EVALUATION OF FLUOROSIS PREVENTION BY IMPROVEMENT OF WATER QUALITY IN JILIN PROVINCE, CHINA

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Endemic fluorosis in Jilin Province, China is caused by consumption of high fluoride (F)-containing drinking water. In the early 1960s water-improvement projects were initiated to reduce F concentrations in drinking water, working from most severe areas to less severe areas. This study is an evaluation of the social and economic benefits of the water improving project over the last 30 years.

Of the most severe endemic villages 60.6% had water improvement implemented, however, the F content of the water-improving project as a whole was still much higher than the national standard.

Over the last 30 years water improvement has brought substantial health, economic, and social benefits. Three investigations (1980, 1985 and 1991) revealed that the occurrence of bone and dental fluorosis has dropped markedly since the water improvement implementation. The total grain product of the endemic area has increased by 39.6% per person and annual income has increased by 43.5% per person. After water improvement 46.3% of all fluorosis patients investigated recovered their ability to care for themselves. Domestic animals have also been benefited.

While the benefits are great, the water improving task is heavy, the resources are few and the investment insufficient. There are still 2110 endemic villages without water improvement and 177 of these are severe. Fund availability is still the largest obstacle.

INTELLIGENCE AND FLUORIDE EXPOSURE IN NEW ZEALAND CHILDREN

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A birth cohort of 1265 children born in Christchurch in 1977 was studied longitudinally including assessment measures of cognitive ability at ages 8 and 9 years using the Wechsler Intelligence Scale for Children (WISC-R). It was possible to study the association between intelligence and fluoride exposure as approximately half of the sample resided in Waimairi County, fluoridated with 1 ppm of fluoride, while the other half resided in non-fluoridated Christchurch with <0.1 ppm. The children were grouped according to the duration of fluoridation exposure to age 7 years with the groups being exposed for 0, 1-3, 4-6 and 7 years. The mean IQs (WISC-R) at 8 years for these groups were 100.0, 99.04, 99.40 and 100.5 (p>0.30). The values at 9 years were 99.9, 99.3, 98.7 and 101.2 (p>0.70). It was evident that there was no trend for IQ to decline with increasing exposure to fluoridated water. In fact those who lived for 7 years in an area with fluoridated water had the highest mean IQ scores, although this difference was not statistically significant. The results can be seen as being consistent with other studies. In the study by Zhao et al on Chinese children intelligence was impaired with drinking water with 4.12 ppm of fluoride but not with 0.91 ppm. In the rat study by Mullenix et al neurotoxicity was present with plasma fluoride levels of 0.059-0.640 ppm which were seen to be similar to those found in humans of 0.076-0.25 ppm drinking water with 5-10 ppm of fluoride. Thus a threshold effect for fluoride toxicity may be present with demonstrable effects being present with water containing 4-10 ppm but not 1 ppm of fluoride. However, recent work by Varner, Isaacson et al suggests that fluoride may have the potential to cause neurotoxicity at a level of 1 ppm if present with trivalent aluminium ions at a concentration of 0.5 ppm.
DENDAL COSTS NOT AFFECTED BY FLUORIDATION – LARGE-SCALE TOOTH DECAY STUDIES SHOW LACK OF ‘BENEFICIAL’ EFFECTS

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Dental care costs were determined for California residents in 1994 and 1995 among counties with various degrees of fluoridation as tabulated by the California State Department of Health. Of 58 counties reporting, cost data were not available for 3.

Since the average dental costs in counties with large populations are more reliable and less variable, and since reliability varies linearly as the square root of the population considered, dental costs were weighted by the square root of the number of eligible recipients of the county.

The average annual Medi-Cal costs for dental work per eligible recipient was $108.48 in 1994 and $110.06 in 1995 in 33 counties with no fluoridation, $113.97 in 1994 and $107.26 in 1995 for 9 counties (one not reporting) with 0.5-10% fluoridation, $125.50 in 1994 and $123.70 in 1995 for 9 counties with 11-40% fluoridation, and $120.01 in 1994 and $125.27 in 1995 for 3 counties with 91-100% fluoridation. Of the three counties with 41-90% fluoridation, only one reported with the necessary data: $96.43 in 1994 and $97.32 in 1995.

Unweighted data showed relatively lower dental costs in nonfluoridated areas. This is due to the generally lower dental costs in counties of low population, which are predominately nonfluoridated. Thus, the 10 large comparably sized counties with 0-10% fluoridation had dental costs of $123.46 in 1994 and $124.45 in 1995 compared to dental costs of $120.01 in 1994 and $125.27 in 1995 for three counties with 90-100% fluoridation.

These data were evaluated in comparison with other large-scale studies. The study done by Yiamouyiannis using 1986/87 data from the U.S. Public Health Service showed a tooth decay rate of 2.06 DMFT and this study showed a 1994/1995 dental cost figure of $141.40 for Los Angeles (5.3% fluoridated) compared to a 1986/87 tooth decay rate of 1.91 DMFT and a 1994/95 dental cost figure of $144.41 for San Francisco (100% fluoridated).

CHRONIC FLUORIDE POISONING IN RURAL AREAS OF JALINGXl PROVINCE, CHINA. 2. PREVALENCE OF DENTAL FLUOROSIS

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In this study, the relationship between fluoride (F) concentrations in drinking water and prevalence of dental fluorosis was investigated in the chronic fluoride endemic areas of Jiangxi Province, China.

Two hundred and two school children, age 8 to 13 (mean age: 10.6), born and raised in these areas, were selected for dental examinations. Prevalence of dental fluorosis was examined according to the Dean's classification. Community fluorosis index (CFI) for dental fluorosis was calculated. The F concentrations in drinking water were determined using an apparatus of flow-injection analysis with a fluoride ion-selective electrode as a detector.

The caries prevalence of the subjects was found to be 51.0% and extremely low compared with that of Japanese school children. The prevalence of dental fluorosis was found to be 73%. The CFI of the area was 1.87. The mean and standard deviation of F concentrations in drinking water were 0.85±0.84 mg/L, ranging from 0.08 to 4.20 mg/L.

A correlation was confirmed between the F levels in drinking water and the severity of dental fluorosis. This suggests that F in drinking water could contribute to dental fluorosis in these areas.
HEALTH EFFECTS OF FLUORIDE POLLUTION CAUSED BY COAL BURNING IN CHINA. 2. EXPOSURE TO FLUORIDE OBSERVED IN TERMS OF DENTAL FLUOROSIS

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Absorption of fluoride (F) into the human body is known to be an inhibitor of tooth formation. Dental examinations on patients were performed deep in the mountains of the southwestern Chinese province of Guizhou to examine the degrees to which schoolchildren aged 8-15 yr and their parents had been exposed to F during the phase of tooth formation. The findings show that about 30% of the children suffered from severe dental fluorosis with a defective tooth structure. In sharp contrast, children with a normal tooth structure accounted for about 10%. Almost every child did not have dental caries. It is evident, therefore, that the degree of exposure differs markedly, depending on the individual response even in one and the same area. A comparison between children and their parents reveals that the prevalence of dental fluorosis was 50% greater in the children than in the parents. From this finding, it is clear that the degree of the children’s exposure to environmental F during tooth eruption was greater than that of the parents.

HEALTH SURVEY OF WORKERS OF AN ALUMINUM PLANT IN JIANGXI PROVINCE, CHINA. 2. BONE MINERAL DENSITY

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The effect of airborne fluoride (F) on bone mineral density of workers of an aluminum plant in Jiangxi Province, China, was investigated. The subjects were 154 male workers aged 21 to 66 (mean 35.7 years).

Bone mineral density values of the left radial distal part were measured using a DXA apparatus (DTX-200, Osteometer Company).

The time workers spent doing electrolysis work was estimated. By summing these time periods, a F exposure period for each individual was made. The relationship between exposure period to airborne F and the bone density value of workers was examined. For determination of airborne F levels, 24 air samples were taken from different sites of the potroom. The average total F level in the air of the workplace was 0.55 mg/m³.

A significant negative correlation was observed (\(\gamma = -0.196\)) between disclosure period and radial bone density as well as between age and bone density (\(\gamma = -0.202\)). The relationship between disclosure period and radial bone density is considered to depend on age as older workers experience longer refinery exposure. It is concluded that at the aluminum plant airborne F does not exert an influence on bone density of the workers.
HOW FAST DOES FLUORIDE ACCUMULATE IN HUMAN BONES?  
A REVIEW AND NEW EVIDENCE FROM THE UK

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No official monitoring of fluoride (F) intake has been undertaken in the UK, despite repeated authoritative recommendations to do so. Templegarth Trust therefore in 1990 funded modern laboratory equipment for use by Good HealthKeeping in the largely unfluoridated East Midlands. Urinary samples from all clients were assayed for F concentration. A proportion were asked to provide 24-hour urine samples for repeat examination.

The results from 648 individuals whose water F status was known indicated sizeable minorities receiving more than 3 mg F daily - 14% in non-fluoridated and 17% in fluoridated areas. These findings prompted us to solicit urine samples from the largest and longest-fluoridated region of the UK (the West Midlands). Of the 151 samples analyzed to date, 60% indicated consumption of 3 mg F daily or more, in a bimodal distribution.

A literature review included the principal references cited by the British Fluoridation Society Ltd in support of the safety of fluoridation. Discrepancies came to light between the findings of Roholm and their interpretation by Hodge up to 1979 and thereafter, which have resulted in errors 2-3 times greater in estimates of the level of F tolerable by humans.

The most important issue, however, concerns the criterion of safety. Industrial fluorides, far more toxic than calcium fluoride salts found naturally, have not yet been regularly consumed for longer than 50 years, anywhere in the world. Since fluorides accumulate lifelong, we have yet to learn the effects of consuming artificial fluorides continuously for an entire lifetime. The danger depends on the rate of accumulation and therefore of consumption. Calculations will be presented that suggest 3 mg F/day is a figure that should never be exceeded, since it virtually guarantees (on present knowledge) a high prevalence of skeletal pathology by age 70.

If artificial fluoridation results in skeletal F accumulation sufficient to damage skeletal health within a normal lifetime, as these considerations suggest, then it should be stopped.

THE IMPACT OF WATER-BORNE FLUORIDE ON BONE DENSITY

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The aim of this study was: (1) to determine the fluoride (F) levels in urine and hair of persons with known water F intake and documented bone mineral density, and (2) to assess whether a correlation exists between bone density and the levels of F in drinking water, urine, and hair.

For this purpose, 282 patients, mostly females, age 24-77 (mean 50), from the Gdansk region were selected. The mineral bone density of left femur bone and vertebra L₂ - L₄ was measured with a Lunar Expert densitometer. Urine and hair samples from the occipital part of the scalp as well as samples of drinking water were collected from these subjects. Fluoride contents in drinking water and urine samples were determined directly after dilution with equal volumes of TISAB. The hair samples were washed and digested with NaOH solution. Fluoride concentrations were measured potentiometrically using a F-specific electrode.

The mean F concentration in water, urine, and hair samples was 1.94 mg/L (range: 0.325-3.07), 2.43 mg/L (range: 0.77-5.35), and 11.41 µg/g (range: 4.13-14.51), respectively. The bone mineral density of vertebra and femur bone was 1.16 g/m³ (range: 0.97-1.39) and 1.01 g/m³ (range: 0.86-1.14), respectively. Positive correlations were found between water F content and bone density (r = 0.366), urinary F content and bone density (r = 0.300), water and urinary F content (r = 0.739), and water and hair F content (r = 0.510), respectively. A negative correlation was found between age and bone density (r = -0.293).

The results of this study indicate that F contents in drinking water as well as in urine and hair have an impact on bone density.
The objective of this study was to examine the changes in the bone, articular cartilage and joint capsules, and intervertebral discs in rats administered with sodium fluoride. The joint was evaluated as a functional unit of articular cartilage, capsule, and subchondral bone tissue and the changes were interpreted from this complex functional point of view. Methods, results, conclusions and interpretation based on previously published works (1-9) are summarized and documented in detail.

Diarthrodial joints have to be considered as functional units of synovial membrane, articular cartilage and subchondral bone tissue. Any changes, or pathological processes in one of these structures may affect consecutive alterations in other tissue components of the involved joints. For example, fragments of articular cartilage cause reactive, secondary synovitis. During the inflammatory process cytokines and enzymes (matrix metalloproteinases - MMPs) are released which further increase the enzymatic destruction of cartilage. The action of tissue inhibitors of MMPs (TIMPs), and the balance between MMPs and TIMPs should also be considered. The damaged articular surface becomes overloaded (unchanged load acting on a smaller intact, congruent surface); the subchondral bone trabeculae may collapse, with rupture of perforating arteries, accompanied by secondary osteonecrosis in small areas. The damaged blood supply in the articular cartilage may cause focal, scattered necrosis of chondrocytes, etc. These vicious circles lead to progressive destruction of the affected joint with the driving circle depending on the primary joint disease. These interrelated processes are schematically summarized in Figure 1.

The morphological changes and destruction of the joint, the speed of progression, the clinical signs and limitation in movement, the complaints and tolerance of pain are also variable and show great individual differences.

FIGURE 1

\[\text{FIGURE 1}\]
HEALTH EFFECTS OF FLUORIDE POLLUTION CAUSED BY COAL BURNING IN CHINA. 3. SKELETAL FLUOROSIS

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The effects of airborne fluoride (F) pollution on the bone health of residents from three coal burning areas in China were studied. For this purpose, the residents from three rural areas with varying degrees of fluoride pollution were selected. The study areas included Xaochang Village in Sichuan Province, known as one of the most polluted areas in China; Minzhu Village in Guizhou Province, a moderately polluted area; and Wanli Village in Jiangxi Province (control), which has the least air pollution problems among the three areas studied. Most of the subjects were in their 40s and 50s and had lived in the same areas since childhood.

All the subjects received x-ray examinations of the skeletal system, including the forearms and lower legs. In addition, the subjects from Xaochang and Minzhu villages received x-ray examinations of the lumbar spine and pelvic bone.

Forty-five out of 49 subjects from Xaochang Village, and 25 out of 49 subjects from Minzhu Village were classified into Stage 3 (severe), according to Singh and Jolly’s classification. In the control area, none of the 47 subjects were classified into Stage 2 or 3. Among the subjects from Xaochang Village, prevalence of dental and skeletal fluorosis was well correlated: 37 out of 41 subjects exhibiting Grades 3 and 4 dental fluorosis showed Stage 3 skeletal fluorosis. In contrast, the results from Minzhu Village residents showed only a weak correlation (5/17). These observations suggest that most of the residents in Xaochang Village may have been exposed to airborne fluoride pollution since childhood, whereas the residents in Minzhu Village may not have been.

PREVENTION OF IODINE DEFICIENCY IN HIGH FLUORIDE AREAS IN TIANJIN CITY, CHINA

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In this paper we studied the efficiency of supplying iodized salt as measured by the incidence of goiter in high-fluoride areas of Tianjin, China. Data before (1994) and after (1997) the provision of iodized salt was compared. The study began in 1994 by dividing the city into 5 areas (north, south, east, west and central). A total of 5281 school children, 8 to 10 years of age, from 50 primary schools were examined for goiter and urinary iodine (I₂) content. Levels of I₂ in the supplied salt was also determined. The study was repeated in 1997, two years after iodized salt had been supplemented. Occurrence of goiter dropped from 28.8% in 1994 to 19.1% in 1997. The levels of I₂ in urine doubled from 128 mg/L in 1994 to 268 mg/L in 1997. Of the salt samples taken from the pupil’s homes, 90.8% met the national standard for iodine content with the average content being 50.4±24.7 mg/L. The results indicate that the levels of I₂ in salt and urine are up to national standards for normal metabolism and that these increased levels are causing a decrease in the occurrence of goiter. However, the goiter incidence rate is still higher than the 5% standard, but this could be time related as goiter responds slowly to treatment. Our primary conclusion is that I₂ absorption by the thyroid is competitively inhibited by F, especially in high-fluoride areas, and is alleviated by the provision of iodized salt.
INFLUENCE OF TIME AND SOIL ENVIRONMENT ON FLUORINE ACCUMULATION IN BONES FROM ARCHEOLOGICAL EXCAVATIONS IN POLAND

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One of the basic factors influencing fluorine (F) accumulation in human bones is the length of time the bones rest in the ground. The second important factor may be the type of soil, particularly the content of F compounds that can penetrate the bone tissue. The purpose of this paper was to determine the influence of soil type on F accumulation in human skulls stemming from archeological excavations in Poland, over various time durations. The studies were performed on 188 human skulls obtained from collections owned by Polish Academy of Sciences and the Department of Anthropology at the University of Wroclaw (Poland).

Soil samples were taken from localities where the skulls had been found for determination of F content. In this way two groups of soil were isolated and classified. In the first soil group the F content was about 150 mg/kg of dry soil, while in the second soil group the F content was on the average 420 mg/kg. In each of these soil groups the F content was analyzed in the excavated human skulls according to the time they were buried in the soil. Thus, the possibility was created to determine two parameters of F accumulation simultaneously, the length of time deposited in the soil as well as the F content of the soil.

In group I where the F content in soil was 150 mg F/kg, there were 4 localities in abbreviation marked as Lu200, Sy700, Sa1000, Zh4500 (the numeric index denotes the time of skulls having remained in the soil). In group II with soil F content of 420 mg F/kg there were 3 localities being marked as W500, C700, G800. In two (Sy700, C700) of the 7 analyzed localities, the deposition time of skulls in the ground was equal (700 years), but the soils differed with regard to F content, being 150 mg/kg and 420 mg/kg respectively. In this situation a larger amount of F in the skulls was found where the amount of F in the soil was higher. The time parameter behaves in another way. The skulls buried a longer time in soil with lower content of F (150 mg/kg) displayed more F than the skulls resting shorter in the soil with greater amount of F (420 mg F/kg). In conclusion it may be ascertained that the main parameter influencing F accumulation in bones stemming from archeological excavations is the duration of deposition in the soil. The second parameter regarding the significance in F accumulation in bones is F content in the soil.

REVIEW OF OSTEOPOROSIS AND THE ROLES OF FLUORIDE, SEX HORMONES AND BISPHOSPHONATES

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Osteoporosis is a common and important cause of morbidity and mortality among post-menopausal women, particularly in industrialized countries. It occurs as a consequence of progressive loss of bone and results in increased risk of fracture. Present conventional therapies are primarily directed at inhibition of bone resorption. They cannot, however, reverse or repair bone loss. At the present time, research continues concerning the mechanisms by which bone mass and trabecular microarchitecture can be restored. In this context, the roles of F, sex hormones and bisphosphonates will be reviewed and evaluated. In addition, the various diagnostic techniques of early bone loss will be reviewed, as well as the various factors that impact on this multifactorial metabolic bone disorder.
FLUORIDE CONCENTRATION IN BONE INFLUENCES PERIPROSTHETIC BONE MINERAL LOSS AFTER UNCEMENTED TOTAL HIP ARTHROPLASTY

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Factors influencing bone remodeling after cementless total hip arthroplasty (THA) with Parhofer prosthesis (Aesculap, Tuttlingen, Germany) were evaluated in a longitudinal study of 18 hips in 18 patients (14 females and 4 males, aged 42-76 years) who had undergone uncemented THA due to osteoarthritis.

Bone mineral density (BMD) in the femoral neck was determined by dual-energy X-ray absorptiometry (DXA) with a Lunar DPX-L densitometer (Lunar Co, Wisconsin, USA) preoperatively. DXA measurements in seven regions of interests (Gruen zones) were performed prospectively 2 weeks, 3, 6, 12 and 24 months after operative treatment.

The concentrations of calcium, magnesium and fluoride were measured in cortical and trabecular bone samples taken intraoperatively from the resected femoral head and neck. The fluoride concentration was measured with "Orion" fluoride ion-selective electrode after dissolving the prepared bone pieces in perchloric acid; calcium and magnesium concentrations were measured by mass absorption spectrometry.

Neither the bone mineral density nor bone fluoride, calcium and magnesium concentrations correlated with patient’s age.

At 12 months after the operation, the regional BMD in all seven zones showed a maximal significant decrease ranging from 7.3 to 38.8% of BMD present at 2 weeks postoperatively. Thereafter the bone density appeared to be stabilized. The most significant postoperative bone loss (12.1-38.8%) was found in the calcar area. The cortical zone below the prosthesis showed lower but still significant decreases (7.3-18.1%).

The analysis of preoperative femoral neck BMD and fluoride content in trabecular bone proved that osteopenia and lower fluoride concentrations correlated significantly with more bone density reduction after THA. No other factors (age, weight, sex, calcium and magnesium concentrations in bone and fluoride concentration in cortical bone) showed significant associations.
RELATIONSHIP OF BONE DENSITY OF THIRD METACARPAL AND PROXIMAL PHALANX TO MENOPAUSE IN POPULATIONS WITH AND WITHOUT ENDEMIC FLUOROSIS

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The present study was conducted to examine the differences in bone mass between urban and suburban women before and after menopause by measuring fluoride (F) levels in urine, bone morphometry, and bone mineral content of the third metacarpal and proximal phalanx. The subjects under study were 186 women age 40 to 59 in the urban and suburban communities near Beijing, China. The urban cohort consisted of 56 premenopausal women (mean age 44.5±4.3) and 35 postmenopausal women (mean age 53.3±3.2), while the suburban cohort consisted of 49 premenopausal women (mean age 45.1±3.4) and 46 postmenopausal women (mean age 52.9±3.6). The suburban residents had been exposed to excessive levels of F in the drinking water for 10-15 years. Quantitative analyses of the midshaft of the third metacarpal and proximal phalanx were made with a DIP method.

The urinary F levels were 0.92-1.16 mg/L higher in the suburban subjects than in the urban subjects, irrespective of menstrual history. There was no evidence of F involvement in the third metacarpal of the suburban subjects. Morphometry revealed marked changes in bone morphometry between pre- and postmenopausal women in the urban cohort. In either community, the values for bone mineral content and bone density were significantly larger in the premenopausal women than in the postmenopausal women, and there was little difference between the two communities. The effects of F on the third proximal phalanx were clearly reflected in the combined cortical bone thickness and metacarpal index, but not in the bone mineral contents.

Fluoride accumulated in the skeleton is released into urine over a long period of time. Our findings suggest that F at 1-2 mg/L affected the bone mineral content and bone density in the hand differently.
INCIDENCE OF CARDIOVASCULAR ABNORMALITIES IN ENDEMIC SKELETAL FLUOROSIS

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Approximately 20 million people in India are afflicted with endemic skeletal fluorosis (ESF). ESF is often associated with secondary hyperparathyroidism. Primary and secondary hyperparathyroidism have been implicated for increased cardiovascular mortality in western population. This prospective study was designed to detect abnormalities in cardiac muscle, valves, and myocardial function. Complete, two dimensional transthoracic echocardiography (by 2 independent observers in a blinded manner) was used to evaluate myocardial mechanical performance, thickness of left ventricular wall, and myocardial calcification in 37 consecutive patients, age 14-56 (16 males, 21 females), with moderate to severe ESF. Twenty age-matched controls from non-endemic area were similarly studied simultaneously. Baseline screening included complete history, physical examination, skeletal radiology, QCT spine, sonography of the abdomen, 12 leads electrocardiogram and echocardiography. At least three consecutive blood pressure readings were taken. Baseline biochemical studies included serum total and ionized calcium, fluoride, phosphate, creatinine, alkaline phosphatase, iPTH, urine 24 h-calcium, phosphorus, creatinine, cAMP and drinking water fluoride. None had associated diseases, such as diabetes, affecting cardiovascular functions.

ESF patients had higher systolic blood pressure and increased left atrial diameter than controls (P<0.05). Mitral valve calcification (38%) and aortic valve calcification (14%) were detected in ESF group while none of the controls had these abnormalities. Myocardial calcific deposits were not recorded in any subjects. No significant differences in left ventricular ejection fraction, end diastolic left ventricular posterior wall, interventricular septal thickness, or QTc alterations were noted. Significant reduction in systolic blood pressure was recorded with daily intake of calcium (1 g calcium carbonate) and vitamin-D (0.25 mg 1oD3, Panacea) supplementation in ESF (p<0.01) after 4-6 months follow up. Our study suggests that patients with ESF should be regularly assessed for cardiovascular abnormalities.

FAST RESPONSE TO FLUORIDE IN HUMANS

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Since 1969 we have been studying the effect of fluoride (F) on osteoporotic patients treated with sodium fluoride (NaF) and on patients suffering from industrial fluorosis. We have reported our results in several ISFR conferences.

In two prospective studies in 1990 and 1992, we treated 82 and 102 osteoporotic patients with 60-80 mg NaF/d and 50-70 mg NaF/d, respectively. In both studies we found a positive effect of the treatment (subjectively, clinically, radiologically, fracture rate) in 85% and 82% of the two studies, respectively. The effective treatment time was 26.5 months on the average, but we also found fast responses in 20% of the first study and 15% of the second study after the treatment of 13 months. We confirmed this fast response by X-ray findings (reossification), a relatively subjective method.

Since 1990 we have used DEXA (Dual Energy X-ray Absorptiometry) for monitoring the fluoride therapy of osteoporosis. Generally, the aim of the F therapy is to increase bone mineral density (BMD) 8-10% per year. In the last 4 years in 7 patients we observed a strong increase of BMD of 24.4 to 43 per cent after 12 to 17 months of treatment.

This fast response was combined with some adverse effects (femoral neck fracture, stress fractures, lower leg pain syndrome) and high fasting F levels in the serum. This fast response adverse effects could be avoided by careful monitoring of the F therapy by DEXA measuring every 12 months and the control of the fasting serum F level every 4 months.

Also in cases of industrial fluorosis we observed a so-called fast responder, i.e., a stage I fluorosis developed after 9 years exposure to F in comparison with the average exposure time of 15 years for stage I. In this case as fast as the bone mineral density (osteosclerosis) increased (9 years) it decreased (6½ years) rapidly after cessation of the F exposure. This fast response is the result of an individual's reaction to F.
NEUROLOGICAL EFFECTS:

FLUORIDE AND THE BRAIN: HIDDEN “HALO” EFFECTS

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Our laboratory studies linking fluoride (F) with alterations in behavior and other studies spotlight the impact of F and/or fluorite on central nervous system (CNS) function. The F-CNS link is a concern for certain clinical therapies and environmental exposures (i.e., those involving anticholinesterases). Risks emerge whenever: 1) multiple sources are allowed to contribute to the body burden of F; 2) fluorination is used to “enhance” biological activity; and 3) side effects are induced such that a predisposition to F toxicity is common.

Long-term administration of adrenocortical steroids, such as dexamethasone in the treatment of childhood leukemia, is a therapy where the F-CNS link may apply. The treated population is susceptible to dental problems and frequently given F. Use of dexamethasone instead of prednisolone is increasing because of its greater cytotoxic effects and penetration into the brain. Both steroids interfere with calcium (Ca) uptake in the gut and increase Ca excretion by the kidney. Decreased total body Ca stores are known to alter susceptibility to the effects of F. Furthermore, the chemical structure of dexamethasone differs from that of prednisolone by a fluorine in the 9a position of the ring B and a methyl group at C 16 on ring D. In humans, the behavioral effects of such fluorination are unknown, as is whether or not F' ions are released when dexamethasone is metabolized. In contrast, rats have multiple pathways for microsomal NADPH-dependent biodehalogenation, any of which can free F' ions.

With respect to behavior, we found that the fluorinated and nonfluorinated steroids were not equal. Behavioral outcome was measured in 6 week-old male rats given either prednisolone (18 mg/kg, s.c.) or dexamethasone (1 mg/kg, s.c.) on postnatal days 17 and 18. Dexamethasone resulted in 23 significant changes in motor act initiations, total time, and time structures, whereas prednisolone changed only 7. Thus, attempts to minimize behavioral problems in this therapy may require further investigation into the role of F.

ALTERATIONS IN NEURONAL AND CEREBROVASCULAR INTEGRITY IN RATS CHRONICALLY ADMINISTERED ALUMINUM-FLUORIDE OR SODIUM-FLUORIDE

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Long-Evans rats were administered one of three treatments for 52 weeks: the control group was administered distilled deionized drinking water (ddw); the AlF3 group received ddw with 0.5 ppm AlF3; and the NaF group received ddw with 2.1 ppm NaF containing the equivalent amount of fluoride as in the AlF3 water. Tissue aluminum levels of brain, liver and kidney were assessed with the direct current plasma technique and its relative distribution in brain and kidney was assessed with histochemistry. In addition to routine histological assessments of brain, kidney, liver, and spleen, sections of brain were immunostained for β-amyloid, amyloid A, and IgM to assess the integrity of the cerebrovasculature. The aluminum levels in brain and kidney were higher in both the AlF3 and NaF groups relative to controls. The extent of alterations in neuronal density and the cerebrovasculature were greater in animals in the AlF3 group than in the NaF group, and greater in the NaF group than in controls.
NEUROTOXICITY OF FLUORIDE IN RATS - NEUROPATHOLOGICAL STUDIES
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The purpose of this study was to investigate the neuropathological changes in rats administered sodium fluoride (NaF) in drinking water. Sixty male rats of Wistar strain were divided into 4 groups. Animals in Group 1 (control) were given ordinary drinking water, whereas those in Groups 2, 3, and 4 were given 60 ppm NaF in drinking water for 21, 42, and 63 days, respectively. At the end of the experiment, the animals were sacrificed under anesthetic ether, and the brains were separated for F determination and neuropathological studies. Tissue F was determined chromatographically, and the results were given as µM F/g protein. Tissue protein content was determined by Lowry's method.

The levels of F in Group 2 rats were significantly higher than in other groups (p<0.05), but there were no significant differences between Groups 3 and 4 and between these two groups and the control. A neuropathological study and computerized morphometric analyses revealed a marked shrinkage of cerebellar granular and Purkinje cells, perivascular myelin swelling, and astroglia reaction, especially in the white matter of brains in the NaF-treated animals. Neuronal and myelin changes appeared to be more pronounced in Group 2 animals than in others (p<0.01), but astroglia reaction was similar to each other in all groups.

This investigation shows that F neurotoxicity in rats may be greater in the early stage of intoxication.

EFFECTS OF FLUORIDE ON THE PHYSIOLOGY OF THE PINEAL GLAND IN THE MONGOLIAN GERBIL MERIONES UNGUICULATUS
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The human pineal gland avidly attracts fluoride (F) from the bloodstream because the gland calcifies physiologically (even in childhood) as hydroxyapatite. For example, hydroxyapatite in the aged human pineal gland contains 8900±7700 mg F/kg. The child's pineal gland is exposed to F at an earlier age and at higher levels following the prophylactic use of fluorides in pediatric dentistry. Does this affect metabolism? Melatonin, the main pineal hormone, has several putative functions including suppression of the reproductive axis. Infants and prepubescent children have the highest nocturnal plasma melatonin concentrations. The aims of this study were to determine whether F alters (i) pineal secretion of melatonin during puberty, and (ii) the age of sexual maturation in experimental animals. To accomplish the aims, the gerbil Meriones unguiculatus was used as the animal model.

Animals were divided into two groups, low-fluoride (LF) and high-fluoride (HF), (12 females, 12 males/group), received food containing 7 and 37 mg F/kg, respectively, and distilled water ad libitum, after weaning at 24 days. In addition, the HF pups received 2.3 µg F/g BW/day orally at 1-23 days. At 7, 9, 11.5, and 16 weeks (at prepubescence, through reproductive maturity, 9-12 weeks, to young adulthood), the urinary excretion of the major Melatonin metabolite, 6-sulphatoxymelatonin (aMT6s), was measured at 3-hourly intervals over 48 hours using radioimmunoassay. Body weight, age at vaginal opening and area of the ventral gland were used as indices of pubertal development. Lighting was 12L:12D. The HF group excreted significantly less urinary aMT6s than the LF group (p<0.01): males at 7, 9, and 11.5 weeks; females at 7 and 9 weeks. Compared to the LF females, HF females were heavier at 7 weeks (p<0.004), ventral glands differentiated earlier (p<0.004); age of vaginal opening occurred earlier (p<0.01). In conclusion, fluoride inhibits pineal gland melatonin synthesis in the immature gerbil. This is associated with an accelerated onset of pubertal development on the female gerbil. If these results can be extrapolated to humans, high plasma-fluoride levels during early childhood may be a contributory factor in the current decline in the age of puberty.