# Histological and Chemical Studies in Man on Effects of Fluoride

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PREVIOUS PATHOLOGICAL and chemical studies (*1–8*) have dealt with changes in human tissues associated with exposure to various fluoride levels for various periods. The primary aim of this study, conducted from September 1955 through August 1960, was to provide additional information on possible changes in human tissues associated with such exposure and to obtain chemical data on the accumulated concentration of fluoride and other chemical constituents in the bodies of deceased persons who had lived in industrial areas of Utah for various periods as well as in those who had lived in nonindustrial areas of the State for various periods of time. The majority of the subjects were from Utah County, where industrial and nonindustrial establishments using high temperatures in treating materials containing fluorine were known to have liberated fluoride into the air in elevated concentrations.

Chronic fluoride intoxication has occurred in some cattle and sheep maintained near major sources of fluoride emission in Utah County after they grazed on, or were fed, forage containing elevated levels of fluoride for prolonged periods. Certain vegetation has also been adversely affected by the elevated fluoride concentrations. Significant differences, however, exist in the relative exposure to fluoride of man and animals living in the same area. Their basic nourishment varies widely. Much of man's diet originates outside his immediate vicinity, while most of the animal feeds originate within the area. In addition, much of the industrially expelled, airborne fluoride settles on vegetation as a surface deposit, which man usually washes from the fruits and vegetables he eats. The study reported here was initiated in part to try to determine whether this apparent difference in exposure would lessen the effect of fluoride on man.

Values for fluoride in air samples collected by impinger at Utah State Hospital at Provo ranged from 0.10 to 0.80 microgram per cubic meter of dry air, with average yearly values of 0.24 microgram per cubic meter of dry air at 760 mm. Hg. pressure and 21.1° C. during the period September 1, 1957, to June 30, 1960. Similar air fluoride values were obtained at the Salt Lake City airport. At Utah State University, Logan, however, a lower average value of 0.06 (0.01 to 0.20) microgram per cubic meter of dry air was obtained under comparable conditions and during the same period.

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**Table 1. Fluoride and ash content in dry, fat-free bones of deceased study subjects 15 years of age or older at death who had resided in Utah, Salt Lake, or Weber Counties, Utah, at least 10 years**

| Subject number and sex | Age (years) | Residence (years) [1] | Calvarium | | Sternum | | Rib | | Iliac crest | | Vertebrae | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Ppm F | Percent ash | Ppm F | Percent ash | Ppm F | Percent ash | Ppm F | Percent ash | Ppm F | Percent ash |
| 1, F | 71 | 32 U | ------ | ------ | 708 | 54.7 | 772 | 60.2 | ------ | ------ | 684 | 58.3 |
| 2, F | 51 | 22 U | 416 | 64.4 | 394 | 64.2 | 320 | 54.0 | 244 | 59.7 | 484 | 55.4 |
| 3, F | 85 | 85 UW | 600 | 66.0 | 692 | 48.1 | 608 | 63.0 | 598 | 62.6 | 760 | 53.1 |
| 4, M | 61 | 61 U | 336 | 66.9 | 402 | 50.0 | 274 | 60.4 | 312 | 60.6 | 394 | 56.0 |
| 5, M | 85 | 24 U | 840 | 67.1 | 786 | 57.7 | 580 | 59.5 | 570 | 61.9 | 620 | 54.8 |
| 6, M | 60 | 12 U | ------ | ------ | 520 | 50.1 | 465 | 61.0 | ------ | ------ | ------ | ------ |
| 7, M | 53 | 19 U | 620 | 64.7 | 427 | 50.7 | 450 | 62.3 | ------ | ------ | 469 | 57.4 |
| 8, F | 73 | 11 U | ------ | ------ | 705 | ------ | 630 | 62.6 | 605 | ------ | 780 | 54.3 |
| 9, M | 66 | 29 U | ------ | ------ | 368 | 54.6 | 366 | 59.0 | 250 | 58.9 | ------ | 55.6 |
| 11, M | 80 | 16 UW | 550 | 63.6 | 565 | 56.6 | 396 | 57.6 | 420 | 57.9 | 478 | 55.5 |
| 14, F | 83 | 10 U | 440 | 63.4 | 526 | 49.4 | 540 | 62.9 | 560 | 57.2 | ------ | 47.1 |
| 15, F | 42 | 42 U | 516 | 63.2 | 348 | 49.7 | 258 | 62.2 | 303 | 58.9 | 369 | 54.5 |
| 17, F | 60 | 22 U | 636 | 61.3 | 730 | 55.8 | 614 | 56.7 | 570 | ------ | 616 | 50.6 |
| 18, M | 45 | 26 U | ------ | ------ | 690 | 48.3 | 598 | 60.1 | 630 | 58.3 | 744 | 54.4 |
| 19, M | 16 | 16 U | ------ | ------ | 91 | 54.8 | 95 | 60.2 | 56 | 56.5 | 87 | 56.6 |
| 20, F | 56 | 10 U | 278 | 63.9 | 273 | 54.0 | 223 | 62.3 | 222 | 56.3 | 279 | 52.4 |
| 23, M | 64 | 64 U | ------ | 66.9 | 1,370 | 52.8 | 1,190 | 59.9 | ------ | 56.1 | 1,550 | 58.8 |
| 24, F | 70 | 40 U | ------ | 69.1 | 1,310 | 57.0 | 1,176 | 64.5 | 1,165 | 62.7 | 945 | 61.7 |
| 25, M | 74 | 20 U | 350 | 66.6 | 300 | 54.1 | 324 | 61.8 | 264 | 45.5 | 315 | 50.1 |
| 26, F | 55 | 22 UW | 320 | 66.8 | 343 | 48.5 | 255 | 65.5 | 292 | 61.8 | 363 | 52.5 |
| 27, F | 79 | 60 U | 400 | 66.8 | 416 | 57.8 | 364 | 64.6 | 396 | 62.1 | 485 | 54.3 |
| 28, M | 66 | 65 U | ------ | 67.7 | 240 | 55.6 | 343 | 64.4 | 296 | 62.2 | 336 | 40.0 |
| 30, M | 78 | 42 U | 600 | 67.0 | 470 | 51.7 | 500 | 59.8 | 462 | 58.6 | 410 | ------ |
| 31, M | 55 | 25 US | 550 | 68.0 | 850 | 57.5 | 544 | 64.2 | 552 | 61.6 | ------ | ------ |
| 32, F | 45 | 16 U | 960 | 68.0 | ------ | ------ | 768 | 63.5 | ------ | ------ | 654 | 61.0 |
| 33, M | 73 | 73 U | ------ | ------ | 250 | 59.1 | 260 | 62.7 | ------ | ------ | 260 | 58.0 |
| 34, M | 47 | 46 WU | 462 | 68.6 | 500 | 57.5 | 448 | 61.2 | 482 | 61.6 | 482 | 53.2 |
| 35, M | 80 | 14 SU | 532 | 67.0 | 580 | 57.9 | 494 | 58.0 | 700 | 62.0 | 474 | 52.6 |
| 36, M | 50 | 50 U | 800 | 65.4 | 840 | 53.1 | 900 | 60.8 | 600 | 57.4 | 740 | 52.2 |
| 38, F | 84 | 73 U | ------ | ------ | 316 | 61.9 | ------ | 60.8 | ------ | 59.8 | 302 | 53.0 |
| 39, M | 49 | 38 U | ------ | ------ | 220 | 58.5 | 220 | 59.0 | 198 | 60.2 | ------ | 59.2 |
| 41, F | 69 | 69 U | ------ | ------ | 334 | 60.6 | 330 | 61.9 | 346 | 61.6 | 350 | 57.5 |
| 42, M | 75 | 18 U | ------ | ------ | 275 | 56.1 | 330 | 60.2 | 345 | 51.5 | 300 | 61.2 |
| 43, F | 49 | 28 U | 364 | 65.3 | 358 | 55.1 | 298 | 62.8 | 304 | 60.3 | 292 | 52.7 |
| 44, M | 61 | 37 U | ------ | ------ | 255 | 58.7 | 203 | 63.0 | 260 | 60.4 | 255 | 56.3 |
| 46, F | 85 | 58 U | 478 | ------ | ------ | ------ | 456 | ------ | ------ | ------ | 510 | ------ |
| 47, F | 26 | 26 U | ------ | ------ | 338 | 59.5 | 118 | 64.6 | 266 | 61.6 | 153 | 60.4 |
| 48, M | 35 | 29 U | ------ | ------ | 282 | 56.5 | 236 | 60.3 | ------ | ------ | 260 | 50.1 |
| 50, F | 71 | 35 U | ------ | ------ | 1,608 | 44.4 | 1,440 | 64.0 | ------ | ------ | 896 | 53.8 |
| 51, M | 82 | 60 S | 548 | 64.9 | 522 | 59.9 | 558 | 65.2 | 595 | 59.7 | 570 | 56.8 |
| 52, M | 29 | 28 U | ------ | ------ | 364 | 57.4 | 296 | 60.1 | ------ | ------ | 364 | 56.7 |
| 54, F | 53 | 48 U | 238 | 64.0 | 242 | ------ | 180 | ------ | 204 | 61.2 | 268 | 59.7 |
| 55, F | 78 | 78 U | 718 | 63.7 | ------ | ------ | 318 | 57.5 | ------ | ------ | 350 | 42.3 |
| 56, F | 66 | 66 SU | 499 | 68.4 | 606 | 61.7 | 373 | 61.4 | 535 | 58.0 | 704 | 53.4 |
| 57, F | 38 | 38 US | ------ | ------ | 496 | 44.1 | 456 | 59.2 | 464 | 61.0 | 338 | 54.1 |
| 58, M | 55 | 55 U | ------ | ------ | 348 | 50.9 | 317 | 59.3 | ------ | 61.0 | 370 | 47.8 |
| 59, M | 70 | 67 U | 271 | 64.1 | 318 | 55.2 | 292 | 58.7 | 260 | 59.0 | 274 | 52.2 |
| 60, F | 50 | 11 U | 220 | 68.1 | 318 | 47.0 | 315 | 60.8 | 235 | 56.5 | 330 | 52.6 |
| 61, M | 77 | 39 W | ------ | ------ | 733 | 57.4 | 735 | 55.4 | 562 | 58.6 | 789 | ------ |
| 62, F | 67 | 67 W | ------ | ------ | 434 | 49.8 | 414 | 60.1 | 420 | 54.8 | 432 | 42.5 |
| 64, M | 49 | 11 S | 426 | 64.7 | 431 | 60.4 | 300 | 66.7 | 481 | 60.9 | 300 | 59.8 |
| 65, M | 55 | 38 W | 600 | 64.7 | 551 | 58.5 | 480 | 62.2 | ------ | ------ | 616 | 58.5 |
| 66, F | 72 | 72 W | 469 | 64.0 | 763 | 61.6 | 575 | 62.2 | 612 | 61.9 | 896 | 61.8 |
| 67, M | 25 | 25 SU | 198 | 63.8 | 199 | 58.0 | 145 | 62.8 | 196 | 60.2 | 249 | 56.6 |
| 71, M | 43 | 10 S | ------ | ------ | 790 | 55.4 | 750 | 61.9 | 700 | 54.1 | 650 | 53.9 |
| 72, F | 53 | 53 SU | 1,090 | 67.7 | ------ | ------ | 1,095 | 63.7 | 1,200 | 62.9 | 1,340 | 55.5 |
| 74, F | 66 | 30 U | ------ | ------ | ------ | ------ | 430 | 64.5 | 295 | ------ | 445 | ------ |
| 75, F | 83 | 83 SU | 900 | 66.0 | 900 | 51.7 | 840 | 60.6 | 900 | 56.1 | 900 | 50.3 |
| 76, M | 44 | 33 U | 750 | 65.4 | 813 | 60.1 | 773 | 61.1 | 758 | 59.5 | 875 | 54.2 |
| 78, F | 80 | 78 U | 1,000 | 64.8 | ------ | ------ | 990 | 56.8 | 875 | 60.9 | 988 | 57.0 |

**Table 1. Fluoride and ash content in dry, fat-free bones of deceased study subjects 15 years of age or older at death who had resided in Utah, Salt Lake, or Weber Counties, Utah, at least 10 years—Continued**

| Subject number and sex | Age (years) | Residence (years) [1] | Calvarium | | Sternum | | Rib | | Iliac crest | | Vertebrae | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Ppm F | Percent ash | Ppm F | Percent ash | Ppm F | Percent ash | Ppm F | Percent ash | Ppm F | Percent ash |
| 79, M | 57 | 40 U | 990 | ------ | ------ | ------ | 883 | 57.0 | 875 | 60.8 | 990 | 65.5 |
| 80, F | 59 | 38 U | ------ | ------ | ------ | ------ | 470 | 61.7 | 556 | 63.7 | 502 | 56.2 |
| 81, M | 60 | 17 U | ------ | ------ | ------ | ------ | 400 | 58.5 | 340 | 58.0 | 595 | 54.7 |
| 82, M | 17 | 17 U | ------ | ------ | 423 | 64.3 | 425 | 53.2 | 350 | 58.6 | 413 | 56.0 |
| 84, M | 72 | 71 US | ------ | ------ | ------ | ------ | 270 | 54.7 | 260 | 57.1 | 250 | ------ |
| 85, M | 70 | 20 U | ------ | ------ | 1,650 | 53.5 | 1,895 | 63.1 | 1,630 | 62.4 | 2,025 | 54.4 |
| 87, F | 15 | 15 U | 225 | 67.3 | ------ | ------ | 230 | 62.4 | ------ | ------ | 250 | 52.9 |
| 93, F | 75 | 75 U | 375 | 61.3 | ------ | ------ | 338 | 54.0 | ------ | ------ | 425 | ------ |
| 94, F | 31 | 31 U | ------ | ------ | ------ | ------ | 300 | 61.0 | 300 | 57.4 | 425 | 52.2 |
| 97, M | 77 | 15 S | ------ | ------ | 1,805 | 59.0 | ------ | ------ | 1,550 | 62.5 | 1,665 | 59.0 |
| 98, M | 57 | 40 S | ------ | ------ | 1,260 | 63.8 | 1,165 | 66.2 | ------ | ------ | 1,070 | 59.5 |
| 100, F | 88 | 63 SU | ------ | ------ | 1,075 | ------ | 813 | 62.6 | ------ | 67.5 | 1,030 | 54.2 |
| 101, F | 84 | 78 S | ------ | ------ | ------ | ------ | 733 | 63.0 | 875 | 58.3 | 800 | 49.9 |
| 102, M | 64 | 64 U | ------ | ------ | ------ | ------ | ------ | 58.2 | ------ | ------ | 1,675 | 58.6 |
| 104, M | 82 | 34 U | ------ | ------ | 1,100 | 58.4 | 1,070 | 60.3 | ------ | ------ | 1,315 | 59.0 |
| 106, F | 76 | 12 U | 1,200 | 68.6 | 1,450 | 58.3 | 1,170 | 61.3 | ------ | ------ | 1,340 | 57.4 |
| 107, M | 79 | 53 U | ------ | ------ | 1,275 | 60.2 | 750 | ------ | ------ | ------ | 780 | 52.9 |
| 110, F | 32 | 32 U | ------ | ------ | 210 | 59.3 | 210 | 60.7 | 220 | 58.1 | 240 | 63.0 |
| 112, F | 61 | 35 US | 600 | 62.8 | 685 | 50.1 | 730 | 60.8 | 575 | 55.0 | 775 | 59.2 |
| 113, F | 79 | 79 U | ------ | ------ | ------ | ------ | 440 | 60.1 | ------ | ------ | ------ | 58.2 |
| 114, M | 70 | 28 U | ------ | ------ | ------ | ------ | 675 | 62.4 | ------ | ------ | 740 | 60.0 |
| 116, M | 77 | 52 U | 610 | 67.2 | 585 | 56.6 | 650 | 60.7 | ------ | ------ | 650 | 58.7 |
| 117, F | 75 | 74 U | ------ | ------ | 410 | 58.0 | 410 | 60.5 | ------ | ------ | 470 | 58.7 |
| 118, M | 79 | 79 U | ------ | ------ | ------ | ------ | 985 | 59.3 | ------ | ------ | 1,030 | 54.8 |
| 125, M | 69 | 40 U | ------ | ------ | ------ | ------ | 635 | 59.7 | ------ | ------ | 635 | 58.6 |
| 127, F | 28 | 24 U | ------ | ------ | ------ | ------ | 100 | 63.0 | ------ | ------ | 175 | 58.6 |
| 128, F | 80 | 10 U | ------ | ------ | ------ | ------ | 285 | 61.7 | ------ | ------ | 365 | 58.5 |
| 130, M | 65 | 16 U | ------ | ------ | ------ | ------ | 665 | 59.8 | ------ | ------ | 675 | 58.2 |
| Mean | 61.8 | 40.1 | 560 | 65.7 | 613 | 55.6 | 537 | 61.0 | 510 | 59.3 | 615 | 55.4 |
| Standard deviation | 18.0 | 22.5 | 251 | 1.9 | 388 | 4.7 | 328 | 2.9 | 314 | 3.3 | 339 | 4.4 |
| Standard error | 1.9 | 2.4 | 39 | .19 | 48 | .5 | 36 | .8 | 40 | .4 | 38 | .5 |

[1] S—Salt Lake County; U—Utah County; W—Weber County.

NOTE: (-------) indicate no chemical determination was done. For results of determinations of calcium and phosphorus, see Documentation Note on page 538.

Analysis of Utah County water supplies revealed less than 0.5 ppm of fluoride. Similar studies on alfalfa and other animal forage crops indicated from about 5 ppm to more than 30 ppm for fluoride on a dry basis. These levels varied widely from area to area within the county. The fluoride levels (about 0.1 ppm to more than 1.0 ppm and usually less than 0.5 ppm on a fresh basis) on locally grown human consumables were consistently lower than those found on forage crops. These differences in fluoride levels in sources of nourishment noticeably affect the relative exposure of animals and man to fluoride even though they live in close proximity.

In recent years, certain industries in Utah County and others in the State have used procedures and equipment which have significantly reduced the output of fluorides.

## Materials and Methods

Studies were conducted on bodies of 127 patients consecutively autopsied by Call and LeCheminant at Utah Valley Hospital and Utah State Hospital except that those for whom no information on residence was available were skipped. Routine autopsies were made, when possible, on unembalmed bodies. Some bodies, however, had been arterially embalmed, but not trocarred, before examination. Samples of embalming fluid from these bodies were analyzed and found to contain no fluoride.

A precise protocol was followed which indicated the location in the body and the type and quantity of tissues to be obtained for histologic study and chemical analysis. The tissues studied were of male and female persons, 15 years of age or older, who had resided at least 10 years in an industrial area of Utah within Utah County, Salt Lake County, or Weber County. This protocol was similar to that used by other investigators (*4*). Data on persons not meeting these criteria are included in this report only for purposes of comparison.

Examination of each body was made with special attention to palpable exostoses and other abnormal bone formations and deformities not associated with trauma. Complete autopsies, including examination of the brain, were performed on bodies of 62 of the 127 subjects. Permission for removal of the brain was not granted for the remaining 65 subjects. Tissues of all organ samples were examined histologically. Special efforts were made in the processing of the bone sections to preserve the periosteum, cortex, and marrow in their proper anatomical relationship. The following tissues were analyzed for fluoride and dry matter: calvarium, lumbar vertebrae, sternum, sixth rib, iliac crest, exostoses (if present), thyroid, aorta, kidney, lung, liver, spleen, heart, pancreas, and brain. Specimens collected from September 1958 through August 1960 were limited to the bones, thyroid, aorta, and kidneys.

Calcium, phosphorus, and ash determinations were made on dry, fat-free bones. All specimens were maintained in a frozen state until chemical analyses were made. Before chemical analysis, the bones were cleaned of adhering soft tissues, broken into small pieces, weighed, and dried in a vacuum oven for 5 hours at 95–100° C. or to constant weight. Some samples were dried overnight in the oven at the same temperature range. Fat was extracted from the dried samples with diethyl ether in a Goldfisch apparatus for 5 hours or until constant weight was obtained. The bone fragments were finely ground, and weighed samples were ashed in a muffle at 550° C. for about 6 hours or to constant weight. The bone fluoride was isolated essentially by the method of Willard and Winter (*9*), with modifications as given by the Association of Official Agricultural Chemists (*10*). Estimation of the fluoride was made by the spectrophotometric method of Megregian (*11*) as modified by Nielsen (*12*).

The soft tissues were ground, mixed, weighed, dried, and ashed in platinum dishes in the presence of calcium oxide of low fluoride content. Fluoride was separated from ashed samples essentially by the procedure of Willard and Winter (*9*) and determined by the procedure of Nielsen (*12*). Dry matter determinations were made on weighed soft tissues by heating them in a vacuum oven for 5 hours at 95–100° C. or to constant weight. Some samples were dried overnight in the oven at the same temperature range. Phosphorus was determined colorimetrically by the method of Chen and associates (*13*). Calcium was determined by a modification of the method of Patton and Reeder (*14*).

The majority of the 127 patients included in this study had died suddenly or shortly after becoming ill. Major causes of death were coronary heart disease, pneumonia, cancer, kidney disease, and trauma. From bodies of the 127 subjects, 1,220 specimens were obtained for fluoride analysis. All specimens were also examined histologically. Special attention was given to the histology of bones and intervertebral cartilages. Of the 442 bones and cartilages studied, none showed any of the pathological changes which have been attributed to fluorosis (*1, 2, 15, 16*).

## Results and Discussion

Histologic findings in the present study are in agreement with those of Geever and associates (*4*), who reported no abnormal histologic changes traceable to fluoride in the tissues of 37 persons who died after having lived at least 10 years in communities with 1 to 4 ppm of fluoride in the water supply.

The levels of fluoride and ash in dry, fat-free bones of persons in our study meeting the criteria of exposure and for others not meeting it are shown in tables 1 and 2. The mean fluoride concentration in bones of those meeting the criteria is 568 ppm in comparison with a mean of 446 ppm for the other group. This difference is significant ($P<0.01$). The average age of persons meeting the criteria (61.8 years) is, however, 18.3 years older than of those not meeting the criteria (43.5 years). Since age has been shown to be a factor in fluoride storage (*17*), age differences may account in part for

**Table 2. Fluoride and ash content in dry, fat-free bones of deceased study subjects who were less than 15 years of age at death or who had resided in Utah, Salt Lake, or Weber Counties, Utah, less than 10 years**

| Subject number and sex | Age (years) | Residence [1] (years) | Calvarium | | Sternum | | Rib | | Iliac crest | | Vertebrae | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | F | Ash | F | Ash | F | Ash | F | Ash | F | Ash |
| 10, M | 67 | 3 U | 498 | 63.3 | 480 | 50.6 | 460 | 52.6 | 466 | 53.2 | 472 | 37.9 |
| 12, M | 41 | 0 | ------ | ------ | ------ | ------ | 242 | 58.5 | ------ | ------ | 238 | 54.6 |
| 13, F | [2] 0 | 0 | ------ | ------ | 57 | ------ | ------ | ------ | ------ | ------ | ------ | ------ |
| 16, M | 42 | 6 U | ------ | ------ | 500 | 57.1 | 477 | 60.5 | 449 | 56.8 | 454 | 55.8 |
| 37, F | 4 | 4 U | 190 | 63.3 | ------ | ------ | 232 | 54.5 | ------ | ------ | 234 | 50.7 |
| 40, M | 55 | 0 | ------ | ------ | 272 | ------ | 276 | ------ | ------ | ------ | ------ | ------ |
| 45, M | 77 | 0 | 480 | 65.4 | 371 | 59.4 | 321 | 64.4 | 339 | 59.2 | 397 | 56.2 |
| 49, M | 17 | 0 | 138 | 64.0 | 143 | 60.2 | 120 | 63.9 | 118 | 61.2 | 128 | 0 |
| 53, M | 25 | 2 U | ------ | ------ | 229 | 58.1 | 173 | 60.5 | ------ | ------ | 323 | 59.3 |
| 63, M | 55 | 0 | ------ | ------ | 260 | 62.0 | 414 | 63.5 | 394 | 61.0 | 473 | 55.6 |
| 68, F | 78 | 0 | ------ | ------ | 369 | 59.8 | 304 | 62.5 | 347 | 62.5 | 371 | 56.9 |
| 69, M | 16 | 5 U | 600 | 66.0 | ------ | ------ | 700 | 63.6 | 725 | 58.5 | 650 | 57.5 |
| 70, M | 28 | 0 | ------ | ------ | 425 | 61.0 | 400 | 62.4 | ------ | ------ | 410 | 60.7 |
| 73, F | 8 | 8 U | 425 | 61.8 | ------ | ------ | ------ | ------ | ------ | ------ | 448 | 57.1 |
| 77, F | 61 | 7 U | ------ | ------ | 1,115 | 54.1 | 1,300 | 59.0 | 740 | 50.3 | 1,075 | 52.8 |
| 83, F | 17 | 8 U | ------ | ------ | ------ | ------ | 135 | 60.4 | 165 | 59.2 | 160 | 56.9 |
| 86, M | 22 | 0 | ------ | ------ | ------ | ------ | 200 | 68.3 | 275 | 62.5 | 338 | 59.4 |
| 88, M | 50 | 2 S | 625 | 60.9 | ------ | ------ | 625 | 61.0 | 583 | 57.3 | 623 | 51.7 |
| 89, M | 4 | 0 | ------ | ------ | ------ | ------ | 150 | 61.3 | ------ | ------ | 125 | ------ |
| 90, M | 4 | 0 | ------ | ------ | 50 | ------ | 40 | ------ | ------ | ------ | ------ | ------ |
| 92, M | 18 | 0 | 225 | 61.5 | 218 | 56.0 | 175 | 58.9 | ------ | ------ | 205 | 54.6 |
| 95, M | 17 | 0 | 235 | 60.3 | ------ | ------ | 205 | 54.3 | ------ | ------ | 290 | 55.6 |
| 96, M | 17 | 0 | ------ | ------ | 180 | 57.0 | 220 | 58.9 | 183 | 57.1 | 235 | 53.8 |
| 99, F | 27 | 0 | ------ | ------ | 625 | ------ | ------ | 67.0 | 500 | 61.8 | 533 | 59.1 |
| 105, M | 63 | 0 | ------ | ------ | 558 | 58.3 | 559 | 62.2 | 535 | 60.9 | 559 | 55.1 |
| 108, F | 8 | 6 U | 125 | 62.3 | ------ | ------ | 100 | 56.4 | ------ | ------ | 150 | 58.9 |
| 109, F | 71 | 9 U | ------ | ------ | 590 | 56.7 | 490 | 60.9 | 450 | 61.7 | 590 | 61.6 |
| 111, F | 82 | 0 | ------ | ------ | 605 | 56.2 | 500 | 57.7 | 535 | 60.4 | 650 | 56.8 |
| 115, F | 85 | 0 | ------ | ------ | 860 | 57.9 | 900 | 61.6 | ------ | ------ | 1,250 | 58.3 |
| 119, M | 62 | 0 | ------ | ------ | ------ | ------ | 870 | 58.1 | ------ | ------ | 1,125 | 61.7 |
| 120, F | 77 | 0 | ------ | ------ | 600 | 52.7 | 525 | 58.5 | ------ | ------ | 675 | 54.4 |
| 121, M | 80 | 0 | 710 | 63.9 | 655 | 52.0 | 450 | 59.0 | 515 | 58.6 | 585 | 56.8 |
| 122, M | 60 | 0 | ------ | ------ | 640 | 54.3 | 525 | 62.2 | ------ | ------ | ------ | ------ |
| 123, M | 60 | 0 | ------ | ------ | ------ | ------ | 890 | 60.4 | ------ | ------ | 1,275 | 57.8 |
| 124, M | 75 | 0 | ------ | ------ | ------ | ------ | 555 | 60.3 | ------ | ------ | 560 | 53.3 |
| 126, M | 65 | 0 U | ------ | ------ | ------ | ------ | 255 | 62.3 | ------ | ------ | 285 | 59.1 |
| 129, M | 43 | 9 US | ------ | ------ | ------ | ------ | ------ | ------ | ------ | ------ | 635 | 56.6 |
| Mean | 43.5 | 2.32 | 387 | 63.0 | 445 | 56.8 | 418 | 60.5 | 431 | 58.9 | 501 | 56.0 |
| Standard deviation | 26.3 | 3.3 | 211 | 1.7 | 150 | 3.2 | 305 | 3.3 | 188 | 3.5 | 307 | 4.4 |
| Standard error | 4.8 | .4 | 63 | .6 | 32 | .8 | 53 | .6 | 44 | .9 | 53 | .8 |
| 91X [3] | 27.0 | 25 U | 500 | 63.2 | ------ | ------ | ------ | ------ | ------ | ------ | ------ | ------ |
| 103X [3] | 0 | 0 | 30 | 62.0 | ------ | ------ | ------ | ------ | ------ | ------ | ------ | ------ |

[1] S—Salt Lake County; U—Utah County. Subjects with 0 years of residence include transients who never resided in these counties and persons resident less than 1 year.

[2] Less than 1 year old at time of death.

[3] Combined bone specimens.

NOTE: (------) indicate no chemical determination was done. For results of determinations of calcium and phosphorus, see Documentation Note on page 538.



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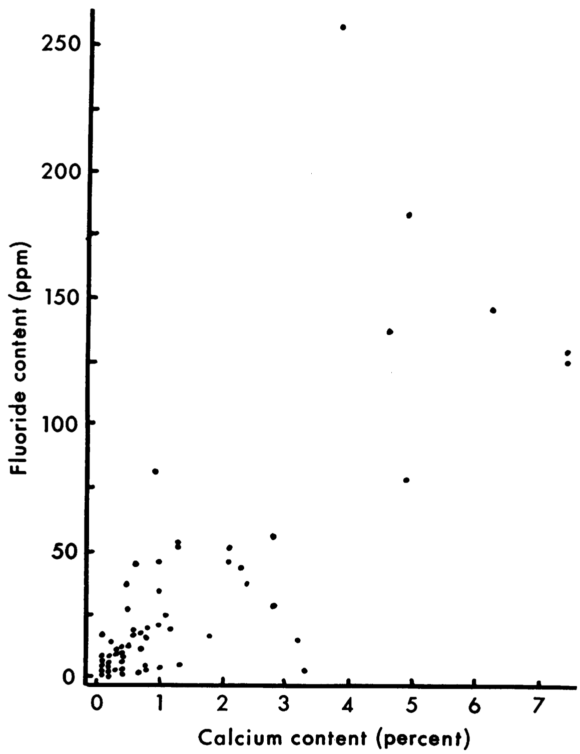
the differences in fluoride concentration between the two groups in our study. Significance of differences in means were calculated according to Fisher's $t$ test. The bone fluoride levels we found are within the general range reported for normal subjects in other studies (*5, 6*). A statistical comparison of mean bone fluoride levels for male and female subjects and controls in our study revealed no significant difference ($P>0.05$).

Comparison of fluoride content in the soft tissues of persons meeting the criteria of exposure to fluoride with the content in soft tissues of persons not meeting the criteria revealed no significant difference ($P>0.05$). This finding indicates that fluoride is not stored in the soft tissues in significant quantities (table 3). The fluoride content was higher in the aorta than in any of the other soft tissues studied, a result in agreement with that of Smith and associates (*7*). An increase in the fluoride content of the aorta was associated with calcification, as indicated by an increase in the calcium content of the tissue (fig. 1). This increase parallels the degree of aortic arteriosclerosis and calcification. The Pearson product-moment correlation coefficient for this relationship (based on analysis of 60 aortas) is 0.93.

**Figure 1. Relationship between the concentrations of fluoride and calcium in the aorta (results expressed on a dry basis)**




When we correlated bone fluoride levels with the patient's disease, it soon became evident that most of the higher levels were found in patients with an advanced chronic renal disease. Giving particular attention to these cases, we classified and studied 44 of them according to type and severity of renal lesions. Table 4 shows this classification along with the patients' re-

**Table 3. Fluoride content (ppm) in soft tissues of subjects who met criteria of exposure to fluoride and in tissues of others who did not**

| Tissue | Met exposure criteria [1] | | | Did not meet exposure criteria [2] | | |
|---|---|---|---|---|---|---|
| | Maximum | Minimum | Mean | Maximum | Minimum | Mean |
| Brain | 6.1 | 0.2 | 1.8 | 3.6 | 0.4 | 1.5 |
| Thyroid | 23.5 | .3 | 5.2 | 8.1 | .1 | 4.0 |
| Heart | 8.1 | .4 | 2.5 | 7.0 | .2 | 1.9 |
| Aorta | 258.0 | .6 | 29.4 | 185.0 | .8 | 28.2 |
| Lung | 17.0 | .6 | 3.9 | 8.0 | 1.0 | 3.5 |
| Liver | 7.7 | .2 | 1.6 | 3.7 | .2 | 1.4 |
| Spleen | 8.6 | .2 | 1.7 | 5.0 | .3 | 1.8 |
| Pancreas | 8.2 | .3 | 1.8 | 4.5 | .4 | 1.7 |
| Kidney | 10.0 | .2 | 2.9 | 5.6 | .6 | 2.3 |

[1] Were 15 years of age or older (mean age 61.8 years) and had resided in Utah, Salt Lake, or Weber County in State of Utah at least 10 years (mean years of residence 40.1).

[2] Less than 15 years of age at death or had resided less than 10 years in Utah, Salt Lake, or Weber County (mean age in years 43.5 and mean years of residence 2.32).

NOTE: See Documentation Note on page 538.

**Table 4. Age, kidney weights, and mean content of fluoride and ash in dry, fat-free bones of subjects with kidney disease**

| Disease classification and subject's number | Age | Kidney weights (grams) | | Mean bone levels | |
|---|---|---|---|---|---|
| | | Right | Left | Ppm fluoride | Percent ash |
| Chronic pyelonephritis, bilateral, marked: | | | | | |
| 23 | 64 | 60 | 60 | 1, 370 | 58. 9 |
| 50 | 71 | 100 | 80 | 1, 315 | 54. 1 |
| 86 | 70 | 150 | 30 | 1, 800 | 58. 3 |
| 106 | 75 | 95 | 75 | 1, 290 | 61. 5 |
| 129 [1] | 44 | 120 | 100 | 635 | 56. 6 |
| Chronic pyelonephritis, bilateral, slight to moderate: | | | | | |
| 27 | 79 | 110 | 90 | 412 | 61. 1 |
| 57 | 38 | 225 | 280 | 438 | 53. 8 |
| 66 | 72 | 125 | 120 | 663 | 62. 3 |
| 113 | 79 | 140 | 100 | 440 | 59. 1 |
| 114 | 70 | 110 | 150 | 707 | 61. 2 |
| 116 | 77 | 165 | 175 | 624 | 60. 8 |
| 118 | 75 | 200 | 200 | 1, 007 | 57. 0 |
| 120 | 77 | 140 | 80 | 600 | 55. 2 |
| 124 | 75 | 130 | 150 | 558 | 56. 8 |
| 126 | 65 | 150 | 190 | 255 | 60. 7 |
| Chronic pyelonephritis, unilateral: | | | | | |
| 5 | 85 | 30 | 210 | 697 | 60. 2 |
| 55 | 78 | 70 | 185 | 495 | 55. 7 |
| 74 | 66 | 100 | 165 | 390 | 64. 5 |
| 119 | 62 | 135 | 70 | 997 | 58. 2 |
| Acute glomerulonephritis: | | | | | |
| 38 | 84 | 170 | 150 | 309 | 58. 9 |
| 81 | 60 | 180 | 210 | 445 | 57. 4 |
| 94 | 31 | 130 | 130 | 342 | 56. 9 |
| Chronic glomerulonephritis: | | | | | |
| 47 | 26 | 90 | 100 | 219 | 61. 5 |
| 83 | 17 | 90 | 95 | 153 | 58. 8 |
| Lower nephron nephrosis: | | | | | |
| 19 | 16 | 190 | 210 | 82 | 57. 0 |
| 48 | 35 | 185 | 190 | 259 | 55. 6 |
| 84 | 72 | 180 | 180 | 260 | 55. 9 |
| 86 | 22 | 270 | 220 | 271 | 62. 4 |
| 89 | 4 | 150 | 155 | 137 | 61. 3 |
| Arteriolonephrosclerosis: | | | | | |
| 45 | 77 | 100 | 150 | 382 | 60. 9 |
| 46 | 85 | 70 | 50 | 481 | -------- |
| 78 | 80 | 140 | 100 | 921 | 59. 9 |
| 80 | 59 | 180 | 180 | 509 | 60. 1 |
| 97 | 77 | 160 | 140 | 1, 673 | 60. 5 |
| 100 | 89 | 100 | 170 | 973 | 61. 4 |
| 107 | 79 | 100 | 130 | 935 | 56. 5 |
| 109 | 71 | 200 | 200 | 530 | 60. 2 |
| 111 | 81 | 130 | 120 | 572 | 57. 8 |
| 128 | 80 | 150 | 140 | 325 | 60. 1 |
| Polycystic disease: 77 | 61 | 250 | 300 | 1, 057 | 54. 0 |
| Glomerulosclerosis, intercapillary: 104 | 82 | 250 | 290 | 1, 162 | 59. 2 |
| Glomerulosclerosis of lupus erythematosus: 127 | 28 | 340 | 320 | 137 | 60. 8 |
| Hydronephrosis due to tumor extension (no pyelonephritis present): 123 | 60 | 280 | 230 | 1, 082 | 56. 8 |
| Wilm's tumor, unilateral: 108 | 8 | 170 | -------- | 125 | 59. 2 |

[1] Congenital polycystic disease also present.

NOTE: For mean bone levels of calcium and phosphorus, see Documentation Note on page 538.

spective kidney weights and the mean levels of fluoride and ash in their bones. Kidney lesions were the primary cause of death in 11 (8.7 percent) of the 127 subjects; lesions of varying degrees were observed in 44 (or 34.6 percent).

We found the highest bone fluoride levels in cases of older adults with the end-stage kidney of bilateral pyelonephritis and in single cases of polycystic disease, intercapillary glomerulosclerosis, and hydronephrosis due to tumor extension. Similar levels were found in scattered cases of arteriolonephrosclerosis and moderately advanced chronic pyelonephritis. Mean bone fluoride levels of persons with kidney disease, by disease group, were compared with cases of the corresponding age group without kidney disease (table 5). Bone-fluoride levels were significantly higher ($P<0.01$ in 5 subjects with marked chronic bilateral pyelonephritis than in 16 subjects in the same age group (60–69 years) without kidney disease. Three subjects with acute glomerulonephritis had lower bone fluoride levels ($P=0.05$) than 16 subjects without kidney disease, all in the age group 50–59 years. A similar observation was made in the age group 20–29 years, in which two subjects who had chronic glomerulonephritis were found to have lower levels than six subjects without kidney diseases ($P<0.05$). The highest levels were in the normal range, and no disease associated with fluorosis was evident.

Possible differences in fluoride metabolism and its patterns of deposition in bones may exist in chronic renal disease. Further study and comparison of fluoride levels in these diseases are needed to evaluate the many other possible factors in the wide differences in bone-fluoride levels in this small collection of cases.

An apparent correlation between age of patients and the fluoride content of their bones has been noted by other investigators. Our results indicate that the fluoride content of bone increases with age (fig. 2) and that fluoride concentration tends to level off at the older ages.

## Summary

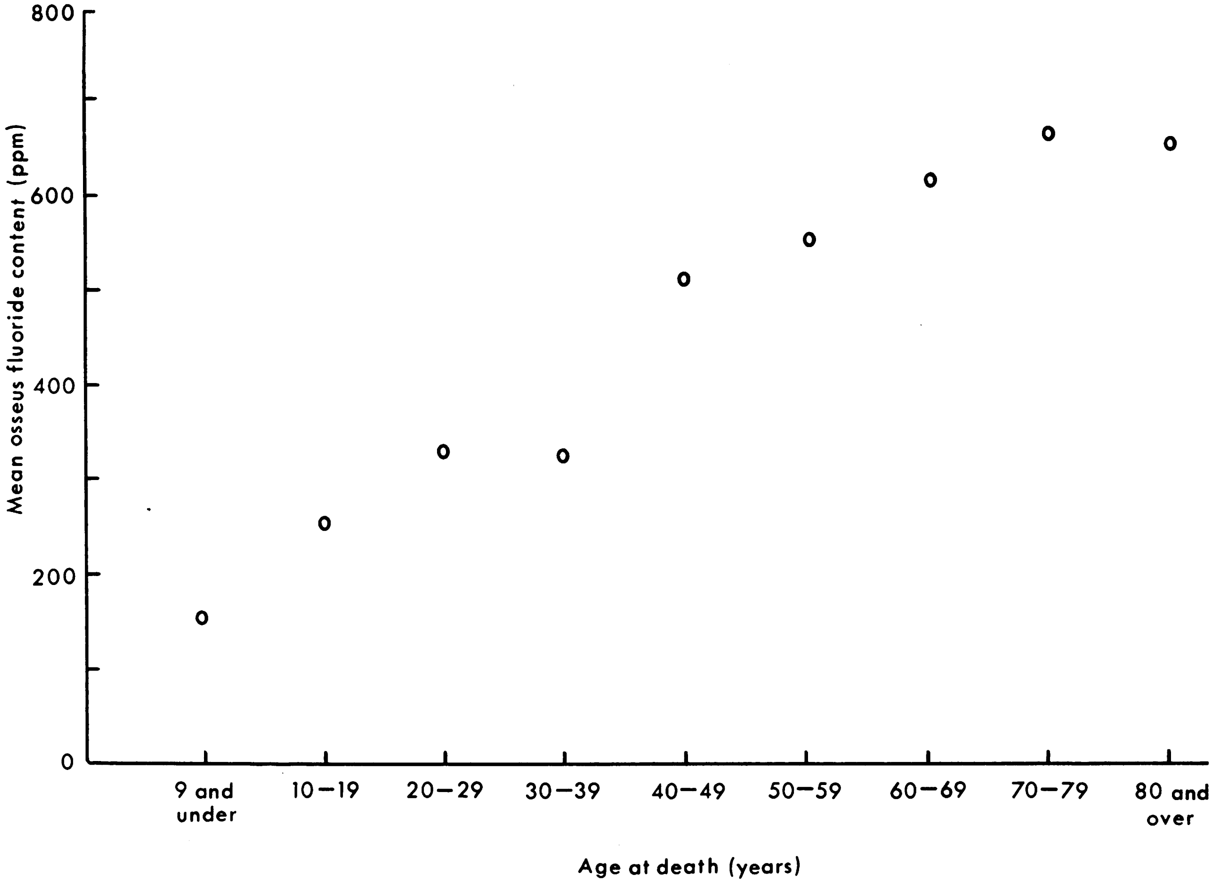
The presence of elevated concentrations of fluorides in the atmosphere has been associated with changes in certain plants and an increase in the fluoride content of forage in certain areas in Utah. Long-term ingestion of such forage by some animals has produced changes characteristic of fluorosis in some of them. It seemed important to determine if man was also

**Table 5. Comparison of mean fluoride content of dry, fat-free bones of subjects who had kidney disease with content in bones of persons in corresponding age groups without kidney disease**

| Disease | With kidney disease | | | | | Without kidney disease | | | | | t test |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean age (years) | Number of subjects | Osseous fluoride (ppm) Mean | SD | SE | Corresponding age group (years) | Number of subjects | Osseous fluoride (ppm) Mean | SD | SE | |
| Pyelonephritis, chronic, bilateral, marked | 65 | 5 | 1,282 | 417 | 186 | 60–69 | 16 | 557 | 330 | 82 | [1] 3.6 |
| Pyelonephritis, chronic, bilateral, slight to moderate | 71 | 10 | 570 | 206 | 65 | 70–79 | 15 | 538 | 258 | 67 | .3 |
| Pyelonephritis, chronic unilateral | 73 | 4 | 645 | 267 | 134 | 70–79 | 15 | 538 | 258 | 67 | .7 |
| Glomerulonephritis, acute | 58 | 3 | 365 | 71 | 41 | 50–59 | 16 | 551 | 313 | 78 | [2] 2.1 |
| Glomerulonephritis, chronic | 21 | 2 | 186 | 47 | 33 | 20–29 | 6 | 374 | 141 | 58 | [3] 2.8 |
| Lower nephron nephrosis | 30 | 5 | 202 | 87 | 39 | 30–39 | 1 | 315 | ------ | ------ | ------ |
| Arteriolonephrosclerosis | 78 | 10 | 730 | 407 | 129 | 70–79 | 15 | 538 | 258 | 67 | 1.3 |
| Other renal diseases | 48 | 5 | 713 | 532 | 238 | 40–49 | 11 | 449 | 221 | 67 | .9 |

[1] Different at $P<0.01$.
[2] Different at $P=0.05$.
[3] Different at $P<0.05$.

**Figure 2. Relationship between age and osseous fluoride content in subjects meeting exposure criteria**




being adversely affected. In this investigation, 127 human bodies were autopsied and studied for gross, histological, and chemical evidence of fluoride intoxication. Eighty-eight of these deceased persons came from geographic areas known to have had elevated fluoride levels in the atmosphere and forage. Analyses for fluoride, calcium, phosphorus, and ash were made on the calvarium, sternum, rib, iliac crest, and lumbar vertebrae. Determinations for fluoride and dry matter were made on the brain, heart, lungs, thyroid, aorta, liver, spleen, pancreas, and kidney.

The highest fluoride levels were observed in older adults showing the end-stage kidney of bilateral pyelonephritis and polycystic disease. Average levels were found in subjects with unilateral pyelonephritis and in subjects with pyelonephritis with only slight to moderate disease. The highest fluoride levels found, in subjects with the most severe kidney disease, were within the normal range, and no disease associated with fluorides was evident. Because the number of cases of chronic renal disease in this series was limited, further studies seem advisable.

Data accumulated in this study indicate that the levels of fluorides to which Utah residents in the area studied had been exposed were not responsible for gross or histological changes in soft tissues or bones.

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**DOCUMENTATION NOTE**

Tables 1, 2, 3, and 4 in more detailed form have been deposited as document number 8419 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D.C. A copy may be secured by citing the document number and by remitting $1.25 for photoprints, or $1.25 for 35 mm. microfilm. Advance payment is required. Make check or money order payable to: Chief, Photoduplication Service, Library of Congress.

## Conference Calendar

*August 12–17, 1965:* American Podiatry Association (annual meeting), Chase Plaza Hotel, St. Louis, Mo.

*October 17–20, 1965:* Medical Group Management, Hilton Hotel, Portland, Oreg.

*October 18–22, 1965:* American Public Health Association, Conrad Hilton Hotel, Chicago, Ill. George Schless, 59 East 54th Street, New York, N.Y., 10022.

*October 20–21, 1965:* Industrial Hygiene Foundation, Mellon Institute, Pittsburgh, Pa. Dr. Robert T. P. de Treville, Managing Director, Industrial Hygiene Foundation, 4400 Fifth Avenue, Pittsburgh, Pa., 15213.

*November 14–19, 1965:* Animal Care Panel (annual meeting), Sheraton Hotel, Philadelphia, Pa. Joseph J. Garvey, Executive Secretary, 4 East Clinton Street, Joliet, Ill., 60434.

*December 8–10, 1965:* National Symposium on Coccidioidomycosis: Del E. Webb TowneHouse, Phoenix, Ariz. Arizona Tuberculosis and Health Association, Inc., 733 West McDowell Road, Phoenix, Ariz., 85007.

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*Announcements for publication should be forwarded to Public Health Reports 6 months in advance of meeting.*