the oesophagus of one.

A follow-up examination was made of 458 patients after they had drunk water of an improved quality of a period of one year. Full recovery was found
to have occurred in 59% of the patients, most of whom had not been seriously ill. A further 23% of the patients had improved giving a total improvement rate of 82%. No new cases of arsenism or fluorosis were found to have developed among the residents.

**DISCUSSION**

Arsenic and fluoride were seen to be able to exert toxic effects independently when present in well water at levels of 0.12 mg/L or more of arsenic and 0.2 mg/L or more of fluoride. Dental fluorosis was present in over 90% of those using water with a fluoride level of 3.5 mg/L or more. As the level of arsenic became higher, the incubation period for arsenism decreased from being 10 years with levels of 0.12 mg/L to being as short as 6 months with levels of 0.6 mg/L. Higher arsenic water levels were associated with higher prevalences of arsenism with a prevalence of 1.4% among those who had drunk water with a level of 0.12 mg/L of arsenic for 10 years but 47% in those who had used water with a level of 0.6 mg/L. More severe degrees of illness were present in those with shorter incubation periods.

Improvement occurred in 82% and the development of new cases was prevented when the quality of the water was improved.

Thus notable progress can be made in the prevention and treatment of disease when the causative factors, in this case high levels of arsenic and fluoride, can be eliminated.

**REFERENCES** (in Chinese)

SKELETAL CHANGES WITH TOXICITY FROM FLUORIDE AND ALUMINUM

X G Chen, S Zhou, J Jiao, Y H Ding and Z Q Zhao
Guiyang, Guizhou, China

SUMMARY: Radiographic examination of 39 patients with toxicity from both fluoride and aluminum showed typical features of metabolic skeletal transformation including osteoporosis in cortical bone and osteosclerosis in cancellous bone. The pro-cortical bones were transformed into soft cortical bones and the pro-cancellous bones were transformed into disordered net-like bones with a large amount of osteoid. These features may be useful in the classification of skeletal fluorosis.

Key words: Aluminum; Fluoride; Radiography; Skeleton; Toxicity.

INTRODUCTION

The radiographic skeletal changes associated with intoxication by both fluoride and aluminum are complicated with features of osteosclerosis, osteomalacia, and osteosclerosis with rickets.¹⁻³ Yang has described skeletal transformation in metabolic skeletal disease ⁴ but this effect has not previously been described in combined intoxication by fluoride and aluminum. These combined effects are reported in the present study.

MATERIALS AND METHODS

Thirty-nine patients, 16 male and 23 female, mean age 12.4 years, were studied from districts of Shui City in Guizhou Province in which chronic fluoride toxicity or fluorosis was endemic. The corn used as the major food source in these areas was commonly contaminated by soil and coal by a method of cooking involving baking with a mixture of mud and coal.⁵ Many of the subjects were symptomatic and had malformations of their limbs and joints.⁵ Serum and urine levels of fluoride, aluminum and calcium were elevated compared to normal controls (Table 1).

<table>
<thead>
<tr>
<th>TABLE 1. Serum and urine levels of fluoride, aluminum and calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Serum aluminum</td>
</tr>
<tr>
<td>Urinary aluminum</td>
</tr>
<tr>
<td>Urinary fluoride</td>
</tr>
<tr>
<td>Urinary calcium</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Values are mean in µg/L ± S.D. * Compared to normal controls p &lt; 0.5</td>
</tr>
</tbody>
</table>

Histological examination was made of bone obtained by biopsy from two patients. Radiographs were taken on all patients of the pelvis, left arm, legs and any malformations present.

Department of Radiology, Affiliated Hospital of Guiyang Medical College, Guizhou, 550001, People's Republic of China.

RESULTS
The changes seen at histology involved decreased ossification, a widening of the spaces between the trabeculae, osteoporosis, dilatation of Haversian canals in cortical bone, a rarity of osteoblasts, and increased osteoid.

Radiographic features of skeletal transformation were seen in the 39 patients with osteoporosis in cortical bone and osteosclerosis in cancellous bone. The osteoporosis of cortical bone was seen most frequently in curved parts of the tibia and fibula (Table 2, Figures 1 and 2).

<table>
<thead>
<tr>
<th>TABLE 2. Radiographic features of osteoporosis in cortical bone (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographic feature</td>
</tr>
<tr>
<td>Widening of cortex with decreased density</td>
</tr>
<tr>
<td>Irregular vertical lucent lines</td>
</tr>
<tr>
<td>Localized areas of ground-glass-like low density cortex</td>
</tr>
<tr>
<td>Subperiosteal bone reabsorption</td>
</tr>
</tbody>
</table>

The osteosclerosis in cancellous bone was seen in the pelvis, distal femur, and the proximal parts of the tibia and fibula (Table 3, Figure 3).

<table>
<thead>
<tr>
<th>TABLE 3. Radiographic features of osteosclerosis in cancellous bone (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographic feature</td>
</tr>
<tr>
<td>Coarse and sparse haziness of trabeculae</td>
</tr>
<tr>
<td>Patchy dense pieces of boneless structure</td>
</tr>
<tr>
<td>Disordered gross range of trabeculae*</td>
</tr>
<tr>
<td>Fusion of thin and thick trabeculae</td>
</tr>
<tr>
<td>Coarse and net-like haziness of trabeculae</td>
</tr>
</tbody>
</table>

* 3-4 times greater diameter, than normal trabeculae

DISCUSSION
The 39 patients who had toxicity from both fluoride and aluminum, as a result of eating corn contaminated with mud and coal, showed radiographic features of skeletal metabolic disease.\(^5\) Dai has shown in animal studies that fluoride and aluminum can produce both independent and interactive effects on bone.\(^6\) Fluoride affected the synthesis of osteo-cytoplasm and resulted in production of increased osteoid. Aluminum affected the mineralization of osteo-cytoplasm and inhibited the calcification of osteoid. Together fluoride and aluminum stimulated osteoclastic activity and the parathyroids resulting in bone reabsorption and skeletal transformation.

Wang described the concept of skeletal transformation in skeletal metabolic disease: bone reabsorption in trabeculae and cortex by osteoclasts is accompanied by ossification by osteoblasts.\(^4\) The result is the transformation of the pro-compact cortex into soft cortical bone with the production of osteoporosis of cortical bone. Similarly, the pro-cancellous bone is changed into a disordered net-like bone with a large amount of osteoid present forming osteosclerosis of cancellous bone.

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FIGURE 1 (left) Frontal radiographs of left and right lower legs showing malformed (curved) tibia and fibula

FIGURE 2 (right) Magnified frontal radiograph of tibia and fibula, showing widened ground-glass-like cortex and disordered ossification of trabeculae

FIGURE 3 Frontal radiograph of pelvis showing bilateral malformation of acetabula, irregular increased bone density, coarse, sparse and hazy trabeculae, patchy ossification and sclerotic zones under the epiphyses of the femoral necks
The radiographic features of the skeletal transformation in toxicity from both fluoride and aluminum have not been described previously. Two features occur. The first involves osteoporosis of cortical bone, and comprises: a) osteoporosis and laminated changes in the cortex, dilatation of Haversian canals; b) decreased density and a ground-glass-like cortex; and loss of the border between the cortex and the medullary space; a bone density similar to that of soft tissue; c) a widening of the cortex caused by the accumulation of a large amount of osteoid; d) haziness of the margin of the cortex resulting from some subperiosteal bone reabsorption. Secondly, osteosclerosis of cancellous bone occurs with: a) coarse and net-like haziness of trabeculae resulting from the accumulation of osteoid on the surface of the trabeculae; b) thin and thick fusion of trabeculae; increased bone density resulting from the occurrence of increased amounts of bone and osteoid; c) localized coarse compact bone resulting from disordered ossification; d) patchy dense areas resulting from accumulations in the medullary space, trabeculae and metaphyses.

Osteoporosis, osteomalacia, osteosclerosis and skeletal transformation may exist together and may not be easily differentiated. For example, in the radiographs of the pelvis of patients with toxicity from fluoride and aluminum, bone density was increased, trabeculae showed gross haziness, and the malformation of osteomalacia was also present. In the diaphysis of the long bones the radiographs showed a curving malformation and a ground-glass-like laminated cortex with decreased density and increased thickness. In the metaphysis the trabeculae of the cancellous bone showed osteoporosis and coarseness together with disordered and compact ossification.

Study of the radiographic features of skeletal transformation in toxicity from fluoride and aluminum may be helpful in interpreting radiographs showing the increased density of osteosclerosis, varieties of osteomalacia, and osteosclerotic osteomalacia. Because the appearances of skeletal transformation include osteoporosis of cortical bone, osteosclerosis of cancellous bone, and osteomalacic malformation, they could be regarded as being a “mixture type” of chronic fluoride toxicity or fluorosis. They may contribute to establishing a new classification of endemic chronic fluoride toxicity.

REFERENCES
RE-EXAMINATION OF ACUTE TOXICITY OF FLUORIDE

Kenji Akiniwa
Tokyo, Japan

SUMMARY: The acute toxic dose of fluoride has been believed to be 2 to 5 mg or 8 mg/kg of body weight. However, acute fluoride poisonings have occurred at doses of 0.1 to 0.8 mgF/kg of body weight in the USA.

In Japan, a school-based anticariogenic program is being carried out with fluoride mouth rinses containing 500 to 2000 ppm sodium fluoride on approximately 158,000 persons, consisting mainly of elementary and junior high school children. Thus the safety problem of this treatment attracts much attention. Fluoride retention is said to be around 15 to 30% in fluoride mouth rinsing. In this paper, on the basis of toxic doses estimated in outbreaks of fluoride poisoning, the potential for acute poisoning by fluoride ingested during mouth rinsing is assessed.

Acute fluoride poisoning is shown to be caused by exposure to lower doses of fluoride than commonly suggested. The toxic dose of fluoride should therefore be re-examined.

Key words: Acute toxicity; Dental fluorosis; Fluoride mouth rinsing; Sodium fluoride.

INTRODUCTION

Excessive intake of fluoride has been re-examined recently in the USA\(^1\) and Canada\(^2\). The World Health Organisation has warned of an unexpected increase in the incidence of dental fluorosis, a form of a chronic fluoride intoxication, and recommended procedures to prevent excess fluoride intake.\(^3\)

Promoters of fluoride mouth rinsing set the acute toxic dose of fluoride at 2 mg/kg body weight,\(^4\) the Ministry of Health and Welfare of Japan at 2 to 5 mg/kg,\(^5\) and some other investigators at 8 mg/kg. However, 0.1 to 0.8 mg/kg of fluoride has been estimated to have caused fluoride poisoning in the USA, resulting from troubles with fluoridated water systems and from ingestion of fluoride-containing products by mistake.\(^7\)-\(^15\)

In Japan, however, a school-based program of fluoride mouth rinsing (500-2000 ppm sodium fluoride) was selected as the second best alternative to fluoridation of the water system, involving almost 158,000 elementary and junior high school children,\(^16\) with a further recent increase involving children under 6 years of age in kindergarten and nursery schools.\(^17\)

The safety problem of this treatment has become increasingly important. Fluoride retention after fluoride mouth rinsing is considered to be 15% to 30% of the rinsing water\(^18\)-\(^21\) (that is, ingested fluoride = fluoride in the rinsing water − fluoride in the rinsing water spat out = fluoride swallowed + fluoride absorbed through the mucus membrane of the mouth). According to the toxic doses estimated in the cases of fluoride poisoning in the USA, this amount of fluoride retention is able to cause acute fluoride poisoning. However there appears to be no clear basis for estimating toxic doses of fluoride currently used.

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Editor of Fluoride Research, Journal of the Japanese Society for Fluoride Research. Address: 3-9-22 Asahi machi, Machida City, Tokyo, Japan 194.
A part of this paper was presented at the Seventh Meeting of the Chinese Society for Fluoride Research, Guiyang, in 1995.
ESTIMATES OF ACUTE TOXIC DOSE

Table 1 shows signs and symptoms of acute fluoride poisoning. Table 2 shows the minimum toxic dose (MTD), probably toxic dose (PTD), safely tolerated dose (STD) and certainly lethal dose (CLD) of fluoride. The toxic dose of

<table>
<thead>
<tr>
<th>TABLE 1. Symptoms of acute fluoride poisoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Salivation.</td>
</tr>
<tr>
<td>2. Nausea</td>
</tr>
<tr>
<td>3. Vomiting</td>
</tr>
<tr>
<td>4. Abdominal pain</td>
</tr>
<tr>
<td>5. Diarrhea</td>
</tr>
<tr>
<td>6. Cramps</td>
</tr>
<tr>
<td>7. Cardiac arrhythmia</td>
</tr>
<tr>
<td>8. Coma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 2. Acute toxic dose of fluoride (NaF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year and name</td>
</tr>
<tr>
<td>1975 USPHS22</td>
</tr>
<tr>
<td>1986 Heifitz &amp; Horowitz6</td>
</tr>
<tr>
<td>1987 Whitford5</td>
</tr>
<tr>
<td>MTD</td>
</tr>
<tr>
<td>NaF 4 mg/kg</td>
</tr>
<tr>
<td>F 1.8 mg/kg</td>
</tr>
<tr>
<td>MTD ≠ PTD</td>
</tr>
<tr>
<td>MTD: Minimum Toxic Dose</td>
</tr>
<tr>
<td>PTD: Probably Toxic Dose</td>
</tr>
<tr>
<td>STD: Safely Tolerated Dose</td>
</tr>
<tr>
<td>CLD: Certainly Lethal Dose</td>
</tr>
<tr>
<td>MLD: Minimum Lethal Dose</td>
</tr>
</tbody>
</table>

MTD: Minimum Toxic Dose - The lowest dosage which causes toxic signs
STD: Safely Tolerated Dose - One fourth of the LCD for fluoride is considered a
CLD: Certainly Lethal Dose
MLD: Minimum Lethal Dose

<table>
<thead>
<tr>
<th>TABLE 3. Summary of Baldwin's Data4</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaF</td>
</tr>
<tr>
<td>250 mg</td>
</tr>
<tr>
<td>90 mg</td>
</tr>
<tr>
<td>30 mg</td>
</tr>
</tbody>
</table>

Fluoride 30 (2) 1997
2 mgF/kg body weight is supposedly based on Baldwin's experiment conducted 100 years ago in which he himself ingested sodium fluoride and reported: 4

"Merely tasting small quantities produced a slight feeling of nausea with slight salivation. 0.03 gram swallowed with some bread produced no effect. Neither did 0.09 gram taken one hour later, except a little salivation. 0.25 gram, however, taken two days afterward on an empty stomach, produced nausea in two minutes. This gradually increased in severity for twenty minutes when the period of greatest intensity was reached. There was a largely increased flow of saliva and some retching but no vomiting occurred at that time although the desire was very great. The nausea gradually subsided so that luncheon could be eaten (without relish), but vomiting took place immediately on its completion which was two hours after taking the poison. Slight nausea continued throughout the following day but disappeared on the second day" [sic].

The amounts of fluoride he ingested were calculated and are shown in Table 3. He did not mention the toxic dose of 2 mg/kg in his report, as seen in the above. But the threshold toxic dose in this case is estimated to be 0.25 mgF/kg or less.

Whitford proposed a toxic dose of 5 mg/kg. 5,23 He considered this dose as the threshold for the "probably toxic dose" (PTD), which is defined as the minimum dose that could cause toxic signs and symptoms, including death, and that should trigger immediate therapeutic intervention and hospitalization. He estimated this dose on the basis of children's fluoride poisoning. He never suggested that doses under 5 mg/kg are safe but reported that the STD of fluoride at which signs and symptoms can be tolerated was unknown.

Horowitz et al. 6 considered the STD to be 8 mg/kg, being a quarter of the lethal dose, 32 mg/kg, as selected by Hodge and Smith, 1965, 24 which was originally based on the report by Black et al., 1949. 25 Whitford 5 commented on the Black et al report:

"Their patients, including some 3½- to 6-year-old children with leukemia, received an average daily dose of 3.4 mg/kg of sodium fluoride (1.5 mgF/kg) for the treatment of malignant neoplastic diseases. So that gastrointestinal distress would not preclude the administration of fluoride, it was given in combination with a 4% suspension of aluminum oxide. This would have markedly reduced the rate and the extent of fluoride adsorption. One 27-kg patient, for whom dosage data were provided, received sodium fluoride intravenously for nine days. The average daily dose was 10.4 mgF/kg; the maximum dose was 13.3 mgF/kg. It was stated that 'there were no signs of acute or chronic toxicity', although the patient expired two months later 'from the progression of the neoplasm'. Overall, the information in this report does not strongly support the conclusion that the STD for fluoride is 8 mgF/kg" [sic].

The above are the toxic doses that have been described, which are higher than the estimated minimum toxic dose.
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"Merely tasting small quantities produced a slight feeling of nausea with slight salivation. 0.03 gram swallowed with some bread produced no effect. Neither did 0.09 gram taken one hour later, except a little salivation. 0.25 gram, however, taken two days afterward on an empty stomach, produced nausea in two minutes. This gradually increased in severity for twenty minutes when the period of greatest intensity was reached. There was a largely increased flow of saliva and some retching but no vomiting occurred at that time although the desire was very great. The nausea gradually subsided so that luncheon could be eaten (without relish), but vomiting took place immediately on its completion which was two hours after taking the poison. Slight nausea continued throughout the following day but disappeared on the second day" [sic].

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The above are the toxic doses that have been described, which are higher than the estimated minimum toxic dose.
SIGN & SYMPTOMS OF ACUTE FLUORIDE POISONING AND THEIR ETIOLOGY

The signs and symptoms of acute fluoride poisoning are based principally on the report of fluoride poisoning in Alaska (in USA, 1992). The mechanism of the occurrence of the symptoms of fluoride poisoning are classified into four categories, A, B, C and D in Table 4.

The symptoms in category A are mostly gastric symptoms caused by hydrofluoric acid. A low toxic dose caused nausea and a higher dose caused vomiting. The gastric formation of hydrofluoric acid has been described. After being ingested into the stomach, 50% of sodium fluoride is converted into hydrofluoric acid (HF), which is absorbed through the mucous membrane of the stomach at the rate of 1,000,000 times higher than F-. Fluoride then circulates in the body and returns to the mouth through the salivary glands. This is why fluoride poisoning is caused by a low dose of sodium fluoride. More HF is formed in the stomach if the pH of the gastric juice is lower.

The effect of fluoride on the glycolytic pathway is given in category B. Fluoride mouth-rinsing results in the inhibition of glycometabolism (glucose-6-phosphate pathway), inhibiting acid production that induces decalcification. Fluoride has also an inhibitory effect on the ATP system.

Categories C and D are illustrated by the case of a 41-year-old man who died of hypocalcemia from an acute fluoride poisoning event in Alaska. Generally, symptoms are believed to persist 1 to 5.5 hours in fluoride poisoning. In this case, however, symptoms persisted for 24 hours with blood fluoride concentrations two to three times higher than normal as determined two weeks after the outbreak and with an abnormal serum chemistry profile persisting for 19 days.

### TABLE 4: Symptoms of acute fluoride poisoning and their etiology (based on report of the acute fluoride poisoning in Alaska, USA)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
</table>
| A | Gastric symptoms: HF (Hydrofluoric acid) NaF + HCl \( \rightarrow \) HF  
- Nausea, salivation  
- Vomit  
- Diarrhea  
- Abdominal pain |
| B | Direct effects of fluoride: Intracellular metabolism  
1. Glycotic enzyme (Glycolytic pathway)  
2. Cholinesterase (Esterase) \( \rightarrow \) Acetylcholine \( \rightarrow \) Choline  
   | Acetic acid |
| C | Inhibition of metabolism  
1. Hyperkalemia  
2. Hypocalcemia  
   | Production of calcium compounds such as \( \mathrm{Ca}_5(\mathrm{PO}_4)_3\mathrm{F} \) in the extracellular fluid  
   | Cardiac dysrhythmias  
   | Cardian arrhythmia \( \rightarrow \) Cardiac arrest  
3. Hypomagnesemia  
4. Hyper phosphatemia |
| D | Persistent abnormal serum fluoride levels (for 19 days)  
1. Mineral homeostasis  
2. Cellular damage  
3. Serum magnesium, serum phosphorus  
4. Lactate dehydrogenase |
TOXIC DOSES ESTIMATED IN OUTBREAKS OF ACUTE FLUORIDE POISONING

At least seven events of acute fluoride poisoning that are related to the fluoridation of drinking water have formally been reported in the USA, where the fluoride concentration in the water systems has been adjusted to prevent dental caries. Table 5 lists the date, place, number of persons involved and their age, water source, cause, the highest fluoride concentration, an estimated dose of fluoride (mg/kg), references and remarks concerning acute fluoride poisoning in the above events, which caused two deaths and 655 cases of fluoride intoxication.

<table>
<thead>
<tr>
<th>Date</th>
<th>Place &amp; Ref. no.</th>
<th>No. of persons and age</th>
<th>Source of water</th>
<th>Cause</th>
<th>Estimated maximum dose of $F^-$</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1974</td>
<td>North Carolina 7</td>
<td>201 6-12 yr; some adults</td>
<td>Water supply (well) fluoridated with NaF</td>
<td>Faulty pump</td>
<td>270 ppm 0.34–2.7 mg/kg</td>
<td>2nd poisoning after start of monitoring system in 1966 (first event not recorded)</td>
</tr>
<tr>
<td>1977</td>
<td>Michigan 8</td>
<td>12 reported cases</td>
<td>Water supply fluoridated with 25% $H_2SiF_6$</td>
<td>Faulty pump</td>
<td>2400 ppm 0.5 mg/kg</td>
<td>0.12 mg/kg induces nausea as reported by Thienes et al in 1972</td>
</tr>
<tr>
<td>1978</td>
<td>New Mexico 10</td>
<td>34 kindergarten and school children</td>
<td>Water supply (well) fluoridated with NaF</td>
<td>Faulty pump switch</td>
<td>375 ppm 0.05–3.0 mg/kg (child 15 kg)</td>
<td>Total amount of F was 1.4 to 90 mg when F concentration altered to 1.5 ppm</td>
</tr>
<tr>
<td>1979</td>
<td>Maryland 11</td>
<td>8 dialysis patients: 4 → hospital, 1 died; + 13 had toxic symptoms</td>
<td>Water supply fluoridated with 25% $H_2SiF_6$</td>
<td>Unreported failure to tighten fluoride tank bulb</td>
<td>50 ppm</td>
<td>It was recorded that an additional 5 events had occurred previously</td>
</tr>
<tr>
<td>1980</td>
<td>Vermont 12</td>
<td>22 9- to 70-yr</td>
<td>Grade school water system fluoridated 2% NaF</td>
<td>Faulty pump</td>
<td>1041 ppm 0.8 mg/kg* (adult 60 g) (7 persons)</td>
<td>This outbreak was formally recorded as the fifth event. Total fluoride amount 47 to 94 mg</td>
</tr>
<tr>
<td>1986</td>
<td>Connecticut 13</td>
<td>53 from 127 families (no record of age)</td>
<td>Water supply fluoridated with $H_2SiF_6$</td>
<td>Initiation of fluoridation</td>
<td>51 ppm 0.21–0.42 mg/kg (adult 60 g) (33 persons)</td>
<td>Fluoride poisoning and copper pipe melting accident occurred simultaneously</td>
</tr>
<tr>
<td>1992</td>
<td>Alaska 14</td>
<td>296 6 mth–73 yr 1 died</td>
<td>Water supply fluoridated with NaF</td>
<td>Faulty pump and other unknown causes</td>
<td>150 ppm 0.3 mg/kg</td>
<td>Final report of Dept. of Health was reviewed in Fluoride 27 (1) 1994</td>
</tr>
</tbody>
</table>
Among these occurrences, the estimated toxic dose was lowest in the 1978 event in New Mexico, which involved children in kindergarten and nursery school with the total amount of fluoride per child of 1.4 to 90 mg, which is calculated to be approximately 0.1 mgF/kg in subjects with a body weight of 15 kg. The estimated minimum toxic doses of fluoride involved 0.21, 0.3, 0.34, 0.5, and 0.8 mg/kg in the other events of acute fluoride poisoning in the list, which are much lower than those reported before. Pediatricians warned of possible poisoning from mouth rinsing with aqueous solutions containing 500 to 2000 ppm sodium fluoride.

Thienes et al in 1972\(^9\) reported that the dose of fluoride which induces nausea is 0.12 mg/kg (7.2 mg of fluorine/60 kg of body weight), which is close to the toxic doses estimated in the events of fluoride poisoning in the USA. In the 1977 Michigan event, the toxic dose was estimated on the basis of the report by Thienes et al. Hyperfluoridation is frequently caused by pump trouble in fluoride concentrate distribution.

Table 6 shows a 1991 report\(^{30}\) of the American Association of Poison Control Centers in the Rocky Mountains, Colorado, which included 87 children with fluoride poisoning from mistaken swallowing of fluoride-containing products during the year January 1 to December 31, 1986. Among the 87 cases, 85 were of mistaken ingestion of fluoride tablets, fluoride drops and fluoridated mouthrinsing water in children 8 months to 6 years of age, the most common age being 2 to 3 years. One child of 8 and another of 9 developed symptoms after receiving a dental fluoride application and a fluoride mouth rinsing at a dental clinic. A 13-month-old child died from ingestion of a fluoride-containing pesticide.

<table>
<thead>
<tr>
<th>Elemental fluoride (F) mg/kg</th>
<th>No of patients with symptoms</th>
<th>Total no. of persons who ingested F</th>
<th>Percent with symptoms</th>
<th>The acute toxic doses of fluoride (mg/kg) which are supported by</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>3</td>
<td>36</td>
<td>8</td>
<td>2: The promoters of fluoride mouth rinsing (20%)</td>
</tr>
<tr>
<td>1-2</td>
<td>1</td>
<td>6</td>
<td>17</td>
<td>2 to 5: The Ministry of Health and Welfare of Japan (50%)</td>
</tr>
<tr>
<td>2-3</td>
<td>4</td>
<td>15</td>
<td>27</td>
<td>8: Considered the dose of F at which no severe symptoms occur despite 100% incidence of symptoms</td>
</tr>
<tr>
<td>3-4</td>
<td>5</td>
<td>10</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>4-8.4</td>
<td>3</td>
<td>3</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>70*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The amount of elemental fluoride was calculated using the ratio of 1 mg of fluoride ion per 2.2 mg of sodium fluoride.

* The amount of fluoride ingested is known in 70 of 87 cases that included no deaths. The 24 hour consecutive monitoring was not available in 31 of the 54 asymptomatic patients, and monitoring was not available for 1 to 6 hours in 23 asymptomatic patients. Three persons who took emetic were excluded from the analysis.
Symptoms of acute fluoride poisoning were identified in 26 of the 87 cases. In Table 6, the dose of fluoride (mg/kg) ingested was investigated in 70 of the 87 cases and in 16 of the 26 cases of intoxication. Ingestion of over 8 mg/kg of fluoride always caused symptoms. A dose of 8 mg/kg, a quarter of the lethal dose, is usually considered to be the safely tolerated dose (STD). A dose of 2 to 4 mg/kg caused symptoms in 50% of the subjects. This dose level is similar to the acute toxic dose (2 to 5 mg/kg) proposed by the Ministry of Health and Welfare in Japan. A dose of 1 mg/kg or less caused fluoride poisoning in 8% of the subjects.

In the same year (1986), 3511 cases were reported in the USA of mistaken ingestion of fluoride products, except fluoride-containing vitamins, of which 91% occurred in children under 6 years old.\textsuperscript{23} Table 7 shows the statistics of the events of mistaken fluoride ingestion that occurred during the six years from 1984 to 1989.\textsuperscript{23,31} During those years, at least 34,853 events of fluoride poisoning were identified and 2898 patients visited clinics. However, the report did not mention estimated toxic doses in these cases.

| TABLE 7. Cases of mistaken fluoride ingestion 1984-1989 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| A               | 20,132          | 1842            | 10,336          | 3579            | 90              |
|                 |                 |                 |                 |                 | 7               |
|                 |                 |                 |                 |                 | 1               |
| B               | 919             | 130             | 538             | 100             | 3               |
|                 |                 |                 |                 |                 | 1               |
|                 |                 |                 |                 |                 | 0               |
| C               | 13,802          | 926             | 8070            | 782             | 28              |
|                 |                 |                 |                 |                 | 4               |
|                 |                 |                 |                 |                 | 0               |
| Total           | 34,853          | 2898            | 18,944          | 4461            | 121             |
|                 |                 |                 |                 |                 | 12              |
|                 |                 |                 |                 |                 | 1*              |

Categories: A, excluding vitamins; B, adult vitamins; C, paediatric vitamins. The “Medical Outcome/Moderate” classification was not listed in the 1984 data.\textsuperscript{*} There was one death in each year in 1986 and 1989 (in Colorado).

RISK OF ACUTE FLUORIDE POISONING FROM FLUORIDE MOUTH RINSING

Tables 8, 9 and 10 show the relationship between the toxic doses estimated in cases of acute fluoride poisoning in the USA and the dose of fluoride ingested at the time of fluoride mouth rinsing in subjects with body weights of 15 kg (younger children), 30 kg (children), and 60 kg (adults).

The dose of fluoride (mg/kg) is plotted on the ordinate against the frequency of fluoride mouth rinsing per week on the abscissa. Fluoride mouth rinsing for the purpose of prevention of dental caries gradually became common in the USA only after 1974. After that, in Japan, fluoride mouth rinsing has been used especially in Niigata prefecture. For practical fluoride mouth rinsing, a person should hold a portion of about 10 mL of the sodium fluoride solution in the mouth, swish it vigorously for 30 seconds to 1 minute and spit it out. WHO suggested that this treatment is contraindicated in preschool children.\textsuperscript{3} A half size amount, 5 mL, (or 7 mL) is used in children at kindergarten. Birkland and other investigators\textsuperscript{18-21} report that fluoride retention is 15 to 30% in fluoride mouth rinsing. The highest retention rate was reported to be 38.5% in Japan.\textsuperscript{32}
In Tables 8, 9 and 10 the open circles at the top of the bar denote the dose of fluoride if the ingestion is 30%, the open circles at the bottom of the bar denote 15% ingestion, and the open circles on the right side denote the dose if the entire volume of the rinsing solution is ingested. In younger children of body weight 15 kg, the amount of fluoride is 0.34 to 0.68 mg if a 500 ppm sodium fluoride solution is used, 0.68 to 1.35 mg if a 1000 ppm sodium fluoride solution is used, and 1.35 to 2.7 mg if a 2000 ppm sodium fluoride solution is used. These amounts of fluoride are reduced to half if 5 ml of rinsing solution is used.

**TABLE 8. Fluoride mouth rinsing and the acute toxic dose estimated in younger children of body weight 15 kg**

The figures become half of those below if 5 mL is used (and 7/10 if 7 mL is used)

<table>
<thead>
<tr>
<th>Frequency/week</th>
<th>NaFppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>500</td>
</tr>
<tr>
<td>2</td>
<td>1000</td>
</tr>
<tr>
<td>1</td>
<td>2000</td>
</tr>
<tr>
<td>5</td>
<td>500</td>
</tr>
<tr>
<td>2</td>
<td>1000</td>
</tr>
<tr>
<td>1</td>
<td>2000</td>
</tr>
</tbody>
</table>
water is used. These amounts are calculated to be 0.02 to 0.05 mg/kg, 0.05 to
0.09 mg/kg, and 0.09 to 0.18 mg/kg, respectively, in 15 kg children, 30 kg
children, and 60 kg adults, which can cause fluoride poisoning on the basis of
the toxic doses of fluoride estimated in the above events of fluoride poisoning
(shown by four lines). Table 9 shows the doses of fluoride in children of body
weight 30 kg, and the amount of fluoride per kilogram of body weight is then
half those in 15 kg children. Table 10 shows the toxic doses in adults of 60 kg,
and the amount of fluoride per kilogram of body weight is a quarter of that in
children of 15 kg and half of that in children of 30 kg.

TABLE 9. Fluoride mouth rinsing and the acute toxic dose
estimated in older children of body weight 30 kg

<table>
<thead>
<tr>
<th>Frequency /week</th>
<th>NaF ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>500</td>
</tr>
<tr>
<td>2</td>
<td>1000</td>
</tr>
<tr>
<td>1</td>
<td>2000</td>
</tr>
<tr>
<td>5</td>
<td>500</td>
</tr>
<tr>
<td>2</td>
<td>1000</td>
</tr>
<tr>
<td>1</td>
<td>2000</td>
</tr>
</tbody>
</table>
Table 11 summarizes the data in Tables 8, 9, and 10 for the same amount of fluoride in each solution of different fluoride concentrations. Serum fluoride levels were determined and are shown in the bottom of the Table. If a 225-ppm fluoride solution is used and if the entire amount is swallowed by children weighing 15 kg, the amount of fluoride ingested is 2.25 mg, which corresponds to 9 mg in adults of 60 kg. Serum fluoride levels are proportional to the amount of fluoride ingested (normal serum fluoride levels are 0.01 to 0.02 ppm).

**TABLE 10. Fluoride mouth rinsing and the acute toxic dose estimated in adults of body weight 60 kg**

<table>
<thead>
<tr>
<th>F (mg/kg)</th>
<th>Fluoride poisoning in 1992</th>
<th>Fluoride poisoning in 1986</th>
<th>THIENES C.H. 1972</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency/week</th>
<th>NaF ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>500</td>
</tr>
<tr>
<td>2</td>
<td>1000</td>
</tr>
<tr>
<td>1</td>
<td>2000</td>
</tr>
<tr>
<td>5</td>
<td>500</td>
</tr>
<tr>
<td>2</td>
<td>1000</td>
</tr>
<tr>
<td>1</td>
<td>2000</td>
</tr>
<tr>
<td>Serum Fluoride Levels (ppm)</td>
<td>Normal (0.01-0.4)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>0.28-0.55</td>
<td>0.14-0.28</td>
</tr>
<tr>
<td>0.46</td>
<td>0.07-0.14</td>
</tr>
<tr>
<td>1.84</td>
<td>1.15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Body Weight of 15 kg</th>
<th>Fluoride Ingested (mg/kg body weight)</th>
<th>Total Amount of Fluoride ppm</th>
<th>ppm</th>
<th>Net ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/10 of those if 17 ml is used</td>
<td>100</td>
<td>15-30</td>
<td>450</td>
<td>225</td>
</tr>
<tr>
<td>In the table if 5 ml is used and the figures become half of those</td>
<td>600</td>
<td>15-30</td>
<td>450</td>
<td>225</td>
</tr>
<tr>
<td>The figures become half of those</td>
<td>1000</td>
<td>15-30</td>
<td>600</td>
<td>300</td>
</tr>
<tr>
<td>10 ml was used at each time</td>
<td>5000</td>
<td>15-30</td>
<td>2000</td>
<td>1000</td>
</tr>
</tbody>
</table>

Re-examination of acute toxicity of fluoride

TABLE 11: Fluoride mouth rinsing and the acute toxic dose
Figure 1 shows time-course changes in serum fluoride levels when ingested at three different doses of fluoride (data from Tsunoda\textsuperscript{33}). The peak of each plot is the highest serum fluoride level and is shown graphically by an equation, $y = x$, in Figure 2.\textsuperscript{34}

**A SITUATION THAT MAY FAVOUR FLUORIDE POISONING**

Figure 3 shows mean levels of calcium intake in various countries.\textsuperscript{35} Calcium intake is lower in Japan, and even lower in China and India, than in Europe and the USA. With a low calcium intake, the harmful effect of fluoride is augmented and thus ingestion of fluoride easily causes symptoms of acute and chronic fluoride toxicity. Therefore, the nutritional status of people should be considered in fluoride poisoning.

**DISCUSSION**

Fluoride poisoning has occurred in the USA because of pump trouble, and from fluoride mistaken ingestion by mistaken use of fluoride. However, fluoride poisoning has also occurred from recommended use of fluoride. This fact suggests that the toxic dose is lower than widely believed. The 1991 Ad Hoc Committee,\textsuperscript{36} another 1991 USA workshop,\textsuperscript{1} a 1992 workshop in Canada,\textsuperscript{2} WHO in 1994,\textsuperscript{3} and the American Society of Pediatrics,\textsuperscript{37} all promoters of fluoride use, have begun to re-examine the daily dose of fluoride because of the increased incidence of dental fluorosis.\textsuperscript{38-40} This increase may be attributable to increased

**FIGURE 1. Changes in serum fluoride levels after oral ingestion of sodium fluoride (Tsunoda 1983\textsuperscript{33})**
FIGURE 2. Peak concentration of fluoride in blood after fluoride ingestion (body wt 60 kg) (Takahashi 1993, Tsunoda).

Blood levels of fluoride (ppmF)

FIGURE 3. Daily calcium intakes and requirements in various countries.
daily fluoride intake from fluoride-containing toothpaste, fluoride mouth rinsing, fluoride tablets and drops, from beverages, especially juices and juice-flavored drinks, \(^{41}\) and from fluoridation of water supply systems.

WHO, in its report, \(^{3}\) recommended that fluoride mouth rinsing should be restricted to persons at moderate to high risk of dental caries. Therefore, subjects for fluoride mouth rinsing should be pre-selected. Medical treatment such as fluoride mouth rinsing should not be performed extensively and indiscriminately for public health at schools. Children under 6 years of age are prohibited from fluoride mouth rinsing. A recent increase in daily fluoride intake and an associated elevation of serum fluoride may predispose to acute fluoride poisoning. Moreover, there is a common situation in the assessment of toxic fluoride doses and in the evaluation of dental fluorosis, a chronic fluoride intoxication. Mild cases of dental fluorosis are usually neglected, and only moderate and severe dental fluorosis are taken into consideration. In acute fluoride poisoning, diarrhea and abdominal pain are regarded as minor transient side effects, and only severe symptoms and critical conditions in which patients need hospitalization are counted among toxic symptoms of fluoride. Kasahara et al estimated the minimum toxic dose of fluoride at about 0.2 mgF/kg. \(^{42}\) They reported that 60 persons took 10 mg amounts of fluoride and more than 90% of them had symptoms. Asou selected 0.1 mgF/kg as the minimum toxic dose. \(^{43}\)

Fluoride mouth rinsing is considered a drug treatment that should be strictly controlled. Evaluation of chronic fluoride intoxication should be reviewed, and a new assessment of the toxic dose of fluoride based on scientific data is urgently needed.

**Acknowledgment:** I am grateful to Dr Shinobu Akiniwa at Kouseikai Hospital, Tokyo, for providing valuable data.

**REFERENCES**


COMBINED TOXICITY OF FLUORIDE AND BENZENE HEXACHLORIDE TO RATS

N Ramesh, E Murali Mohan, C A Y Banu Priya, V Amalan Stanley, K S Pillai and P Balakrishna Murthy,
Tamil Nadu, India.

SUMMARY: Sprague-Dawley rats were given various treatments of 10 ppm fluoride, 25 ppm fluoride, 25 ppm benzene hexachloride (BHC), 10 ppm fluoride + 25 ppm BHC, or 25 ppm fluoride + 25 ppm BHC for 16 weeks ad libitum. Rats showed a decrease in body weight gain, which could be attributable to BHC alone. A synergistic effect of fluoride and BHC was seen only in females given 25 ppm fluoride + 25 ppm BHC: a decrease in red blood cells (RBC) and relative weight of the ovary. Females were more susceptible to the toxicity of fluoride and BHC than males.

Key words: Benzene hexachloride (BHC), Fluorosis; Rat; Synergism.

INTRODUCTION

Several independent studies on the toxicity of fluoride (F)\textsuperscript{1-2} and benzene hexachloride (BHC)\textsuperscript{3} have been carried out in different parts of the world. However, not many attempts have been made to understand the combined toxicity of BHC and F in laboratory animals. Fluorosis, a crippling disease due to the intake of excessive fluoride in drinking water, is found in several parts of the world.\textsuperscript{4} BHC is still used extensively in third world countries, particularly in India,\textsuperscript{5} where endemic fluorosis is a major health problem.\textsuperscript{6} Studies carried out in India have shown that residues of BHC exist in adipose tissue, breast milk,\textsuperscript{7} bovine milk\textsuperscript{8} and vegetables\textsuperscript{9}.

The present study aims at understanding the combined toxicity of F and BHC to rats when given for sixteen weeks in drinking water.

MATERIALS AND METHODS

Male and female Sprague-Dawley rats (80-100 g) procured from National Animal House, Central Drug Research Institute, Lucknow, India, were acclimatized to the laboratory conditions (temp. 22 ± 2°C, relative humidity 50-70%; 12 h light and 12 h dark rhythm), and divided into six groups housed in polypropylene cages, sex wise (6 rats/cage) with autoclaved paddy husk as the bedding material. Group 1, the control, received normal feed and water ad libitum. Group 2 received 10 ppm F, Group 3 25 ppm F, Group 4 25 ppm BHC, Group 5 10 ppm F and 25 ppm BHC, and Group 6 25 ppm F and 25 ppm BHC. Both F (Ranbaxy Chem, India) and BHC (BHC 50% WP, Vaigai Chem, India) were given in drinking water. Both drinking water and feed (Lipton, India) were given ad libitum. Weekly body weight gain and feed consumption were recorded. At the end of week 16, blood was drawn for haematology from the orbital sinus of anaesthetised animals. Then the animals were sacrificed under overdose of anaesthetic ether, and the organs isolated for weight determination. Haematological parameters were analysed on an Erma Particle Counter (Erma PC 605, Japan). The data were subjected to Barlett’s test, ANOVA and Student’s t test.\textsuperscript{10}
RESULTS AND DISCUSSION

Both F and BHC are known to cause mortalities in laboratory animals in long term experiments. It has been stated that mortalities occurred in rats exposed to increased concentrations of fluoride. Dikshith et al. reported mortality in guinea pigs treated with 500 mg/kg body weight BHC dermally for 30 days. In the present study, five mortalities were observed: in Group 3 (25 ppm F) one male died in week 13; in Group 4 (25 ppm BHC) one female died in week 12; in Group 6 (25 ppm F + 25 ppm BHC) 2 females died, in weeks 7 and 15, and one male died in week 15.

Body weight gain of groups of rats was correlated with the exposure time (weeks) by linear regression equations. From the slopes of the equations, it may be stated that body weight gain of male rats of Groups 2 (10 ppm F) and 3 (25 ppm F) was marginally higher than that of the control rats (Group 1). Male rats belonging to Groups 4 (25 ppm BHC), 5 (10 ppm F + 25 ppm BHC) and 6 (25 ppm F + 25 ppm BHC) had less body weight gain. The latter two groups had the least body weight gain compared to the other two groups (Table 1a). Body weight gain in females of Group 2 (10 ppm F) increased, whereas in other groups it decreased, being least in Groups 4 (25 ppm BHC) and 5 (10 ppm F + 25 ppm BHC), followed by Group 6 (25 ppm F + 25 ppm BHC) (Table 1b). Studies

\[ Y = a + bX, \text{ where } Y = \text{Body weight gain}; \ X = \text{week (1-16)}; \ a = \text{intercept}; \ b = \text{slope} \]

<table>
<thead>
<tr>
<th>Group</th>
<th>Equation</th>
<th>( r^2 )</th>
<th>Standard error of Y estimates</th>
<th>Standard error of coefficient(b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>( Y = 17.05 + 5.29X )</td>
<td>0.92</td>
<td>7.16</td>
<td>0.43</td>
</tr>
<tr>
<td>10 ppm fluoride</td>
<td>( Y = 18.02 + 5.97X )</td>
<td>0.92</td>
<td>7.92</td>
<td>0.47</td>
</tr>
<tr>
<td>25 ppm fluoride</td>
<td>( Y = 18.09 + 5.86X )</td>
<td>0.93</td>
<td>7.24</td>
<td>0.43</td>
</tr>
<tr>
<td>25 ppm BHC</td>
<td>( Y = 18.18 + 5.21X )</td>
<td>0.96</td>
<td>5.05</td>
<td>0.30</td>
</tr>
<tr>
<td>10 ppm fluoride + 25 ppm BHC</td>
<td>( Y = 17.55 + 4.99X )</td>
<td>0.93</td>
<td>6.57</td>
<td>0.39</td>
</tr>
<tr>
<td>25 ppm fluoride + 25 ppm BHC</td>
<td>( Y = 19.05 + 5.07X )</td>
<td>0.93</td>
<td>6.23</td>
<td>0.37</td>
</tr>
</tbody>
</table>

\[ Y = a + bX, \text{ where } Y = \text{Body weight gain}; \ X = \text{week (1-16)}; \ a = \text{intercept}; \ b = \text{slope} \]

<table>
<thead>
<tr>
<th>Group</th>
<th>Equation</th>
<th>( r^2 )</th>
<th>Standard error of Y estimates</th>
<th>Standard error of coefficient(b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>( Y = 8.52 + 2.53X )</td>
<td>0.96</td>
<td>2.30</td>
<td>0.14</td>
</tr>
<tr>
<td>10 ppm fluoride</td>
<td>( Y = 8.04 + 2.67X )</td>
<td>0.95</td>
<td>2.81</td>
<td>0.17</td>
</tr>
<tr>
<td>25 ppm fluoride</td>
<td>( Y = 8.55 + 2.46X )</td>
<td>0.95</td>
<td>2.65</td>
<td>0.16</td>
</tr>
<tr>
<td>25 ppm BHC</td>
<td>( Y = 6.58 + 1.74X )</td>
<td>0.86</td>
<td>2.92</td>
<td>0.17</td>
</tr>
<tr>
<td>10 ppm fluoride + 25 ppm BHC</td>
<td>( Y = 5.84 + 1.76X )</td>
<td>0.94</td>
<td>2.09</td>
<td>0.13</td>
</tr>
<tr>
<td>25 ppm fluoride + 25 ppm BHC</td>
<td>( Y = 11.86 + 2.10X )</td>
<td>0.94</td>
<td>2.54</td>
<td>0.15</td>
</tr>
</tbody>
</table>

\[ Y = a + bX, \text{ where } Y = \text{Body weight gain}; \ X = \text{week (1-16)}; \ a = \text{intercept}; \ b = \text{slope} \]
have shown that fluoride decreased body weight gain in laboratory animals.\textsuperscript{13} Decrease in body weight observed in rats treated with BHC in the present study is in contrast with that of the mice receiving BHC by oral or dermal route for 80 weeks.\textsuperscript{14}

Males of Group 6 (25 ppm F + 25 ppm BHC) showed a decrease in weight of brain (Table 2a) whereas females of Group 4 (25 ppm BHC) showed an increase (Table 2b). Abalis et al.\textsuperscript{15} showed that BHC has an important effect particularly on the central nervous system. Lu et al.\textsuperscript{16} have stated that fluoride adversely affects various central nervous system agents in rats. Males and females of Group 3 (25 ppm F) and females of Groups 2 (10 ppm F) and 5 (10 ppm F + 25 ppm BHC) showed a decrease in the heart weight. Caruso et al.\textsuperscript{17} showed various cardiovascular defects, including hypertrophy of the ventricles and vasodilation, upon fluoride ingestion. Females of Group 4 (25 ppm BHC) showed an increase in the weight of the kidney. Philip et al.\textsuperscript{18} showed histopathological changes in kidney of Mus booduga following BHC treatment. Females of Group 6 (25 ppm F + 25 ppm BHC) showed a significant decrease in the weight of the ovaries. Even though fluoride and BHC per se failed to produce any change, the combination of both affected the weight of the ovaries.

### TABLE 2a. Relative organ weight (%) of male rats given fluoride or BHC or combination of fluoride and BHC

<table>
<thead>
<tr>
<th>Groups</th>
<th>Brain</th>
<th>Heart</th>
<th>Kidney</th>
<th>Ovaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.55 ± 0.05</td>
<td>0.32 ± 0.014</td>
<td>0.31 ± 0.03</td>
<td>0.45 ± 0.03</td>
</tr>
<tr>
<td>10 ppm F</td>
<td>0.52 ± 0.03</td>
<td>0.33 ± 0.003</td>
<td>0.35 ± 0.006</td>
<td>0.51* ± 0.02</td>
</tr>
<tr>
<td>25 ppm F</td>
<td>0.50 ± 0.06</td>
<td>0.28* ± 0.03</td>
<td>0.33 ± 0.05</td>
<td>0.50 ± 0.05</td>
</tr>
<tr>
<td>25 ppm BHC</td>
<td>0.53 ± 0.05</td>
<td>0.31 ± 0.006</td>
<td>0.32 ± 0.03</td>
<td>0.47 ± 0.07</td>
</tr>
<tr>
<td>10 ppm F + 25 ppm BHC</td>
<td>0.49 ± 0.03</td>
<td>0.30 ± 0.039</td>
<td>0.33 ± 0.04</td>
<td>0.43 ± 0.06</td>
</tr>
<tr>
<td>25 ppm F + 25 ppm BHC</td>
<td>0.48* ± 0.08</td>
<td>0.33 ± 0.037</td>
<td>0.36 ± 0.03</td>
<td>0.46 ± 0.04</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± Standard Deviation (n = 6) * Significant (P < 0.05)

### TABLE 2b. Relative organ weight (%) of female rats given fluoride or BHC or combination of fluoride and BHC

<table>
<thead>
<tr>
<th>Groups</th>
<th>Brain</th>
<th>Heart</th>
<th>Kidney</th>
<th>Ovaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.74 ± 0.11</td>
<td>0.39 ± 0.05</td>
<td>0.33 ± 0.02</td>
<td>0.05 ± 0.03</td>
</tr>
<tr>
<td>10 ppm F</td>
<td>0.69 ± 0.11</td>
<td>0.30* ± 0.01</td>
<td>0.30 ± 0.05</td>
<td>0.05 ± 0.006</td>
</tr>
<tr>
<td>25 ppm F</td>
<td>0.67 ± 0.11</td>
<td>0.30* ± 0.01</td>
<td>0.30 ± 0.05</td>
<td>0.05 ± 0.02</td>
</tr>
<tr>
<td>25 ppm BHC</td>
<td>0.87* ± 0.12</td>
<td>0.40 ± 0.05</td>
<td>0.37* ± 0.01</td>
<td>0.03 ± 0.02</td>
</tr>
<tr>
<td>10 ppm F + 25 ppm BHC</td>
<td>0.75 ± 0.04</td>
<td>0.34* ± 0.03</td>
<td>0.34 ± 0.05</td>
<td>0.03 ± 0.015</td>
</tr>
<tr>
<td>25 ppm F + 25 ppm BHC</td>
<td>0.75 ± 0.06</td>
<td>0.38 ± 0.06</td>
<td>0.35 ± 0.01</td>
<td>0.03* ± 0.009</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± Standard Deviation (n = 6) * Significant (P < 0.05)
None of the haematological parameters (WBC, RBC, HGB, HCT, MCV, MCH and MCHC) of males evaluated in the study showed a change due to the treatment of F, BHC or combinations of F and BHC.

Decrease in white blood cells (WBC) was evident in females of all the groups, except Group 5 (10 ppm F + 25 ppm BHC). It is apparent that a marginal decrease in WBC occurred in this group also. A decrease in WBC was reported in rabbits given 20 mg/kg body weight of F orally for 30 days.19 No significant change in WBC was observed in a study conducted in rats to evaluate the toxicity of BHC.20 Therefore it may be assumed that fluoride was solely responsible for decreasing WBC in female rats.

A decrease in RBC was observed in females of Group 6. Pillai et al21 observed a decrease in RBC in mice given a single dose of 17.3 mg F/kg body weight. Rats given 150 ppm F in drinking water for 75 days showed a decrease in red cell count.22 Similarly a decrease in erythrocyte count was observed in rats treated with BHC.20 As no change in RBC occurred in other groups, it may be assumed that a synergistic effect of fluoride and BHC on RBC took place at the higher dose level (25 ppm).

From the marked decrease in slopes of regression equations established between body weight gain and exposure weeks, it is presumed that the females are more vulnerable to the toxicity of fluoride and BHC than males. Females showed changes in relative weight of a greater number of organs than males. BHC was responsible for decreasing the body weight of rats. Other than decrease in RBC and relative weight of the ovary of females of Group 6 (25 ppm F + 25 ppm BHC), the present findings do not confirm a synergistic interaction between F and BHC.

Acknowledgment: The authors are grateful to the management of the Fredrick Institute of Plant Protection and Toxicology for the facilities provided to carry out the work. The authors also thank Mr A. Selvam for maintaining the animals during the course of the study.

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THE METABOLISM AND TOXICITY OF FLUORIDE
by Gary M Whitford
(2nd, revised edition, Karger, Basel 1996)
Reviewed by Bruce Spittle\textsuperscript{a} and John Colquhoun\textsuperscript{b}

This second edition covers fluoride metabolism thoroughly, in 104 pages, but appears to be uncritical in accepting the beneficial effects attributed to fluoride, and to be unbalanced in its coverage of chronic toxicity to which five pages are given. Other sections refer to dental caries and fluoride in the oral environment (five pages), and acute fluoride toxicity (25 pages).

The section dealing with fluoride absorption from the gastrointestinal tract has been revised to include the absorption of monofluorophosphate, and the effect of dietary calcium and endogenous fluoride concentrations, which can reduce fluoride absorption. Information is given on the effect of plasma fluoride levels on renal clearance of fluoride in infants. The fluorosis-like effects on enamel of acidosis and hypobaric hypoxia are considered. The dynamic relationship between fluoride in blood and bone is reviewed and the minimal effect of caffeine on the pharmacokinetics of fluoride noted. The effects of fluoride on the gastric mucosa are commented on.

It is stated that the remarkable decline in dental caries that has occurred throughout much of the world can be largely attributed to the use of the ingested and topical forms of fluoride. Fluoride is seen as being widely regarded as the cornerstone of modern preventive dentistry. The early fluoridation studies are accepted quite uncritically and the works of authors like Sutton\textsuperscript{1} and Diesendorf\textsuperscript{2} who critically re-examined those studies are ignored and omitted. Similarly, no mention is made of the recent comprehensive studies reporting little or no fluoride benefit in reducing dental caries.\textsuperscript{3-12}

In considering chronic fluoride toxicity, it is noted that, following the "equivocal evidence" for a link between high fluoride exposure and osteosarcoma in male rats, three recent reviews of the literature have been published.\textsuperscript{13-15} A summary is given of the conclusions of the US Public Health Service report\textsuperscript{14} and further discussion given of fluoride and bone fractures. It is concluded, in line with these reviews, that fluoride has little or no effect on bone strength, and that if there is an effect, either beneficial or detrimental, it is rather subtle. No reference is made to other reports and reviews which arrived at a quite different conclusion.\textsuperscript{16,17} Nor is there any reference to the work of Alhava\textsuperscript{18} and Arnala\textsuperscript{19} on fluoride accumulation in bone. The question of fluoride leading to osteosarcoma is dealt with by the statement that there is no detectable risk of cancer in humans associated with the consumption of optimally fluoridated water. The report by Cohn\textsuperscript{20} is not referred to, nor are the critiques by Lee\textsuperscript{21} and Yiamouyiannis\textsuperscript{22}.

No discussion is given of the evidence for, or even the possibility of, central nervous system effects from fluoride. It is suggested that the unusually high

\textsuperscript{a} Dunedin School of Medicine, University of Otago Medical School, PO Box 913, Dunedin, New Zealand.
\textsuperscript{b} Education Department, University of Auckland, Auckland, New Zealand.
brain concentrations reported by Phyllis Mullenix\textsuperscript{23} in weanling rats were likely to be the result of an analytical error.

Similarly, no reference is made to allergy or hypersensitivity, except to note that various “claims” were reviewed by Taves, 1979,\textsuperscript{24} who concluded that “the data used to support the claims that fluoridation causes adverse effects in humans are not convincing”.

Thus the book provides extensive information on the metabolism of fluoride and has gained a place in the training of dentists and public health specialists. However, because of the author’s uncritical acceptance of evidence for the efficacy of fluoride in reducing dental caries, and for its safety when consumed on a long-term basis, we are unable to assess this book as being truly scientific in its approach.

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FLUORIDATED WATER AND DOWN'S SYNDROME

Albert W Burgstahler
Lawrence, Kansas, USA

Reports appearing between 1956 and 1963 indicated a positive association between the congenital malformation known as Down's syndrome (DS, trisomy 21 or mongolism) and the fluoride content of drinking water in north central regions of the United States. Although widely disputed or ignored, these findings are supported by results of later investigations that, after further analysis, also confirm the additional important observation of higher rates of DS births among younger mothers living in fluoridated areas.

Here, in this paper, related findings on the occurrence of DS in Lower Michigan during the period 1951-1964 are presented. The data, based on over 2,000 recorded cases, indicate a 10 to 30 percent higher rate of DS births by maternal residence in urban areas with, or after, fluoridation of the municipal water supply. Overall, with all cities of 2,500 or more residents included (1950 census), the rate was 1.06 DS births per 1,000 live births in fluoridated communities compared to 0.94 in non-fluoridated communities (0.88 if the very large city of Detroit is excluded). For all cities of 25,000 to 200,000 population, the rates were 1.04 vs. 0.73. These differences, by the Chi-square test, have \( P < 0.065, 0.008, \) and \( 0.001, \) respectively. Besides this agreement with results of previous investigations by others, the present work also revealed a higher frequency of DS births among younger mothers in the fluoridated communities.

Key words: Down's Syndrome; Fluoridation.
Address: Department of Chemistry, The University of Kansas, Lawrence, Kansas 66045-0046, USA.

EXPERIMENTAL OSTEOFLUOROSIS AND ARTHROFLUOROSIS IN RATS

M Bély, G Ferencz, K Itai* and H Tsunoda*
Budapest, Hungary and Morioka, Japan*

OBJECTIVE: to study qualitative and quantitative changes of bone tissue and articular cartilage in rats exposed to sodium fluoride.

MATERIALS AND METHODS: 75 female Wistar rats, each weighing about 200 g, were divided equally into three groups. Animals in Groups 1 and 2 received daily doses of 0.5 mg and 5 mg of NaF, respectively, through intraperitoneal administration, whereas those in Group 3 (controls) received physiological saline solution only. The experiments were run for a period of 3 months.\(^1\) Histological and histochemical studies were carried out on adjoining bones, femur and tibia, and lumbar vertebrae III-V of the animals. The materials used for histological studies were fixed in a 10% formaldehyde solution, decalcified at room temperature in a solution composed of 24 ml 85% formic acid, 50 ml 55% HCl, and 126 mL distilled water. Sections were stained with haematoxylin and eosin (H-E), picrosirius red F3BA,\(^2,3\) and exposed to toluidine-blue at pH 6 and pH 3.5.\(^4\) The ultrastructural changes of bone tissue and articular cartilage were investigated by polarization optical methods.\(^5,6\) The fluoride content of bone tissue was determined by ion selective analysis. The fluorapatite crystals were identified by electron diffraction.

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RESULTS: The bone tissue mass, the osteoid surface and osteoid volume increased, the enchondral ossification and the mineralisation of osteoid were delayed, and the proportion of newly formed woven bone increased in correlation with the administered dose of fluoride. A sporadic, scattered necrosis of osteocytes and chondrocytes, and a progressive disorientation in the bone and articular cartilage, were shown in rats exposed to NaF. Compared with the controls, the specimens obtained from NaF-treated animals showed marked decreases in orientation of capsular and intercapsular collagen fibers and glycosaminoglycans in the preexisting bone tissue and articular cartilage.

The structural changes were correlated with the dose of administered NaF, and with the fluoride content of bone tissue (in Group 1: 1.10 mgF/g, in Group 2: 1.44 mgF/g, and in Group 3 (control): 0.423 mgF/g).

The fluorapatite crystals, in spite of decalcification, could still be identified in the animals of Group 2.

CONCLUSIONS AND INTERPRETATION: The quantity of bone tissue increased and the quality diminished with increase in NaF levels administered. The enlarged bone mass may be caused by increased bone formation and/or by decreased bone resorption. The augmented bone (osteoid) formation can be caused by either the relatively or absolutely greater number, increased activity, or longer life span, of osteoblasts. The cause of diminished bone resorption may be due to absolutely or relatively reduced number, decreased activity or shorter life span of osteoclasts. The reduced solubility of fluorapatite may play an important role also. According to our interpretation the increased bone and osteoid volume is caused by decreased bone resorption. The ultrastructural disorientation of bone tissue and articular cartilage are connected to the necrosis of osteocytes and chondrocytes, and may be accepted as a toxic effect of fluoride.

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Key words: Arthofluorosis; Bone; Osteofluorosis; Rat.
Addresses: National Institute of Rheumatology and Physiotherapy, Department of Pathology, Budapest 114, PO Box 54 H-1525, Hungary, and IWate Medical University, Department of Hygiene and Public Health, IWate 020,19-1 Uchimaru, Morioka, Japan.
A STUDY ON THE CHANGES OF ORGANIC ACIDS, FLUORIDE AND OTHER IONS IN DENTAL PLAQUE

T Yasui and S Nakao
Sakado, Saitama, Japan

By using 100 ppm F solution of sodium fluoride and sodium monofluorophosphate, the concentrations of some selected organic acids, fluoride ion, phosphorus ion, and calcium ion were measured before and after the application of 10% glucose solution. The relationship between the organic acid production in dental plaque and fluoride was analysed and discussed. The results obtained were as follows: 1) In the control group without fluoride application, distinct production of lactate in the surface solution of dental plaque was recognized after the application of 10% glucose solution. 2) In the group for sodium fluoride application, production of lactate in surface solution of dental plaque was clearly inhibited after the application of 10% glucose solution. Fluoride ion increased with statistical significance, and calcium ion decreased significantly. 3) In the group for monofluorophosphate application, production of lactate in the surface solution of dental plaque was inhibited clearly after the application of 10% glucose solution. Although fluoride ion showed a tendency to increase and calcium ion showed a tendency to decrease, these amounts of change were less than those in the case of sodium fluoride. 4) As a result of topical application of 100 ppm fluoride, it was demonstrated that the acid production in plaque was inhibited, fluoride ion increased and calcium ion decreased in the surface solution.

Key words: Dental plaque; Organic acids; Monofluorophosphate; Sodium fluoride.
Reprints: Meikai University School of Dentistry, 1-1 Keyakidai, Sakado, Saitama 35002 Japan.

THE CONTROVERSY OVER WATER FLUORIDATION

Zan-Dao Wei
Guiyang, China

On looking back at past international conferences on fluoride research, we realize that the controversy over water fluoridation has been a key background influence for a long time.

With progress in fluoride research, it has become evident that the toxic effects of excess fluoride involve all body systems. These health problems occur with water fluoridation. However, some scholars still support fluoridation and assert it is a safe and reasonable method to control tooth decay. This controversy has continued for half a century, ever since water fluoridation was proposed by Dean in 1942, and initiated in the United States in 1945. Actually, the relevant research was started by Black in 1916, so the story goes back 80 years.

The purpose of fluoride research should be to improve the health of human beings. Yet scientists working on fluoride still have differing viewpoints on water fluoridation. Up to now, our people in China have experienced many benefits from fluoride research. So what is the problem, internationally?
In China, we tried water fluoridation in Guangzhou in 1965. My colleagues and I carried out research which revealed high prevalences of fluorosis, and established that multiple sources of fluoride contributed to total fluoride intake. The results showed that the water fluoridation program had provided little benefit, but a lot of harm. The total F intake for adults was up to 4 mg/day, well above the permissible 3 mg/day now set as the standard. The water fluoridation program in Guangzhou was ended in 1983.

Key words: Fluoridation controversy; Guangzhou; Total fluoride intake.
Address: Guiyang Medical College, Guizhou 550004, China

WATER FLUORIDATION RESULTING IN HIGH PREVALENCE OF DENTAL FLUOROSIS IN GUANGZHOU

Y Guo, H Zhang, W Lim and R Yi
Guangzhou, China

In the city of Guangzhou, water was fluoridated at the level of 0.8 ppm for prevention of dental caries. Unfortunately it resulted in a high prevalence of dental fluorosis. Based on the fact that this affliction develops mainly between birth and the age of 5 years, the authors made a study of the particular environment of infants and young children - their common habits, fluid and food intakes, as well as the water fluoride concentration of the tap water. The results of extensive surveys and statistical analysis showed that fluoride intake comes not only from the water supply but also from various other sources. In recent years, many authors have reported the “halo” effect. It is recognized that dental fluorosis occurs not only in districts with fluoridated water but also in non-fluoridated areas. This is compatible with the first author’s theory of the multiple origin of dental fluorosis. However, water fluoride is the main cause of the high prevalence of dental fluorosis. We feel that the discontinuance of water fluoridation in this city was justified as a proper public health measure to eliminate harmful effects.

Key words: Dental caries; Dental fluorosis; Water fluoridation.
Address: Sun Yat-Sen University of Medical Sciences, Guangzhou, China.

MILK FLUORIDATION: AN ALTERNATIVE METHOD FOR CARIES PREVENTION

J Bánoéczy
Budapest, Hungary

Dental caries is still one of the most common diseases affecting a considerable number of children and adults in many countries.

Milk fluoridation, as an alternative to water or salt fluoridation, was first introduced in Switzerland in the mid 1950s. Since then, fluoridated milk projects have been carried out in the USA, Scotland and Hungary, while the International Milk Fluoridation Program, implemented by the World Health Organization and the Boro Dental Milk Foundation, brought good results at the national level in Bulgaria. The aim of this report is to present the results of the Hungarian milk fluoridation project.
Milk fluoridation in Hungary was initiated in 1979. Started with institutionalized, healthy children, with standardized living conditions, of kindergarten age (2-5 years), the program was extended one year later to children aged 6-14 years. The children consumed 200 mL of milk daily, supplemented with 0.4-0.75 mg F\(^{-}\), according to age. Mean DMF (decayed, missing and filled) values were evaluated after 2, 3, 5 and 10 years of consumption, and the data were compared with those of a group of similar institutionalized children without preventive measures. The five-year evaluation, comparing 165 test and 122 control children, showed statistically significant reductions in both the primary and permanent dentitions - in the latter between 60 and 67%. After 10 years consumption, the ratio of caries-free children was 10% higher in the test than in the control group; the reduction of DMFT(teeth) was 36.78% and the reduction of DMFS(surfaces) 40.02%. The milk fluoridation programs were accompanied by monitoring urinary fluoride, plaque fluoride, and enamel fluoride content (Kertész et al. 1992, Tóth et al. 1989).

In conclusion, milk fluoridation proved to be effective in home children. Early starting age increased the protective effect considerably. Similarly the results of the large-scale scheme in Bulgaria after five years give evidence to recommend milk fluoridation on a community level.

Key words: Dental caries; Hungary; Milk fluoridation.
Address: Professor J Bánóczy, Department of Conservative Dentistry, Semmelweis University of Medicine, Mikszáth Kálmán tér 5, H-1088, Budapest, Hungary.

**FLUORIDE IN THE TREATMENT OF OSTEOPOROSIS AN OVERVIEW: 35 YEARS OF CLINICAL RESEARCH**

J Franke
Bad Liebenstein, Germany

It has long been known that fluoride ingestion through drinking water in areas naturally rich in fluoride, or ingestion or inhalation of fluoride containing gases or dusts, leads to osteosclerosis, known as endemic or industrial fluorosis.

We studied over 100 cases of industrial fluorosis developing after 10 to 20 years of fluoride exposure, and we found hypermineralization, hyperossification also in the peripheral bones, and an increase in the bone strength.

The first suggestion that fluoride be used in the treatment of osteoporosis was made by Rich and Ensinck in 1961. Despite 35 years of research, fluoride treatment for osteoporosis still remains controversial.

Fluoride has a dual effect on osteoblasts. On the one hand, it causes proliferation and differentiation of osteoblasts, while on the other hand it has a toxic effect on the osteoblasts with alteration of the composition of the bone matrix and impairment of mineralization with higher doses.

In Europe in the late sixties some research groups successfully started sodium fluoride (NaF) therapy for osteoporosis. We also started in 1969. Since that time we have carried out four prospective studies together on 263 patients. We used pure NaF powder (20-60 mg/d) at the beginning or some slow release NaF preparations (60 to 80 mg/d or 1 mg NaF/kg body weight and day) in the later studies for 2 to 5 years of treatment.
Clinically about 80% of the patients recovered distinctly or became symptom-free. In 64% we detected radiologically a distinct reossification of the spine, and in a further 20% this reossification was questionable. In summary, we found about 20% were fast-responders (reossification after 11 to 16 months), 60% were responders and 20% were non-responders.

The vertebral fracture rate decreased from 750 fractures per thousand patient years in the first year of treatment to 96.2 fractures in the second year and to zero in the third and fourth year. There was no increase of proximal femur fracture rate.

These fractures should not be confused with the stress fractures, observed in 3.7% peripherally and in 4.9% at the femoral neck, which do not cause serious problems, because they heal quickly with discontinuation of the fluoride intake. In the last study with a dose of 1 mg NaF/kg and day a careful monitoring of the fasting morning serum fluoride level (7.5-12 μmol/L) we could reduce this stress fracture rate to 0.95%.

These results are in agreement with other studies from Europe and the USA, except the studies of Riggs et al. (1990) and Kleerekoper et al. (1991) who found, in spite of a distinct increase of the bone mineral content in the spine (15%), no significant decrease of the vertebral fracture rate.

The cause of this disagreement was: both study groups used too high doses (60 to 90 mg NaF) and fast release sodium fluoride preparations. In 1995 Pak et al. confirmed our results in a randomized controlled trial with slow release sodium fluoride.

Side effects of the fluoride therapy are gastrointestinal intolerance and the painful lower extremity syndrome.

Five years ago we started using more and more disodium monofluorophosphate (MFP) preparations. MFP remains soluble in the presence of calcium, is better absorbed in the duodenum, and there are fewer gastric and intestinal side effects.

Because we very often observed a vitamin-D-hypovitaminosis in our patients with osteoporosis, and because the possibility that fluoride could cause a calcium deficiency osteomalacia, we also give our patients an adequate calcium supply (1 g/d) and low doses of vitamin D (1000 IU/d).

According to Marx et al. (1992) the combination of estrogen and fluoride together is additive. Therefore we also use this combination in severe cases of osteoporosis.

In conclusion, the therapeutic window of fluoride is narrow, but by careful monitoring of the treatment (determination of the morning fasting serum fluoride level and of alkaline phosphatase every 4 months, and control of the spine X-rays and the spinal bone mineral content every year) fluoride therapy for osteoporosis is beneficial and safe.

Key words: Fluoride therapy; Osteoporosis.
Address: Department of Orthopaedic Rehabilitation, Heinrich Mann Hospital, D-36448 Bad Liebenstein, Germany.
ANTIRESORPTIVE THERAPY, ANABOLIC THERAPY, AND EXERCISE EFFECTS ON BONE MASS, STRUCTURE, AND STRENGTH ASSESSED IN A RAT MODEL

Prevention and treatment of osteoporosis
Charlotte Hasselholt Søgaard MD
Aarhus, Denmark

Abstracted from PhD thesis, University of Aarhus, Denmark, 1994

Osteoporosis can be therapeutically approached in two different ways: by use of antiresorptive agents (for example estrogen and bisphosphonates) or by use of anabolic agents (for example parathyroid hormone (PTH) and fluoride). Osteoporosis becomes clinically relevant when the patient presents with a fracture. Because of a high surface to volume ratio, disproportionately more trabecular than cortical bone is lost. Consequently, the typical osteoporotic fractures are those of the spine (vertebral compression fractures), the femoral neck (hip fracture), and the distal radius (Colles’ fracture); all of which are sites of large amounts of trabecular bone. The most serious osteoporotic fracture is that of the femoral neck, as it is painful, necessitates hospitalization and causes considerable morbidity and mortality.

For more than 30 years, sodium fluoride (NaF) has been a commonly used therapy for established osteoporosis. Its anabolic effect on trabecular bone mass, particularly in the spine, has been repeatedly documented. However, structural abnormalities or mineralization defects in the bone formed during fluoride administration have been demonstrated in several studies, thus indicating that the increase in bone mass is not necessarily paralleled by an improved bone quality.

Furthermore, long-term clinical investigations using fracture rate as a true end-point have now become available, and the results are conflicting. Some studies have shown that NaF reduces vertebral fracture rate. In contrast, three recent controlled trials have failed to demonstrate any therapeutic advantage of NaF over placebo with respect to vertebral fracture rate. In addition, there have been several reports of an increased incidence of non-vertebral fractures during fluoride administration.

Not much attention has been paid to fluoride’s effect on bone biomechanics. Bone biopsies for measurement of bone strength in fluoride-treated osteoporotic patients are not readily available, and to our knowledge only one such investigation has been performed. In that study, a dramatic decrease in iliac crest bone strength and quality was found after 5 years of therapy (Søgaard et al. Bone 15 (4) 393-399 1994, abstract in Fluoride 27 (4) 229 1994).

There have been several animal studies focusing on bone strength during fluoride administration. No study to date has focused on the effect of fluoride on bone quality at a site of combined cortical and trabecular bone.

The vast majority of the clinical studies evaluating the effect of different preventive and therapeutic strategies in osteoporosis have used bone mass or bone histomorphometry as an end-point. This is logical, since bone biomechanical competence is not a readily available parameter in humans.
It has, however, recently become apparent that bone mass should be combined with determination of bone strength and quality when treatment regimens for osteoporosis are evaluated. In order to avoid invasive intervention in humans, bone strength can be evaluated only by making fracture rate the true end-point in clinical research. Since fracture occurs late in life, and preventive strategies should be initiated maybe 15 years ahead, such studies will be of long duration, unless they are of cross-sectional nature.

Seen in that light, longitudinal studies on small animals are attractive. Many of the animal experiments concerning the effect of various therapeutic agents or exercise on the skeleton have been based upon measurement of bone mass or on bone histomorphometry. Only a minority have focused on bone biomechanics, and then cortical bone strength has usually been the parameter measured.

To achieve a more clinically relevant evaluation, the present investigation has chosen to measure the effects of the various regimens on bone strength in the skeletal sites typical for osteoporotic fracture, namely the femoral neck and the vertebral body.

The purpose of the present investigation was to evaluate the effect on bone biomechanical competence of current therapies (fluoride and estrogen) or potential therapies (PTH, bisphosphonates, PTH co-therapy with an anti-resorptive agent, and exercise) in treatment or prophylaxis of osteoporosis, assessed in either rat femoral neck and rat femoral body, or both.

SUMMARY AND CONCLUSIONS

A The present study has confirmed that the rat skeleton is capable of reacting to mechanical and hormonal stimuli in a manner very similar to the human skeleton, and thereby it supports previous investigations finding the rat model suitable for osteoporosis research.

B The present investigation has shown PTH to exert a highly anabolic effect on two clinically relevant sites of the rat skeleton: the vertebral body and the femoral neck. This effect is reflected in an increased bone strength as well as an increased bone quality and is independent of the presence of gonadal hormones. This study therefore provides further support for PTH being a promising agent in treatment of postmenopausal osteoporosis.

C The present study has also shown a light, physiological, long-term exercise regimen to exert anabolic actions on the rat skeleton. This effect was most pronounced in the femoral neck, and the gain in bone strength seemed to be due partly to an increased bone mass and partly to an earlier maturation of the skeleton. But the less weight-bearing vertebral body was also found capable of responding positively to exercise, and long-term moderate physical training therefore seems promising as a part of the prevention strategy against osteoporosis for treatment of vertebral osteoporosis.

D In contrast, the present study has found that the apparently anabolic action of fluoride is not reflected in a concomitant increase in bone strength. Therefore this study provides further evidence for a possible detrimental effect of fluoride on bone quality, and as such agrees with previous investigations recommending discontinuance of the general use of fluoride in treatment of
osteooporosis until further clinical trials, using fracture rate as an end-point, have been performed.

E This investigation has shown only a modest effect of antiresorptive therapy on the rat skeleton. Estrogen and Risedronate seemed capable of maintaining bone mass and strength at control levels, but proved to be much less efficient than treatment with the anabolic agent PTH. When antiresorptive therapy was combined with PTH, a marked effect was found, but this was not more advantageous than treatment with PTH alone. One exception was concurrent treatment with Risedronate+PTH. This regimen showed a significant sustained increase in vertebral bone mass and strength throughout the whole treatment period, and it cannot be excluded that a long-term regimen combining PTH and bisphosphonates may prove more successful than PTH mono-therapy for treatment of vertebral osteoporosis.

F Finally, this investigation has found the same agent to exert divergent effects on the vertebral body and on the femoral neck. This may be due partly to different ratios of cortical and cancellous bone, partly to different loading patterns at these two sites. However, the fact that the femoral neck, in contrast to the vertebral body, is not covered with periostum and therefore can not undergo periostal modeling (or remodeling) is an important matter that should be borne in mind when considering therapeutic intervention in osteoporosis.

Key words: Anabolic therapy; Antiresorptive therapy; Bone mass; Bone strength; Exercise; Fluoride therapy; Osteoporosis; Rat model.
Reprints: Dr Charlotte H Søgaard, Department of Connective Tissue Biology, University of Aarhus, DK-8000 Aarhus C, Denmark.

PREVENTION AND MANAGEMENT OF OSTEOPOROSIS:
Consensus Statements from the Scientific Advisory Board of the Osteoporosis Society of Canada
7. Fluoride therapy for osteoporosis [Review]

T M Murray and L G Ste-Marie
Toronto, Ontario, Canada

Abstracted from Canadian Medical Association Journal 155 (7) 949-954 1996

New data indicate that fluoride therapy should be re-evaluated as a potentially effective treatment of osteoporosis with minimal side effects. More studies are needed of slow-release fluoride formulations, intermittent treatment schedules and calcium supplementation of fluoride. Studies should be undertaken to see if it is advantageous to initiate treatment with antiresorptive agents before or in combination with fluoride. Conclusive data have not been presented regarding the benefit of any specific type of calcium supplement. Further studies on the basic mechanism of action of fluoride on the skeleton are necessary to evaluate fluoride’s potential to stimulate bone formation therapeutically.

Key words: Fluoride therapy; Osteoporosis.
Reprints: Ms Mary Bowyer, Osteoporosis Society of Canada, 33 Laird Drive, Toronto, ON M4G 3S9, Canada.
WATER FLUORIDATION AND OSTEOPOROTIC FRACTURE [REVIEW]
S Hillier, H Inskip, D Coggon and C Cooper
Southampton, England

Abstract from Community Dental Health 13 (Suppl 2) 63-68 1996

Osteoporotic fractures constitute a major public health problem. These fractures typically occur at the hip, spine and distal forearm. Their pathogenesis is heterogeneous, with contributions from both bone strength and trauma. Water fluoridation has been widely proposed for its dental health benefits, but concerns have been raised about the balance of skeletal risks and benefits of this measure. Fluoride has potent effects on bone cell function, bone structure and bone strength. These effects are mediated by the incorporation of fluoride ions in bone crystals to form fluoroapatite, and through an increase in osteoblast activity. It is believed that a minimum serum fluoride level of 100 ng/mL must be achieved before osteoblasts will be stimulated. Serum levels associated with drinking water fluoridated to 1 ppm are usually several times lower than this value, but may reach this threshold at concentrations of 4 ppm in the drinking water. Animal studies suggest no effect of low-level (0-3 ppm) fluoride intake on bone strength, but a possible decrease at higher levels. Sodium fluoride has been used to treat established osteoporosis for nearly 30 years. Recent trials of this agent, prescribed at high doses, have suggested that despite a marked increase in bone mineral density, there is no concomitant reduction in vertebral fracture incidence. Furthermore, the increase in bone density at the lumbar spine may be achieved at the expense of bone mineral in the peripheral cortical skeleton. As a consequence, high dose sodium fluoride (80 mg daily) is not currently used to treat osteoporosis. At lower doses, recent trials have suggested a beneficial effect on both bone density and fracture. The majority of epidemiological evidence regarding the effect of fluoridated drinking water on hip fracture incidence is based on ecological comparisons. Although one Finnish study suggested that hip fracture rates in a town with fluoridated water were lower than those in a matching town without fluoride, a later study failed to show differences. Ecological studies from the United States and Great Britain have, if anything, revealed a weak positive association between water fluoride concentration and hip fracture incidence. Two studies examining hip fracture rates before and after fluoridation yielded discordant results, and are complicated by underlying time trends in hip fracture incidence. Only two studies have attempted to examine the relation between water fluoride concentration and fracture risk at an individual level. In one of these, women in a high fluoride community had double the fracture risk of women in a low fluoride community. In the other, there was no relationship between years of fluoride exposure and incidence of spine or non-spine fractures. In conclusion, the epidemiological evidence relating water fluoridation to hip fracture is based upon ecological comparisons and is inconclusive. However, several studies suggest the possibility of a weak adverse effect, which warrants further exploration. Data on the relationship between fluoride intake and hip fracture risk at the individual level, and data

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relating fluoridation to bone mineral density are required. Until these become available, the burden of evidence suggesting that fluoridation might be a risk factor for hip fracture is weak and not sufficient to retard the progress of the water fluoridation programme.

Key words: Fluoridation; Fractures; Osteoporosis.
Reprints: Dr Cyrus Cooper, MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton SO16 6YD, England.

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CALCIUM DEFICIENCY IN FLUORIDE-TREATED OSTEOPOROTIC PATIENTS DESPITE CALCIUM SUPPLEMENTATION

B A Dure-Smith, S M Farley, S G Linkhart, J R Farley and D J Baylink
Loma Linda, California, USA

Abstract from Journal of Clinical Endocrinology and Metabolism. 81 (1) 269-75 1996

To test the hypothesis that the osteogenic response to fluoride can increase the skeletal requirement for calcium, resulting in a general state of calcium deficiency and secondary hyperparathyroidism, we assessed calcium deficiency, spinal bone density, by quantitative computed tomography, and serum PTH in three groups of osteoporotic subjects. Two of the three groups had been treated with fluoride and calcium (at least 1500 mg/day) for 32 ± 19 months. Group I consisted of 16 fluoride-treated subjects who had shown rapid increases in spinal bone density (+ 3.8 ± 2.6 mg/cm² month), group II consisted of 10 fluoride-treated subjects who had shown decreases or only slow increases in spinal bone density (- 0.05 ± 0.6 mg/cm³ month), and group III consisted of 10 age-matched untreated osteoporotic controls. Calcium deficiency was assessed by measurement of calcium retention after calcium infusion. The results of our studies showed that 1) 94% of the subjects in Group I were calcium deficient compared with only 30% in groups II and III (P < 0.01 for each); 2) the subjects in group I retained more calcium (79%) than the subjects in group II (60%, P < 0.001) or the subjects in group III (64%, P < 0.005); 3) calcium retention was proportional to serum PTH (r = 0.37, n = 36, P < 0.03); and 4) calcium retention was proportional to the (previous) fluoride-dependent increase in quantitative computed tomography spinal bone density (in groups I and II, r = 0.48, n = 26, P < 0.02).

To test the hypothesis that the calcium deficiency and the secondary hyperparathyroidism that were associated with the positive response to fluoride would respond to concomitant calcitriol treatment, a subgroup of 7 calcium-deficient subjects were selected from group I and treated with calcitriol (plus fluoride and calcium) for an average of 7 months. The calcitriol therapy reduced the calcium deficit in all 7 subjects, decreasing calcium retention from 80% to 62% (P < 0.02), and decreasing PTH from 50 to 28 pg/mL (P < 0.02). Together, these data indicate that fluoride-treated osteoporotic subjects may develop calcium deficiency in proportion to the effect of fluoride to increase bone formation, and this calcium deficit is responsive to calcitriol therapy.

Key words: Calcium; Fluoride therapy; Osteoporosis.
Reprints: David J Baylink MD, c/o Research Service (151), Jerry L Pettis Memorial Veterans Hospital, 11201 Benton Street, Loma Linda, Ca 92357, USA.
ALUMINUM POTENTIATES THE EFFECT OF FLUORIDE ON TYROSINE PHOSPHORYLATION AND OSTEObLAST REPLICATION
IN VITRO AND BONE MASS IN VIVO

J Caverzasio, T Imai, P Ammann, D Burgener and J P Bonjour
Geneva, Switzerland


Osteosclerosis in workers exposed to fluoride (F) and aluminum (Al) (industrial fluorosis) led to the use of F as a treatment to increase bone mass in osteoporosis patients. Because the influence of traces of Al on the effects of F on bone formation is heretofore unknown, we have investigated this issue both in vitro and in vivo. We have found that minute amounts of Al (< or = 10^-5 M) potentiate the effects of F in vitro such that osteoblast proliferation increased by 15 ± 2.7% at 50 microM (p < 0.001) and by 117.6 ± 5.1% at 750 microM (p < 0.001), concentrations of F with no mitogenic effect alone. F + Al time-dependently modulated a growth factor signaling pathway(s) associated with enhanced tyrosine phosphorylation (TyrP) of several proteins (p90 [2.9x], p77 [4.9x], p68 [9.6x], and mitogen activated protein kinases [3x]). TyrP was only slightly or not at all changed by F and Al alone, respectively. The effects of F + Al on TyrP and cell proliferation were markedly reduced by 100 microM tyrphostin-51, a tyrosine kinase inhibitor. Protein kinase A (PKA) and protein kinase C (PKC) pathways were not involved in this response. In vivo, F + Al administered for 8 months, at doses that had no effect when the minerals were administered individually, significantly enhanced proximal tibia bone mineral density (BMD) by 6.3 ± 1% compared with initial values and by 2-fold compared with control ovariectomized rats (p < 0.0001). These effects are consistent with a crucial role of Al in osteosclerosis observed in industrial fluorosis. The results suggest that the combination of F + Al modulates a growth factor-dependent TyrP pathway enhancing mitogen-activated protein kinase and osteoblastic proliferation and bone mass.

Key words: Aluminum; Bone; Industrial fluorosis; Osteoblasts; Tyrosine phosphorylation.
Reprints: J Caverzasio, Department of Medicine, University Hospital of Geneva, 24 Rue Micheli Crest, CH-1211 Geneva 14, Switzerland.

TWO CASES OF SKELETAL FLUOROSIS IN THE HAND [FRENCH]

M H Sy, P Sene, M M Dion and S Dion
Geneva, Switzerland

Abstract from Annales de Chirurgie de la Main et du Membre Superieur 15(2) 109-114 1996

Skeletal fluorosis is well known, particularly in the spine, pelvis and forearm. However, the hand may also be involved. The authors report two cases of this site in endemic areas in Senegal, after ingestion of large amounts of fluoride in the water. Fluorosis consisted of deforming metacarpal and phalangeal osteoarthrosis in one case and peri-articular ossifications and calcifications of the attachments of the ligaments and capsule in the other case. They review the literature concerning skeletal fluorosis and discuss the rarity of hand involvement its clinical features and particularly its radiological features. Lastly, they emphasize the differential diagnosis with certain metabolic, infectious and neoplastic diseases.

Key words: Hand; Senegal; Skeletal fluorosis.
Reprints: Service d'Orthopedie et de Traumatologie, Centre de Traumatologie et d'Orthopedie de Dakar (CTO), BP 3270, Dakar, Senegal.
SUPPRESSION BY MEDICAL JOURNALS OF A WARNING ABOUT OVERDOsing FORMULA-FED INFANTS WITH FLUORIDE

Mark Diesendorf and Angela Diesendorf
Sydney, Australia

Abstracted from Accountability in Research 5 225-237 1997

The authors explain: “The work reported in this paper may be considered to be an unplanned experiment to investigate the power structure of medicine in the area of fluoride science in general and water fluoridation in particular. This paper also seeks to alert scientists and medical practitioners to the existence of a particular subgroup of the population in fluoridated areas which ingests much higher doses of fluoride than average.”

In January 1990, a short letter was sent to the editor of the international medical journal, Pediatrics, to alert its readers that the standard, highly quoted paper by Singer and Ophaug on fluoride intake by infants, published in 1979 in the same journal, required revision/correction in order to protect one group of infants from receiving substantial overdoses of fluoride. This group comprises infants who are fed almost entirely on powdered formula which is reconstituted with fluoridated water.

The letter was based on the well-established pediatric guidelines of water intake by infants and the fundamental toxicological principle of protecting groups at highest risk. It did not question the fluoridation of public water supplies. Nevertheless, the letter, together with a response to it by Ophaug, was rejected by the editor of Pediatrics, “due to a large backlog of articles.” Following a protest, the letter was reviewed by three referees, two of whom conceded its main point, but was still not published.

In the present paper, the original, previously unpublished letter on fluoride intake by infants is first reproduced verbatim, and then the comments of the referees and editors are reported and examined. It is concluded that the most plausible explanation for the rejection of the letter is that it might assist the anti-fluoridation movement. Another possible contributing explanation is that publication of the letter might reduce the status of the scholars who had defended the previous position and might be perceived to diminish the status of the journal.

Key words: Fluoridation; Fluoride intake; Infant formula; Overdose; Intellectual suppression.

Reprints: Institute for Sustainable Futures, University of Technology Sydney, PO Box 123, Broadway NSW 2007, Australia.

COMPARISON OF RECOMMENDED AND ACTUAL MEAN INTAKES OF FLUORIDE BY CANADIANS

D W Lewis and H Limeback
Toronto, Ontario, Canada

Abstract from Journal of the Canadian Dental Association 62 (9) 708-709 712-715 1996

The findings of two separate 1993 reports, one of the actual intake of fluoride by Canadians and the other on their recommended fluoride intake, are summarized and compared. Recent increases in very mild and mild dental fluorosis suggest that the gap between current fluoride intake and recom-

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mended intake is narrowing. The daily swallowing of fluoride dentifrice makes a large contribution to the actual total daily fluoride intake, especially in children seven months to four years of age, the age group most susceptible to fluorosis in the anterior permanent teeth. Because of the available data and methods used in each study, the reported actual and recommended fluoride intakes vary greatly both within and between age groups. It is likely that individual variation in fluoride intake also varies greatly. Comparison of the data in the two reports revealed that, for breast-fed infants and nearly all other age groups without fluoridated water, the ranges of the estimates of actual intake are lower than the recommended ranges. However, for formula-fed infants and all other age groups using fluoridated water, the estimates of actual intake greatly exceed the recommended intake, especially for the seven months to four years age group. Ingestion of fluoride at these levels during tooth development will contribute to dental fluorosis. All of the age groups have fluoride intake estimates below levels at which skeletal signs of fluoride exposure are noticed. Nevertheless, exposure to fluoride should be closely monitored and inappropriate use of discretionary fluorides curtailed.

Key words: Canada; Dental fluorosis; Fluoride intakes.
Reprints: Faculty of Dentistry, University of Toronto, 124 Edward Street, Toronto, ON M5G 1G6, Canada.

TOTAL FLUORIDE INTAKE IN CHILDREN AGED 3 TO 4 YEARS A LONGITUDINAL STUDY.
N Guha-Chowdhury, B K Drummond and A C Smillie
Dunedin and Wellington, New Zealand

Abstract from Journal of Dental Research. 75 (7) 1451-1457 1996

Several previous studies using food consumption tables or diet records have estimated that children aged 1 to 12 years resident in fluoridated (1 ppm) areas receive, on average, between 0.05 and 0.07 mg fluoride/kg body weight from foods and drinks alone. In this study, the duplicate-diet approach, which is a more accurate method of determining nutrient intake, was used to determine if levels of fluoride intake from foods and drinks are similar to those estimated from food consumption tables or diet records. Duplicate portions of all foods and drinks consumed over 24 hours by 66 children aged 3 to 4 years resident in fluoridated and low-fluoride areas of New Zealand were collected on three separate days over a period of 12 months and analyzed for fluoride. Fluoride intake from the use and ingestion of toothpastes and fluoride supplements was also determined for each child. It was hypothesized that the total amount of fluoride received by children in low-fluoride areas from diet, toothpastes, and fluoride supplements was similar to that received by children in fluoridated areas from diet and toothpastes. The mean fluoride intake from foods and drinks alone in the low-fluoride areas was 0.008 ± 0.003 mg/kg body weight (0.15 ± 0.06 mg/day; n = 34) and in the fluoridated areas was 0.019 ± 0.009 mg/kg body weight (0.36 ± 0.17 mg/day; n = 32). The mean fluoride intake from foods and drinks and toothpastes in the low-fluoride areas was 0.027 ± 0.012 mg/kg body weight (0.49 ± 0.25 mg/day) and in the fluoridated areas was 0.036 ± 0.015 mg/kg body weight (0.68 ± 0.27 mg/day). Fluoride intake from diet alone did not exceed 0.04 mg/kg body weight (0.74 mg/day), and fluoride intake from diet
and toothpaste did not exceed 0.07 mg/kg body weight (1.31 mg/day). The results suggest that levels of fluoride intake from foods and drinks alone as estimated by the duplicate-diet approach are much lower than previously estimated from food consumption tables or diet records. It was calculated that if all children in the low-fluoride areas were to take currently recommended dosages of fluoride tablets, which have been based on dietary surveys and diet records, then the total fluoride intake of some children in the low-fluoride areas would exceed that of their counterparts in the fluoridated areas. The results suggest that currently recommended dosages of fluoride tablets need to be further reduced if dental fluorosis in children is to be avoided.

Key words: Dental fluorosis; Dietary record; Fluoride intake.
Reprints: Dental Research Unit, Health Research Council, Wellington School of Medicine, PO Box 27007, Wellington, New Zealand.

ASSESSING FLUORIDE CONCENTRATIONS OF JUICES AND JUICE-FLAVORED DRINKS
Wellington and Dunedin, New Zealand

Abstract from Journal of the American Dental Association 127 (7) 895-902 1996

Few studies have investigated fluoride exposures from juices and juice-flavored drinks manufactured with water. In this study, the authors analyzed 532 juices and juice drinks for fluoride. Fluoride ion concentrations ranged from 0.02 to 2.80 parts per million, in part because of variations in fluoride concentrations of water used in production. Children's ingestion of fluoride from juices and juice-flavored drinks can be substantial and a factor in the development of fluorosis.

Key words: Dental fluorosis; Fluoride intake; Fruit juices; Fruit-flavored drinks.
Reprints: Dental Research Unit, Health Research Council, Wellington School of Medicine, PO Box 27007, Wellington, New Zealand.

RISK FACTORS FOR ENAMEL FLUOROSIS IN A NONFLUORIDATED POPULATION.
D G Pendry, R V Katz and D E Morse
Farmington, Connecticut, USA

Abstract from American Journal of Epidemiology 143 (8) 808-815 1996

The purpose of this case-control investigation was to investigate the possible association between mild-to-moderate enamel fluorosis and exposure during early childhood to fluoride supplements, fluoride toothpaste, and/or infant formula use in nonfluoridated communities. Analysis was performed on 460 10-to 13-year-old children, born after 1979, who were residents of six nonfluoridated communities in Massachusetts and Connecticut. The fluorosis status of the subjects was determined on the basis of a clinical dental examination using the Fluorosis Risk Index (FRI). Risk factor exposure was ascertained via a mailed questionnaire with a response rate of 90% and a questionnaire reliability of 87%. Logistic regression analyses revealed a moderate association between mild-to-
moderate enamel fluorosis on early forming (FRI classification I) enamel surfaces and both fluoride supplement use (odds ratio (OR) = 2.25, 95% confidence interval (CI) 1.08-4.69) and early toothbrushing habits (OR = 2.56, 95% CI 1.34-4.88). There was a strong association between mild-to-moderate fluorosis on later forming (FRI classification II) enamel surfaces and both supplement use (OR = 7.97, 95% CI 2.98-21.33) and early toothbrushing habits (OR = 4.23, 95% CI 1.72-10.41). Infant formula was not found to be associated with fluorosis on either FRI classification I or II surfaces.

Key words: Dental fluorosis; Fluoride supplements; Fluoride toothpastes; Infant formula.
Reprints: D G Pendrys, School of Dental Medicine, University of Connecticut Health Center, MC 3910, Farmington CT 06030, USA.

THE EFFECT OF DOMESTIC WATER FILTERS ON WATER FLUORIDE CONTENT.
Y S Ong, B Williams and R Holt
London, England

Abstract from British Dental Journal 181 (2) 59-63 1996

The effect of filtration on water fluoride level was investigated in a study using commercially available filters. Testing was carried out in London (low fluoride), Braintree (optimum fluoride, naturally occurring) and Birmingham (optimum fluoride, artificially adjusted). It was found that none of the filters removed fluoride. In Birmingham, but not in either Braintree or London, there was a small, clinically insignificant increase in fluoride levels with filtration using two of the five filters. It is concluded that the water filtration systems tested will not affect the advantage offered by optimum water fluoride levels. Fluoride dietary supplements should not be prescribed for children living in optimal fluoride areas, irrespective of whether they use household filters.

Key words: Water filters; Water fluoride content.

A SIMPLE METHOD FOR DEFLUORIDATION OF DRINKING WATER AT VILLAGE LEVEL BY ADSORPTION ON ANDO SOIL IN KENYA
C Zevenbergen, L P van Reeuwijk, G Frapporti, R J Louws and R D Schuiling
Rotterdam, The Netherlands

Abstract from Science of the Total Environment 188 (2-3) 225-232 1996

In this paper a new and simple defluoridation method is presented using local Kenyan soil derived from volcanic ash (e.g. Ando soils or soils with 'andic' properties) as a fluoride sorbent. The ability of Kenyan Ando soil to adsorb fluoride was determined experimentally. These results were extended to possible technical application using a one dimensional solute transport model. Based on the results it is concluded that the use of Ando soils appears to be an economical and efficient method for defluoridation of drinking water on a small scale in rural areas of Kenya and other regions along the Rift Zone. Further research is warranted to evaluate its practical applications and social acceptance.

Key words: Defluoridation; Kenya;
Reprints: IWACO BV, NL-3009 AM, Rotterdam, The Netherlands.

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SEVOFLURANE VERSUS ISOFLOURANE FOR MAINTENANCE OF ANESTHESIA: ARE SERUM INORGANIC FLUORIDE ION CONCENTRATIONS OF CONCERN?

M E Goldberg, J Cantillo, G E Larjiani, M Torjman, D Vekeman and H Schieren
Camden, New Jersey, USA

Abstract from Anesthesia and Analgesia 82 (6) 1268-1272 1996

Sevoflurane administration can result in increased serum inorganic fluoride ion concentrations, which have been associated with inhibition of renal concentrating ability. We measured serum fluoride levels, renal function, and recovery variables as a function of time in ASA grade I-III patients administered general anesthesia with isoflurane or sevoflurane for at least 1 h. Fifty patients were exposed to sevoflurane (< or = 2.4% inspired concentration) or isoflurane (< or = 1.9% inspired concentration) for maintenance of anesthesia as part of a multicenter trial. Blood was collected for determination of serum fluoride ion concentration, electrolytes, blood urea nitrogen, and creatinine at various time points pre- and postoperatively. Mean serum fluoride levels were significantly increased in sevoflurane versus isoflurane groups at all time points; the mean peak serum levels were 28.2 ± 14 µmol/L at 1 h for sevoflurane and 5.08 ± 4.35 µmol/L at 12 h for isoflurane. Sevoflurane-mediated increases in serum fluoride levels peaked at 1 h and, in general, decreased rapidly after discontinuation of the anesthesia. Three of 24 patients exposed to sevoflurane had one or more fluoride levels > 50 µmol/L. One of these patients had a serum inorganic fluoride ion level > 50 µmol/L at 12 h after sevoflurane, and an additional patient had fluoride levels > 33 µmol/L for up to 24 h after sevoflurane discontinuation. Those two patients also demonstrated an increase in serum blood urea nitrogen and creatinine at 24 h after sevoflurane administration compared with baseline. The elimination half-life of serum fluoride ion was 21.6 h. The results of this study suggest the possibility of sevoflurane induced nephrotoxicity.

Key words: Anesthesia; Renal function; Serum fluoride concentration; Nephrotoxicity.
Reprints: Department of Anesthesiology, Cooper University Medical Center, 1 Cooper Plaza, Camden, NJ 08103, USA.

THE PREVALENCE OF DENTAL CARIES IN EUROPE 1990-1995

T M Marthaler, D M O'Mullane and V Vrbic
Zurich, Switzerland

Abstract from Caries Research 30 (4) 237-255 1996

Caries prevalence data from recent studies in all European countries showed a general trend towards a further decline for children and adolescents. However, in several countries with already low caries prevalence in primary teeth, there was no further decrease. Regarding the permanent dentition, further reductions were observed in the 12-year age group, these being even more evident at the ages of 15-19 years. In some Central and Eastern European countries, caries prevalence in children and adolescents was still high. Few data were available on young adults, but the benefits of prevention are becoming manifest. The available data on the use of toothbrushes, fluorides and other pertinent items provided few clues as to the causes of the decline in caries prevalence.

Key words: Dental caries; Europe.
Reprints: Dental Institute, University of Zurich, PO Box CH-8028, Zurich, Switzerland.
NO ASSOCIATION BETWEEN FLUORIDATION OF WATER SUPPLIES AND SUDDEN INFANT DEATH SYNDROME

E A Mitchell, J M D Thompson and B Borman
Auckland and Wellington, New Zealand

Abstracted from New Zealand Medical Journal 104 500-501 1991

This short study 1) reviewed the scientific literature on the relation between fluoridation and SIDS (sudden infant death syndrome); and 2) examined whether water fluoridation was associated with SIDS mortality in New Zealand by obtaining SIDS mortality rates, mean annual daily temperatures, and median fluoridation concentrations (g/m³) for each of the 14 official health districts.

The authors found no publications dealing with fluoridation and SIDS. They presented a Figure depicting no SIDS/fluoridation relationship, and concluded:

"The effect of average temperature on SIDS mortality rate in New Zealand must be taken into account in any study that examines the effect of region on mortality. In our study we found that mean daily temperature was highly correlated with SIDS mortality. The addition of fluoridation concentration to the model showed no improvement in the model. If anything the higher the SIDS mortality rate the lower the fluoride concentration. This study clearly shows there is no indication of a relationship between fluoridation of the water supply and SIDS in New Zealand. The study has not attempted to address the question of the value of fluoridation. It does, however, highlight the unethical scare tactics used by some in the antifluoridation lobby. The publication of unfounded theories by the media causes much distress to the families who have lost an infant from SIDS."

Key words: Fluoridation; SIDS (sudden infant death syndrome); Unethical scare tactics.

Reprints: Department of Paediatrics, University of Auckland School of Medicine, Private Bag, Auckland, New Zealand.

[Editor's comment: We publish this abstract because the study is a good example of its kind, especially the expectation that a correlation must be linear, and also because Professor Albert Schatz has offered a critique (pages 131-133). This critique, and the letter from Dr Hans Moolenburg (pages 134-135), as well as the earlier article by Dr Richard Foulkes (Fluoride 29 (4) 230-236 1996), draw attention to the possibility of paradoxical effects when looking at relationships.]
PARADOXICAL EFFECTS: CRITIQUE OF A STUDY
(Col death/fluoridation study by Mitchell, Thompson and Borman)

The authors of Our Stolen Future,¹ and Richard Foulkes (in Fluoride 29 (4) November 1996),² drew attention to the importance of the "paradoxical dose response curve" when examining effects of toxic substances. In 1964, in the first review of paradoxical effects,³ we pointed out: "Since numerous chemical and physical agents cause paradoxical effects by different mechanisms in many biological systems, these reactions will no doubt become increasingly important in pharmacology, toxicology, chemotherapy drug idiosyncrasies, air pollution, chemical carcinogenesis, fluoridation, fallout, radiation effects, nutrition, biogeochemistry, the weathering of rocks and minerals, soil formation and soil fertility, and many other areas." Unfortunately, health agencies and professionals have failed to pay attention to this important fact about very low doses which often produce effects greater than or opposite to much larger doses. The following critique examines an example of such failure.

The report by Mitchell et al., "No association between fluoridation of water supplies and sudden infant death syndrome"⁴ purported to exonerate fluoride as a possible contributor to sudden infant death syndrome (SIDS). The authors stated: "Analysis was carried out to find the correlation between variables and then simple linear regression was used." The arbitrary selection of linear regression provided a straight line which is very different from the curve of a paradoxical effect, and led to the erroneous conclusion which their title reflects.

The typical paradoxical effect curve that I have inserted in their figure, reproduced below, shows the increase in deaths when fluoride concentration is in the very low range. Professor A W Burgstahler, of the University of Kansas Department of Chemistry, kindly provided the paradoxical effect curve. This was derived by a computer generated least squares best line fit.

![Paradoxical Effect Curve](Fluoride 30 (2) 1997)

**Figure.** Mean SIDS mortality rates (1980-1984) and median fluoridation in reticulated water supplies for New Zealand health districts.
With paradoxical effects, there can be a critical dose below which one observes an increased adverse effect. The Mitchell et al. data suggest such a situation. Within a low concentration range, there are more infant deaths at the low doses than at the higher doses - an inverse relationship. At concentrations above the low concentration range, dose-responses show the direct, linear relationship with which we are familiar: increasing doses are increasingly toxic until a particular dose kills most or all of the test subjects. So there are two different dose-responses to fluoride - a paradoxical effect at very low levels and a linear relationship at higher levels. These two dose-responses are not mutually exclusive; one does not preclude the other.

Most research which purports to demonstrate the safety of fluoridation has not been concerned with very low concentrations of fluoride, at which paradoxical effects occur, for three reasons. 1) individuals vary significantly in fluoride uptake; 2) there is considerable individual variation; 3) it has been unjustifiably assumed that there is a threshold level, namely, the sacrosanct one part per million in drinking water, below which fluoridation is claimed to be safe. The occurrence of paradoxical effects at very low levels of fluoride means that there is no threshold level below which low-level fluoridation is safe.

It is paradoxical that statistics, employed to assure the validity of conclusions drawn from data, can be responsible for concealing paradoxical effects. The fact that statistical analysis of experimental data does not reveal paradoxical effects does not mean that such phenomena do not exist. On the contrary, statistical methods of analysis can effectively prevent recognition of paradoxical effects if the methods do not consider these phenomena. With scattered points, statistical methods are too frequently used to determine where a straight line should be drawn. Too often, the statistical approach assumes that straight lines are the correct lines. Deviations or irregularities caused by paradoxical effects have too often been attributed to experimental variation or errors.

There are additional reasons why the conclusions of Mitchell et al. are questionable. The variables they considered were SIDS, mean daily temperature and median fluoridation. They did not consider other important variables, especially the significant intake of fluoride from sources other than fluoridated water, and from baby formulas prepared with fluoridated water. In an earlier study, Mitchell and others found a significant correlation between SIDS and non-breast feeding. In this later study, a correlation between mean daily temperature and SIDS was reported. People generally drink more liquids in warmer weather. In neither study did they estimate each infant's total daily fluoride intake.

Another variable they overlooked is general nutrition, especially calcium intake. The consumption of milk, which is the major source of calcium for infants, is especially important. Our research on fluoridation in Chile (like many other studies) showed that malnourished infants comprise the human population that is most susceptible to fluoride toxicity. It is also well known that calcium protects against fluoride. When Salvador Allende MD became president of Chile in 1970, he initiated a government program under which free
milk was delivered daily to pregnant mothers, nursing mothers and every child under the age of 15. At that time, half the children in Chile under 15 years were undernourished, and 600,000 were mentally retarded thorough lack of protein, especially during the first months of life. That was the health status of half the children who were being fluoridated in Chile. I am not implying that malnutrition and/or calcium deficiency were significant factors in SIDS researched by Mitchell et al. No one knows because Mitchell et al did not provide that and other information. To properly evaluate the role of fluoride in SIDS, it is necessary to consider nutrition, especially calcium intake, and total fluoride intake.

Albert Schatz
Professor Emeritus
6907 Sherman Street
Philadelphia
Pennsylvania 19119
USA

REFERENCES
3 Schatz A, Schalscha EB, Schatz V. The occurrence and importance of paradoxical concentration effects in biological systems. Compost Science 5 22-30 1964.
PARADOXICAL EFFECTS

When I studied medicine (1945-1952) our Professor in Internal Diseases speaking about the subject of syphilis (still rampant just after the war) called it a monkey under the diseases, as it was able to mimic nearly every other illness.

We are nearly half a century later and syphilis has dwindled to near non-existence in our country, but another monkey has taken its place. Fluoride medication can and does imitate many other illnesses. (I call fluoride medication an illness because fluoride does not belong in our bodies). The substance is full of paradoxical surprises.

When during the seventies we looked into the physical complaints due to fluoridation of our water supplies (before this measure was forbidden by law) we tried to prove in a scientific way that fluoride was the culprit in skin troubles, gastrointestinal complaints, headaches, arthritis-like complaints, blurred vision, lack of concentration etc, so we started a series of double blind tests.

Some of the patients reacted quite according to plan: Fluoridated water caused the complaints, nonfluoridated water cured them again. On the other hand there existed a minority of patients who reacted in a different way. They did not show their physical effects when they drank the fluoridated water for a short time, but on day 1 of the next nonfluoridated bottle, their complaints suddenly appeared. We called this the rebound effect and afterwards thought that perhaps it could be linked to the general adaptation syndrome of Hans Selye, the patients bounding back in another phase of the syndrome when the fluoride was withdrawn.

Recently I read an article by Professor Schatz about the similarity in physical effects between low level fluoridation and low level radiation, and also about the concept of non-linear relationships. It struck me that here was an elegant way of explaining why sometimes more harmful effects are seen with 1 ppm fluoridated water than with the massive dosage until recently used in the treatment of osteoporosis before that method became obsolete. It can also explain why some patients reacted on dwindling amounts of fluoride.

Moreover, it ties in with the meticulous research by the German scientist L Kolisko, who in his book, *Physiological and Physical Demonstration of the Effect of Extreme Small Dosages*, tells about curious phenomena. He put gladiolus seeds in increasing dilutions of metal-salts and as soon as they had sprouted he planted them and followed their development. He found an undulating curve showing the relationship that existed between, alternatively, growth and flowering inhibition and growth and flowering enhancement when the dilutions slowly increased. Higher dilutions of the rather poisonous metal-salts often gave more severe inhibitions in growth and flowering than lower dilutions. For instance a dilution of 1:1000 could show normal growth and flowering while a dilution of 1:10,000,000,000 gave stunted growth and no flowers. These experiments could be repeated *ad infinitum* and gave the same results.

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It seems probable that the concept of non-linear relationships also ties in with that other most interesting new concept: The "windows in time" as explained by Colborn, Dumanoski and Myers in their book *Our Stolen Future*. They show that a poisonous effect on the fetus can play havoc at a specific short period of the fetal development, a short window in time, while either before or after that window is open, nothing happens at all.

![Growth and flowering inhibition in gladiolus sprouted in 10th and 11th decimal dilutions of iron sulfate. No such effect in previous dilutions.](image)

These new concepts can go far in at last explaining why so many controversial findings exist about the poisonous effects of fluorides.

Hans Moolenburgh  
Oranjeplein 11  
2012 LN Haarlem  
Holland

[Dr Moolenburgh, author of *Fluoride: The Freedom Fight*, describes in that book (pages 81-82, and 103-107) the research, involving double-blind tests, which he and fellow physicians carried out before water fluoridation was made illegal in the Netherlands. The preliminary work was published in this journal: Grimbergen GW. A double blind test for determination of intolerance to fluoridated water (preliminary report). *Fluoride* 7 (3) 146-152 1974. Later findings were presented at the VIth Conference of the International Society for Fluoride Research in Zandvoort, the Netherlands, in February 1976.]

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REPLY TO CRITIQUE

Thank you for drawing our attention to Mr Wilson's comments (Fluoride 30 (1) 71-72 1997) on our paper. The purpose of this study was to contribute some factual information into the ongoing debate on whether communities are becoming exposed to more and more fluoride - and whether this can be considered excessive. The study was only coincidently relevant to previous published papers by Cutress et al (1985) or Colquhoun (1984). Mr Wilson's supposition that this study was set-up to disprove Colquhoun's or any other study is surprising and quite without substance. Anyone knowledgeable on the issue knows full well the difficulties of debating the subject objectively. Reliable and comparable data bases (diets, urine, hair etc) stretching across 30 years are simply not available - this we explained in our paper. Teeth, of course, are the most lasting of human tissues and also a marker of exposure to fluoride during a specific developmental period. Our approach was unique and made possible only because of a collection of teeth with reasonable data on the donors and access to the sophisticated methodology. While Mr. Wilson may be of the opinion that "their latest study itself diminishes support for fluoridation", he provides no logic to support this personal viewpoint. On the other hand we did. Even if our two papers (1985 and 1996) were indeed at variance (which they are not) this would not be a problem. As investigators we are not wedded to a 'conviction' or determined to hold to a conclusion if new evidence advances our knowledge. While we are of the opinion that the need for 1 ppm fluoride in water is less necessary now than 30 years ago we still advocate an average daily exposure to 1 mg fluoride sourced from water and other source, - toothpaste in particular.

Mr. Wilson is, however, correct in identifying some imperfections in the study.

1. Sample size: we would, of course, have wished to include more teeth in the study. Our small numbers were the end result of a careful selection from a large number of teeth taking into consideration age, geographic origin, period of tooth development. A statistically relevant sample size is desirable but not always possible. I would point out that it is not possible to obtain such teeth by mail order; teeth formed in the 1950s are not being made any more! On Mr Wilson's rationale most of the science human anthropology would be discarded based as it is on fragments of bone and teeth from a few individuals.

2. Age and scattergram discrepancies: these are minor matters which do not significantly alter the findings. We are confident that we got it 99%+ right - for Mr Wilson to use these few indiscretions to claim that they, 'lessen any confidence in the conclusions' is a distortion of commonsense.

3. History of teeth: Mr. Wilson does not state what other history details he would find useful. We thought a congratulatory comment would have been in order in recognition of the foresight we had to accumulate, over 35 years, a valuable tooth bank documented with details of age and origins.

4. Credibility of the fluoride content of teeth: we are uncertain of Mr. Wilson's criticism. The value of using F profiles is increased because of the relative short period of development incorporation. The tooth holds a record of F availability during a known, short time frame. This ensures a more precise measure of F exposure over a matter of just a few years. Hence the remarkable consistency of the F profiles we found across the deeper enamel and the dentine. This is in
fact a strength not a weakness of our evaluation procedure. The fluoride locked into the enamel/dentine is a sound marker of the F environment of the time. The fluoride content of the bulk of enamel and dentine remains constant until the tooth is destroyed.

5. Computer generated mean values: the suggestion of the value of computer generated mean values is again for our situation academic. The work involved would have been substantial - when commonsense indicated that differences between visually estimated and computer calculated values would not have been significant.

6. Colquhoun article (1984): reference to this paper was of passing interest as was the balancing reference to Cutress et al (1985). We would take this opportunity to expand and again emphasise the well-known fact (60 years) that fluorosis is associated with the prevalence of fluoride and hence when water level of fluoride naturally occurring in drinking water is supplemented, say upwards to 1 ppm from 0.1 ppm, then the prevalence of very mild fluorosis increases - in fact it becomes the same as in people drinking water with natural levels of 1 ppm fluoride. We saw no reason to engage in, for this paper, irrelevant discussion - a reference was sufficient.

As Mr. Wilson raised the point, we would further comment that our suggestion (1985 paper) that the level of fluoride in drinking could be reduced without risk of caries increasing was based on the present contribution of fluoride from toothpaste. A reduction in water fluoride concentration would probably reduce the prevalence of minor fluorosis which occurs at 1 ppm.

T W Cutress
Wellington School of Medicine
Dental Research Group
PO Box 7343
Wellington South
New Zealand

REJOINDER

In spite of the assurance that the reference to Colquhoun’s 1984 paper¹ was coincidental, the fact remains that they cited this paper, which reported that the prevalence and severity of dental fluorosis has increased, without citing their own 1985 paper,² which reported very similar data. They then presented data in the 1996 paper, which claimed to show only “optimal” fluoride levels.

I thank the authors for providing the logic supporting my statement that “their latest study diminishes support for fluoridation”. Answering the six points:

1. One of the “imperfections” in their study is that the sample sizes are not statistically relevant, which the authors implicitly accept. It follows that the comparison of statistically irrelevant mean values with a “highly debatable” data base is of little value. The authors’ view, about my rationale, of “human” anthropology (are there other kinds?) is wrong. That science has never advocated adding cumulative toxins to water supplies without informed consent.

2. I note the authors’ preference for commonsense rather than accuracy.

3. The authors’ silence, about the availability of more detailed history of fluoride exposure during the teeth development years, again implies the invalidity of this comparative study.
4. It is true that the teeth hold a record of F availability over the development period. However the small sample sizes and insufficient detail of the history of the teeth do not add strength to this particular study.

5. I note again the authors’ preference for the commonsense view rather than accuracy. Computer programs to handle statistical evaluation of this type of data are almost certainly available at any university. I wrote such programs in the 70s and 80s.

6. The 1984 and 1985 papers are of more than passing interest because this 1996 study claimed that fluoride levels are not excessive. The 1984 and 1985 papers reported 3.6% pitted and discoloured teeth and 2.5% occurrence of cosmetically poor or doubtful teeth respectively in fluoridated areas which, according to the 1996 paper, occurred at “optimum levels” of fluoride. This contradicts the assertion that only minor fluorosis ensues at this level, indicating that fluoride levels are indeed excessive. Further, the 1984 and 1985 papers reporting almost identical levels of dental fluorosis (24.9% and 25% respectively) plus the 1985 authors’ admission that “a reduction of the water fluoride concentration would probably reduce the prevalence of minor fluorosis which occurs at 1 ppm”, strongly supports Colquhoun’s position that fluoride levels are too high.

Many people will drink at least two litres of liquid during a hot working day followed by a few drinks with friends after work. It is easy to deduce from first principles that these people will ingest well above 2 mg, when fluoride from food, soft drinks, toothpaste etc is also taken into account. Many fluoride papers resemble the theological debate about how many angels can dance on the head of a pin. Since it is now accepted that the topical effect of fluoride predominates, water fluoridation is unnecessary and the dubious benefits of fluoride can be provided by toothpaste. This would restore free choice to those who have no wish to ingest this cumulative toxin and wish to lessen the environmental pollution by fluoride and its associated heavy metals.

Bill Wilson
118 Forrest Hill Road
North Shore City
Auckland
New Zealand

REFERENCES AND NOTES.

1 Colquhoun J. Disfiguring dental fluorosis in Auckland, New Zealand. Fluoride 17 234-242 1984. (Reported previous year’s survey of dental fluorosis prevalence among 7-12 yr-old children: in fluoridated areas 24.9%, with 10% having front teeth affected and 3.6% having discoloured or pitted enamel; in non-fluoridated areas only 4.9% had very mild fluorosis.)

2. Cutress TW, Suckling GW, Pearce EIF, Ball ME. Defects in tooth enamel in children in fluoridated and non-fluoridated water areas of the Auckland Region. New Zealand Dental Journal 81 12-19 1985. (Reported bilateral “diffuse mottling” prevalence among 9-yr-old children: in fluoridated areas 25%, with 15% having front teeth affected and 2.5% having “cosmetically poor” or “cosmetically doubtful” appearance; in non-fluoridated areas overall prevalence was not reported, but 4.25% had front teeth affected and none of these had cosmetically “poor” or “doubtful” appearance.)
OPTIMAL INTAKE: PROFESSOR JENKINS REPLIES

Dr Foulkes writes (Fluoride 30 73 (1) 1997) that my description of fluoride as an “inessential food constituent with beneficial effects” is based on my belief that fluoride makes a useful contribution to health. I certainly do believe this, being familiar with the world-wide evidence and having seen the effect in my own city of Newcastle upon Tyne. I do not deny, of course, that high doses of fluoride are toxic but if, as Dr Foulkes writes, “there is no minimum safe dose” then the whole human race must be at risk as no human food or drink is entirely free from fluoride. Can Dr Foulkes tell us what the signs and symptoms are of this alleged toxic effect from which he thinks we are all suffering?

G Neil Jenkins
4 Jesmond Dene Terrace
Newcastle upon Tyne
NE2 2ET England

DR FOULKES RESPONDS

Of course, Professor Jenkins is correct in his statement that “no human food or drink is entirely free from fluoride”. But, as he is aware, fluoridation has increased the dietary burden for both those living in fluoridated communities and those who do not, by virtue of the “halo effect”.

Perusal of back issues of Fluoride alone shows a number of possibilities associated with this increased burden. It would require no genius to construct the signs and symptoms that may represent the possible clinical effects. These could range from the obvious dental fluorosis to chronic dyspepsia, tendinitis, stiff back, arthritis, abnormal electrocardiogram, etc. I suggest that he re-read Kaj Roholm’s treatise¹ and recognize that the level of daily fluoride intake that Roholm postulated for osteosclerosis is now reached or exceeded by those who are residents of fluoridated areas for 20 to 40 years.

A problem is encountered in obtaining “proof” of a fluoride etiology for the vague symptoms encountered in medical practice. This requires a high index of suspicion that most physicians lack, and adequate laboratory and imaging resources. In most areas, these are either incompetent or unwilling to participate in confirming a suspicion of chronic fluoride intoxication.

Roholm¹ expressed his difficulty in establishing a minimum dose and time interval for osteofluorosis due to industrial exposure. He did not have to deal with the “paradoxical effect” and the possibility that very low levels of fluoride acting on the fetus may have disastrous effects. It was this latter that inspired my comment regarding the lack of knowledge concerning a minimum safe dose.

Professor Jenkins and I see the fluoridated world in the context of different belief systems. Perhaps we can discuss these some day over a pint in Professor Jenkins’ local or in the Bellingham Marina in 1998.

Richard G Foulkes
PO Box 278
Abbotsford BC
Canada


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With pleasure we learn that Rutgers, the State University of New Jersey, has awarded the Rutgers Medal, the university's highest honor, to Professor Albert Schatz, the microbiologist who, over 50 years ago, discovered the antibiotic streptomycin while working as a graduate student in one of the university's basement laboratories. The antibiotic was subsequently manufactured and used to virtually wipe out the dreaded disease of tuberculosis. The citation which accompanied the medal states:

As a descendant of emigrant farming parents from Czarist Russia, you expressed an early interest in agriculture and soil microbiology. These interests brought you to the College of Agriculture of Rutgers University where you earned your Bachelor of Science degree in soil chemistry, followed by the Doctor of Philosophy degree in soil microbiology after studying under the direction of Professor Selman A Waksman, another emigrant of Czarist Russia. It was during this latter period, in 1944, that you became the co-discoverer of the important antibiotic, streptomycin, the first useful chemotherapeutic substance for the treatment of the "Great White Plague," or tuberculosis. This great discovery was made possible, in part, by your courageous use of virulent pathogenic cultures of Mycobacterium tuberculosis in your bioassay procedures. The isolation of the special strain of Streptomyces griseus that produced streptomycin, followed by its isolation and purification, led to the discovery of its in vivo efficacy against tuberculosis. The worldwide impact of this discovery is now part of medical history. Many institutions and countries have recognized the importance of your discovery and bestowed upon you awards, medals, prizes and honorary degrees. You, thus, have brought distinction and honor to Rutgers, The State University of New Jersey.

By virtue of my office as President of Rutgers, The State University of New Jersey and with deep personal appreciation of your service to mankind, I am pleased to present you the Rutgers University Award for which this medal is the symbol.

Francis L. Lawrence  
President

CALL FOR PAPERS: Members are reminded of the 2nd International Workshop on Fluorosis and Defluoridation of Water, to be held in Addis Ababa, Ethiopia, November 19-22, 1997. Full papers should be submitted before August 15, 1997, to Dr Eli Dahi of the International Organising Committee, Technical University of Denmark, DK-2800, Lyngby, Denmark. Phone +45 45255929 Fax +45 45255922 E-mail cdc@unidp.uni-c.dk  
The Registration fee is US$200 (US$150 for authors).

CORRECTION: In the report “Fluorosis in children and sources of fluoride around Lake Elementaita Region of Kenya” by R W Kahama et al., pages 19-25 in the last issue of Fluoride (February 1997), the concentration expressions \( \mu g/mL^-1 \) and \( \mu g/g^-1 \) throughout the article should be \( \mu g/mL \) and \( \mu g/g \) (without the superscripts). We extend our sincere apologies to the authors and to our readers for having made this error. - The Editors

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Abbreviations or Acronyms. Define, either in brackets or in footnotes, when they first appear.

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