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**AN EPIDEMIOLOGICAL STUDY OF THE EFFECT OF FLUORIDES IN DRINKING WATER
ON THE FREQUENCY OF SLIPPED CAPITAL FEMORAL EPIPHYSIS†**

Slipped epiphysis of the head of the femur is one of the common orthopedic disorders of adolescents, yet little is known of its etiology. Various factors have been suggested as the cause of slipped epiphysis, including abnormalities of the bone or cartilage in the head of the femur¹⁻³¹ such as those brought about by endocrine irregularities,^{3,7,9-11,16,18,19,23-26,28-31} trauma,^{5,31-33} mechanical factors^{7,12,28,34-36} and heredity.³⁷ However, in view of the many anatomic and physiological changes which take place in an adolescent, it would seem likely that a variety of factors, rather than any single etiologic agent, are actually involved in its causation. One factor not mentioned in the literature is fluoride in drinking water, which could explain in part the low frequency of slipped epiphysis reported by orthopedists in the Southwestern region of the United States,³⁸ where many communities have natural fluorides in their water supply. There is some evidence that fluorides in drinking water protect against such bone diseases of adults as osteoporosis, collapsed vertebrae, and fractures,³⁹⁻⁴¹ although results from two studies^{39,42} have suggested that fluoride levels of higher than the 1 part per million (ppm) recommended for protection of teeth may be necessary before a reduction in incidence of bone diseases occurs.

Animal experimentation indicates that there may be some basis for considering the possibility that fluorides protect against slipped epiphysis. It has been found that fluoride is deposited more rapidly in the bones of young growing rats than in mature rats,⁴³⁻⁴⁶ that fluoride tends to go to the regions of greater bone growth and better blood supply,⁴⁷⁻⁴⁹ that more fluoride is deposited in the epiphysis than in the diaphysis of long bones,^{47,49,50} and that the area of greatest concentration of fluorides, at least immediately following administration, is in the region of the epiphyseal cartilage, probably in the most recently calcified bone just below the epiphyseal plate.⁴⁷

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In addition, the ingestion of large quantities of fluoride has been reported to have had beneficial effects on patients with multiple myeloma,⁵¹⁻⁵⁴ and to have resulted in positive calcium balance in patients with osteoporosis and Paget's disease, producing increases in bone mineralization and accretion rates.⁶⁵⁻⁶⁴ These findings, which are based on small numbers of patients, have been disputed,⁶⁵⁻⁶⁷ and cannot be considered definitive. Some authors⁶⁸⁻⁷² have emphasized the importance of dosage and suggest that a threshold may have to be reached before fluoride has a demonstrable effect on bone.

In a slipped epiphysis the actual separation usually takes place through the layer of hypertrophied cartilage cells adjacent to the zone of calcified cartilage of the epiphyseal plate.^{21,73-76} A possible increased rate of mineralization from exposure to fluorides could result in a stronger link between the calcified cartilage and the layer of hypertrophied cartilage cells, thus decreasing the likelihood of a slipped epiphysis.

Since there is some evidence, both from epidemiological and laboratory studies, that fluoride contributes to stronger bones, and since within the bone slipped epiphysis occurs in an area which is known to take up much fluoride when it is available, it seemed reasonable to postulate that fluorides might protect against slipped epiphysis.

This paper describes a study which tests the hypothesis that fluorides in community water supplies protect against slipped capital femoral epiphysis. Because of the possibility that a threshold level of fluorides exists below which no effect might be seen, this hypothesis was examined in Connecticut, where some communities have water supplies with artificial fluoridation of 1 ppm, as well as in the Southwestern United States, where many towns have natural fluorides in their water supplies, including some with levels of 2 ppm or more.

METHODS

The ascertainment of cases and controls and the methods of estimating incidence in Connecticut⁷⁷ and in Southwestern United States⁷⁸ have been described previously. Briefly, cases of slipped epiphysis diagnosed among Connecticut residents during the years 1960-1966 were determined by means of diagnostic indexes in all general hospitals in and near the state and in the Newington Hospital for Children, which admits patients from all over Connecticut for relatively long-term care. In a probability sample of Connecticut general hospitals, cases were also located by means of operating room log books. By using both sources of cases, an estimate was made of the ratio of the total number of cases found from the diagnostic indexes and the operating room log books to the number of cases found from the diagnostic indexes for the hospitals in the sample. This ratio was used to estimate the total number of cases diagnosed in all Connecticut general hospitals. Cases among Connecticut residents found in out-of-state hospitals and in the Newington Hospital for Children were added to this to provide an estimate of incidence of slipped epiphysis among all Connecticut residents, and among

those living in communities with fluoridated and non-fluoridated water supplies. In all, 253 cases among Connecticut residents were ascertained and 286 cases were estimated to have occurred from 1960 to 1966.

The populations at risk in towns with fluoridated water supplies and in towns without fluoridation were considered to be all persons under age 25 years living in these areas during the years 1960-1966. The total number of child-years at risk was estimated by applying the rates of increase indicated by school enrollment figures for these communities during the years 1961-1966 to the population enumerated in the 1960 census.

In order to permit further comparison of cases with other children of their age, three matched control groups were chosen for the slipped epiphysis cases in certain hospitals:

1. Orthopedic controls: in seven hospitals, the next patient admitted to an orthopedic service after the slipped epiphysis patient, of the same sex and age (within two years).
2. Other controls: in seven hospitals, the next patient admitted to any other service after the slipped epiphysis patient, of the same sex and age (within two years).
3. Cancer controls: patients reported to the Connecticut Tumor Registry by the fourteen general hospitals in which both the diagnostic index and operating room log book had been used, matched to slipped epiphysis patients by age (within three years), sex, and time of diagnosis (within one year).*

It was believed that although incidence estimates by the ratio method and differences seen in a single case-control comparison are each subject to slight error and bias, any trends consistently found in all of these types of data are likely to be real. Also, one of the control groups, the "cancer" controls, came from a different source (the Connecticut Tumor Registry) from the other two (the same hospitals as the cases), so that the selective factors operating in one group are not likely to be the same as those operating in the others.

Communities in Connecticut which had artificially fluoridated water supplies (all of which were at the level of 1 ppm fluoride), along with the date fluoridation was initiated, are listed in *Fluoridation Census 1966*;⁷⁹ all other Connecticut municipalities had negligible amounts of natural fluorides in their water.^{80,81} Thus, Connecticut cases and controls could be classified as residing either in communities with 1 ppm fluoride in their water supplies or in communities with negligible amounts of fluoride in their water. Although the water supplies of a few small Connecticut towns were fluoridated before 1960, fluorides were first added to the water of the populous Hartford area in January 1960, so that a possible effect would probably not be apparent until 1960 or later. No communities in Connecticut had their water supplies fluoridated between 1961 and 1966 inclusive.

In the Southwestern part of the country, 19 general hospitals and two hospitals for crippled children were selected for study. Hospitals were chosen which would be most likely to serve patients from some communities with relatively high levels of fluorides in their drinking water in Arizona, Colorado, New Mexico, and Western Texas. Diagnostic indexes and operating room log books were searched in all hospitals to find cases diagnosed during the years 1953-1967; a total of 179 cases was found. Orthopedic and other controls were selected in a manner similar to that used in Connecticut. No cancer controls, however, were available. In the Carrie Tingley Hospital for Crippled

* Four males and one female could only be matched within four years of age, and one male was matched within 13 months of the time of diagnosis rather than 12 months.

Children in New Mexico, admissions are limited to children with orthopedic disorders, so its seven cases were matched only to orthopedic controls.

In addition to having one fewer control group in the Southwest than in Connecticut, analysis of data from these two areas differed in two other respects. First, in the Southwest, incidence rates according to fluoride exposure were not estimated, since the hospitals visited had not been chosen on a probability basis. Second, case-control comparisons for the Southwestern patients were made using fluoride levels in water supplies as a continuous variable, since fluoride levels ranged from 0.1 ppm to greater than 5 ppm. In Connecticut exposure was either to 1 ppm or to a negligible amount and was treated as a dichotomous variable.

Data on fluoride levels in the water supplies of the communities in which these Southwestern patients lived were obtained from various sources.⁷⁹⁻⁸⁷ In 11 case-control comparisons (7 percent), the slipped epiphysis case or one of his controls came from a community without a public water supply so that fluoride levels were unknown; these 11 comparisons had to be eliminated from the analysis. In instances in which the water supplies of the cases or controls had been artificially fluoridated between 1953 and 1967, the case was considered to have been exposed to artificial fluoridation if his slipped epiphysis was diagnosed at least a year after the fluoridation was initiated; the control was considered exposed if he was admitted to the hospital at least one year after the fluoridation had been started.

In both parts of the country, in order for the slipped epiphysis to be included, the diagnosis had to be based on x-ray evidence and only the first slipped epiphysis in bilateral cases was counted. An urban area was considered to be a core city as defined by the U. S. Bureau of the Census.⁸⁸ The rest of the Standard Metropolitan Statistical Area was classified as suburban, and all other regions as rural.

RESULTS

Table 1 shows that in Connecticut incidence rates in communities with artificial fluoridation were similar to incidence rates in localities without fluoridated water supplies, the average annual incidence rates for the two

TABLE 1. CONNECTICUT—ESTIMATED ANNUAL INCIDENCE OF SLIPPED EPIPHYSIS IN COMMUNITIES WITH AND WITHOUT ARTIFICIALLY FLUORIDATED WATER SUPPLIES, 1960-1966

<i>Fluoridation status</i>	<i>No. cases</i>	<i>Incidence per 100,000 per year*</i>
	Males	
Fluoridated	54.4	5.62
Non-fluoridated	152.4	4.67
	Females	
Fluoridated	13.3	1.36
Non-fluoridated	65.9	2.08
	Both sexes	
Fluoridated	67.7	3.48
Non-fluoridated	218.3	3.39

* In population under age 25.

sexes combined being estimated at 3.48 per 100,000 in towns with artificial fluoridation and 3.39 per 100,000 in those without fluoridation. In Table 2 it can be seen that there has been no decrease over the seven year period in the percentage of cases coming from communities with fluoridated water, or, in other words, as length of time of fluoride exposure has increased.

Case-control comparisons are given in Table 3. No differences are apparent when cases are contrasted with orthopedic or cancer controls, but when other controls are considered, the difference is in the direction of a protective effect and approaches statistical significance ($.05 < p < .10$).

TABLE 2. CONNECTICUT—PERCENTAGE OF CASES FROM COMMUNITIES WITH ARTIFICIALLY FLUORIDATED WATER SUPPLIES BY YEAR OF DIAGNOSIS

Year	No. cases	Percentage from communities with fluoridated water supplies
1960	32	25.0
1961	27	37.0
1962	38	26.3
1963	46	23.9
1964	37	35.1
1965	29	31.0
1966	44	31.8
Total	253	Percentage of total 29.6

TABLE 3. CONNECTICUT—COMPARISON OF COMMUNITY OF RESIDENCE OF CASES AND MATCHED CONTROLS ACCORDING TO WHETHER THE WATER SUPPLY WAS FLUORIDATED (F+) OR NOT FLUORIDATED (F-), BY SEX, 1960-1966

Comparison of cases with	Number of pairs with				Total	X ²	P
	Case F+ Control F+	Case F+ Control F-	Case F- Control F+	Case F- Control F-			
Orthopedic controls							
Males	19	14	9	34	76	0.70	>.10
Females	6	7	7	15	35	0.00	>.10
Both sexes	25	21	16	49	111	0.43	>.10
Other controls							
Males	25	8	17	26	76	2.56	>.10
Females	11	4	7	13	35	0.36	>.10
Both sexes	36	12	24	39	111	3.36	<.10
Cancer controls							
Males	7	13	14	40	74	0.00	>.10
Females	2	7	2	17	28	1.78	>.10
Both sexes	9	20	16	57	102	0.25	>.10

This difference, however, is also suggested by a case-control comparison for 1960 alone (data not shown here), when it would have been unlikely that exposure could have taken place for long enough for an effect to be noted, since fluoridation in the Hartford area was only begun in January of 1960, and before 1960 for cases and controls from the Newington Hospital for Children, when the matching procedure was extended into the years 1958 and 1959 in order to examine this trend. Thus, it would seem that the difference in fluoride exposure between slipped epiphysis cases compared to other controls, if indeed such a difference cannot be attributed to chance, is related to characteristics of these areas other than their fluoridation status. Seven years of artificial fluoridation in Connecticut appears to have had no effect on the incidence of slipped epiphysis.

Table 4 considers the mean fluoride levels in the water supplies of the communities of residence of cases and controls in the Southwestern states individually, and in the four states combined. Except for the low average levels of fluorides for other controls in Arizona, differences are slight indeed, and the analysis of variance indicates that the small amount of variation between cases and controls is not statistically significant.

However, as the study progressed, it became apparent that there were systematic differences among the cases and control groups. First, the cases and orthopedic controls were much more likely than the other controls to have come from rural areas in which there were no orthopedists to serve them. Second, and to a lesser extent, cases tended to be residents of poorer communities than did orthopedic or other controls,⁷⁸ and the poorer communities were also generally in the outlying areas. In addition, there were systematic differences between urban, suburban, and rural regions in the mean fluoride levels of their water supplies, for, in general, rural areas had higher fluoride levels than suburban or urban regions.

Therefore, mean fluoride levels for cases and controls in the entire region were adjusted by analysis of covariance, using urban and rural residence as covariates.* Table 5 shows these adjusted means along with the analysis of covariance. It can be seen that differences between cases and controls remain slight.

Because the association between fluoride levels and residence was not the same in all Southwestern states, individual analyses of covariance were computed for each state, and the adjusted means weighted and averaged, as shown in Table 6. With this procedure, differences were smaller than ever, and it can be observed that the low average fluoride levels previously

* Urban and suburban regions were combined since they were generally similar in respect to fluoride levels and since there were small numbers from suburban areas in two of the states.

noted for nonorthopedic controls in Arizona are mostly accounted for by the tendency of these controls to live in urban areas with low levels of fluoride in their water supplies.

DISCUSSION

These data indicate that seven years of artificial fluoridation in Connecticut have not altered incidence rates of slipped epiphysis. Nevertheless, it would still be possible that fluorides are protective, but require either a level greater than 1 ppm or exposure for longer than seven years. In the Southwest, exposure to fluorides occurred at higher levels and over longer periods of time, but still no protective effect was observed.

Before discarding the fluoride hypothesis, possible bias which might have masked any effect should be considered. This includes choice of control groups and actual exposure to fluorides. In retrospect, the "other" control group was not a good choice, since the population using the orthopedic services of Southwestern hospitals is different from that using other services and even the orthopedic controls came from communities with higher median income than cases. Adjusting for residence in the analysis of covariance should have controlled for socio-economic differences to a large extent, however, so it is felt that the negligible differences in mean fluoride

TABLE 4. SOUTHWESTERN STATES—MEAN FLUORIDE LEVELS, IN PPM, IN WATER SUPPLIES OF PLACE OF RESIDENCE OF CASES AND CONTROLS, BY STATE

State	No.	Mean fluoride levels		
		Cases	Nonorthopedic controls	Orthopedic controls
Colorado	41	1.051	0.995	1.005
Arizona	56	0.564	0.366	0.607
New Mexico	11*	0.727	0.636	0.500
Texas	33	2.064	2.188	2.118
Total	141	1.069	0.996	1.082

Analysis of variance for total				
Source of variation	Degrees of freedom	Mean square	F	P
Among matched groups	140	1.6785	4.437	< .01
Among cases and controls	2	0.2991	0.790	> .10
Residuals	280	0.3784		

* Patients and controls from the Carrie Tingley Hospital for Crippled Children, which admits only patients with orthopedic problems, have been excluded to insure comparability with non-orthopedic controls.

levels to which cases and controls were exposed are indicative of the true situation and that cases are no more likely to come from communities with low levels of fluorides in their water supplies than are controls.

Other problems in this study are related to the actual exposure to fluorides. Some residents of communities with high levels of fluorides in their public water supplies drink bottled "fluorine-free" water, and pre-school children are strongly recommended to do this.⁸⁰ In Lubbock, Texas, the city with the highest fluoride levels of those visited in this survey, it was estimated that 50% of preschool children and 10% of the entire population drank bottled water in 1968 (the year the data were being collected).⁸⁰ This would obviously decrease total fluoride exposure; most children older than

TABLE 5. SOUTHWESTERN STATES—MEAN FLUORIDE LEVELS, IN PPM, IN WATER SUPPLIES OF PLACE OF RESIDENCE OF CASES AND CONTROLS BEFORE AND AFTER ADJUSTMENT FOR URBAN OR RURAL RESIDENCE BY ANALYSIS OF COVARIANCE

<i>Group</i>	<i>Mean before adjustment</i>	<i>Mean after adjustment</i>
Cases	1.069	1.065
Nonorthopedic controls	0.996	1.002
Orthopedic controls	1.082	1.080

<i>Analysis of covariance adjusting for urban or rural residence</i>				
<i>Source of variation</i>	<i>Degrees of freedom</i>	<i>Reduced mean square</i>	<i>F</i>	<i>P</i>
Among matched groups	140	1.5426	4.072	< .01
Among cases and controls	2	0.2357	0.622	> .10
Residuals	279	0.3788		

TABLE 6. SOUTHWESTERN STATES—MEAN FLUORIDE LEVELS, IN PPM, IN WATER SUPPLIES OF PLACE OF RESIDENCE OF CASES AND CONTROLS, ADJUSTED FOR URBAN OR RURAL RESIDENCE, INDIVIDUAL ADJUSTMENT FOR EACH STATE

<i>State</i>	<i>No.</i>	<i>Adjusted mean fluoride level</i>		
		<i>Cases</i>	<i>Nonorthopedic controls</i>	<i>Orthopedic controls</i>
Colorado	41	1.044	0.995	1.011
Arizona	56	0.518	0.434	0.587
New Mexico*	11	0.724	0.639	0.500
Texas	33	2.088	2.157	2.124
Weighted mean, 4 states	141	1.033	1.016	1.063

* 8 cases and 8 orthopedic controls from Carrie Tingley Hospital for Crippled Children are excluded.

age five should nevertheless have had considerable exposure to fluorides in their drinking water.

An additional confounding variable is migration into and out of the Southwest. Although it would be unlikely that communities with high levels of fluorides would be affected to a markedly different extent from those with low levels of fluorides, it would be more difficult to document an association.

It is concluded that further pursuit of the hypothesis that fluorides in drinking water protect against slipped epiphysis would not be worthwhile, and that the variables of greatest interest in the causation of this condition are related to abnormalities of growth and maturation and to mechanical factors.^{77,78,91} It must be stressed that although fluorides cannot be shown to prevent slipped capital femoral epiphysis, this finding in no way detracts from other beneficial effects of fluorides.

SUMMARY

An epidemiological study of slipped capital femoral epiphysis indicated that fluorides in drinking water had no effect on the frequency of this disease, either in Connecticut, where some communities had artificially fluoridated water supplies of 1 ppm fluoride, or in the Southwestern part of the United States, where some localities had fluoride levels of 2 ppm or higher in their water supplies. These findings, however, in no way invalidate results of studies showing that fluorides in drinking water do protect against other diseases.

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