EDITORIAL REVIEW

FLUORIDE AND DOWN'S SYNDROME (MONGOLISM)*

Despite extensive research, the specific cause or causes of the human congenital malformation known as Down's syndrome or mongolism (1) are still uncertain. This defect exhibits considerable variation in severity and type (2) and occurs worldwide, with most large-scale studies indicating an average incidence rate of 0.8 to 1.9 cases per 1,000 total (or live) births (3, 4). Cytogenetically, it arises by nondisjunction in the G chromosome group, most often leading to a complete extra chromosome (trisomy 21); less frequently it involves translocations to other chromosomes and, occasionally, mixoploidy or mosaicism (2, 4). Although its incidence increases with advancing maternal age, especially after age 40 (4, 5), the extent to which this reflects intrinsic or extrinsic factors affecting the later phases of the reproductive period remains open to debate.

Recent reports of mutagenic effects of fluoride naturally raise the question of a possible role of fluoride in the etiology of Down's syndrome. For example, Jagiello and Lin (6) have described in vitro experiments indicating that sodium fluoride "can be a potent *meiotic* mutagen" in mouse, ewe, and cow oocytes. Mohamed and Kemner (7) have demonstrated that hydrogen fluoride produces gene mutations which affect viability in Drosophila melanogaster. Similar second chromosome lethals are also found in natural Drosophila populations in polluted areas. And, as reported elsewhere in this issue of FLUORIDE (page 47), Gileva, et al. (8) have observed significant alterations in the chromosomal integrity of bone marrow cells - but not in the mitotic activity of corneal epithelial cells - of white rats exposed to airborne cryolite or hydrogen fluoride. These authors conclude that further study of the mutagenic properties of fluorides in relation to their potential impact on human cell biology is urgently needed.

Epidemiological Evidence

During the years 1956-1963, a series of still highly controversial papers (9-13) appeared reporting statistically significant correlations between the occurrence of mongolism and the fluoride content of municipal water supplies in the north central part of the United States. The author was the late Ionel Rapaport, M.D., a French-trained physician specializing in research on mental disorders, who was then (1954-1961) on the staff of the Psychiatric Institute of the University of Wisconsin.

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Early in his investigations, Rapaport became aware of the high incidence of cataracts among mongols, especially after childhood. He then noticed that nearly 40 per cent (17 out of 43) of the mongols, but only 17.5 per cent (7 out of 40) of the epileptics, at one of the State colonies, were born in the city of Green Bay, Wisconsin, where the prevalence of reportable blindness from senile cataracts was also abnormally high (14). Combining these observations with the low incidence of dental caries among mongoloid children also recorded earlier by Benda (15), Rapaport directed his attention to the Green Bay area water supplies and noted that they had a comparatively high natural fluoride content (1.2-2.8 ppm).

Pursuing this lead, he proceeded to ascertain the place of birth of all institutionalized mongols in Wisconsin, North and South Dakota, and Illinois. He then grouped each of the more than 800 urban cases according to the reported fluoride content of the municipal drinking water and found a statistically significant, two-fold greater prevalence of mongoloid births per 100,000 inhabitants in communities with 1 ppm or more lifetime fluoride in the water supply as compared to those with practically no fluoride (9, 10). These findings were presented to the French National Academy of Medicine in November 1956 (9).

Application of Van Valen's formula (16) indicates a combined statistical probability that the entire set of correlations from all four states was due to chance is less than 1 in 125,000. The same parallelism between the prevalence of mongolism and the fluoride content of drinking water at the place of birth was subsequently corroborated by data supplied by 46 superintendents of institutions in other areas of the United States (17).

Rapaport further showed that the age of the mother played a decreasing role in the frequency of Down's syndrome in the high fluoride areas. In Wisconsin he found a mean maternal age of 34.26 years in the low (0.1-0.5 ppm) fluoride areas, whereas in the 1.0 ppm fluoride areas it was 33.17 years, and in the high (1.2-2.8 ppm) fluoride areas it was 29.81 years (9, 10). Later he suggested (13) that the occurrence of certain types of mongolism, particularly of the translocation variety, might be more susceptible to the influence of fluoride, thereby leading to a greater incidence of cases in the high fluoride areas than in the low ones.

Second Investigation

Shortly after the appearance of Rapaport's first reports (9,10), W. T. C. Berry (18) of the British Ministry of Health published results of a study in England in which a special effort was made to ascertain all cases of Down's syndrome rather than just those in institutions. Berry

found only a small difference in the incidence of 199 cases of mongolism when he compared the distribution of mongoloid births over a 10-year period between three cities with 0.7 to 2.0 ppm fluoride in the drinking water and six cities with 0.2 ppm fluoride or less (1.43 versus 1.54 per 1,000 live births, respectively). In contrast to Rapaport, he did not determine whether there were any maternal age-dependence differences. Moreover, his data covering 27 mongoloid births over a 5-year period in Essex County, an area where all the water districts were included, indicated a 38 per cent higher incidence where the fluoride content of the water was 0.2 to 4.0 ppm than where it was less than 0.25 ppm (0.91 versus 0.66 per 1,000 live births).

Meanwhile, Rapaport had undertaken a new investigation reflecting the advice of Dr. A. L. Russell of the U. S. Public Health Service, whose unpublished criticisms of Rapaport's original study are still widely cited (19). In this second investigation, Rapaport compiled all officially recorded cases of mongolism born in the State of Illinois from 1 January 1950 through 31 December 1956, whose mothers were habitual residents before the births in cities of 10,000 to 100,000 inhabitants. The data, as reported in 1959 (11) and in amplified form in 1960 (12) and in 1963 (13), indicated an extraordinarily high degree of statistical significance and consistency (see Table).

The inverse relationship seen between the percentage of older mothers of mongoloid children and the fluoride content of the water may at first seem surprising. But it is what one would expect if fluoride does indeed play a role in the etiology of mongolism. At higher levels of intake the effects of fluoride should be felt more strongly at an earlier maternal age, especially in the production of the translocation type of mongolism (13). The latter, in fact, is reported (2, 4) to have a higher incidence among younger mothers.

Other data from Rapaport's second investigation showed that the frequency of mongolism in cities of 5,000 to 10,000 inhabitants increased in the same manner as in the larger cities (13). Another interesting fact that emerged upon further analysis of the relevant data (13) was an apparent decrease in the frequency of mongolism with increasing calcium content in the water. Calcium, as Rapaport pointed out, has long been noted for its ability to reduce the toxic effects of fluoride.

As for the seeming discrepancy between Berry's findings (18) and his own, Rapaport (11-13) drew attention to the higher fluoride intake (at that time) in the typical British diet. In particular, he emphasized the considerable amount of fluoride — ca. 2.55 mg/day for adults, according to Cook (20) — resulting from the ten-fold greater consumption of tea in the United Kingdom than in the U. S. Midwest. Thus the total fluoride intake in the low-fluoride communities in Berry's

work was probably comparable to that in many of the high fluoride areas in Rapaport's. A striking correlation by Fedrick (21) of the incidence of anencephalus in relation to maternal tea drinking lends further support to this interpretation.

TABLE

Frequency of Mongoloid Births from 1 January 1950 through 31 December 1956
Illinois Cities of 10,000 to 100,000 Inhabitants[a]

Number of cities	Total number of births	Fluoride in water supply (ppm)	Cases of mongolism		Cases of mongolism[b] maternal age < 40		Percent of mothers age 40 and over
			Number	Rate per 1,000 births	Number	Rate per 1,000 births	
15	63,521	0.0	15	0.24	12	0.19	20.0
24	132,665	0.1-0.2	52	0.39	39	0.29	25.0
17	70,111	0.3-0.7	33	0.47	29	0.41	12.1
12	44,640	1.0-2.6	26	0.58	23	0.52	11.5
	22,413	1.0 art.	22	0.98	20	0.89	9.1
68	333,350	0.0-2.6	148	0.44	123	0.37	16.9
			$X^2 = 22.58$ $P < 0.001$		$X^2 = 26.17$ $P < 0.001$		

[a]Adapted from refs. 12 and 13. [b]This column eliminates the age-dependence effect caused by the universally high incidence of mongoloid births among mothers age 40 and over.

Recent Massachusetts Study

Rapaport's correlations of the frequency of mongolism with fluoride in drinking water have recently come under further scrutiny by Needleman, Pueschel, and Rothman (22) in a report concerning the occurrence of Down's syndrome in Massachusetts. Their study was modeled after an earlier one by Stark and Mantel (23) covering 2,431 mongoloid births on a county basis in Lower Michigan for the period 1950-1964. The Michigan data seemed to reveal little spatial-temporal clustering

and gave an overall incidence rate of 0.89 cases per 1,000 live births – not very different from the upper end of Rapaport's figures for his second Illinois investigation (11-13).

Utilizing data previously collected by Fabia and Drolette (24), the authors of the Massachusetts study (22) determined the geographical distribution of 2,469 cases of mongolism born to resident mothers among a total of 1,833,452 live births from 1950-1966. The births were classified with respect to occurrence in 321 nonfluoridating communities with less than 0.3 ppm fluoride in their water supplies and 30 communities with a variable and sometimes brief history of fluoridation; of the latter, nine ceased to fluoridate during the 17-year study period. Although the authors state that all mongoloid births were included, it is unclear how those in rural areas were classified.

The incidence rate for the cases in the nonfluoridating communities was 1.34 per 1,000 live births and 1.53 during periods of fluoridation in the fluoridating ones. The difference was attributed largely to a slightly higher maternal age in the fluoridating cities – stated to be 34.0 years compared to 33.2 years in the nonfluoridating ones – and to "a slight upward trend [of 'about 1 per cent per year overall'] in the rates of Down's syndrome" during the study period.

The first of these suggestions must be questioned, however, since Fabia and Drolette (24) tabulated and commented on a mean maternal age of 33.9 years for the bulk (2,411) of <u>these very same cases</u>. (For 1,553 cases without other attendant malformations it was 34.1 years, and for 858 remaining cases with one or more defects besides the syndrome itself it was 33.5 years.) Needleman et al. (22) do not indicate why their maternal age figures differ so markedly from those of Fabia and Drolette from whom they obtained most of the case records. It would appear, therefore, that the figures given by Needleman et al. are simply reversed, and that the mean maternal age for the 2,345 cases in the nonfluoridating communities was actually 34.0 years (<u>not</u> 33.2 years), whereas for the 124 cases in the fluoridating communities it was really 33.2 years (<u>not</u> 34.0 years). This point is most significant, for a trend toward lower maternal age in the fluoridating communities would actually corroborate Rapaport's work.

Needleman et al. also suggested that the upward trend in annual incidence rates accounted for most of the small increase in incidence from 1.46 to 1.53 cases per 1,000 live births observed between the 36-month pre- and post-fluoridation periods in an unstated number of communities. On the other hand, the fact that this pre-fluoridation incidence figure exceeds that of the nonfluoridating communities as a whole might well reflect some factor other than simply a secular increase. It is especially regrettable, therefore, that data were not

included for a lower fluoride-level classification of communities in the 0.0-0.1 ppm range (see Table of Rapaport's findings).

In his first study, Rapaport (9, 10) also found only a comparatively small increase in the prevalence of mongolism following short periods of fluoridation. In his second investigation in Illinois, the increase appeared to be larger, but the data were rather limited (12). In the report of the Massachusetts study (22), annual occurrence figures were unfortunately not presented, nor were the communities differentiated sufficiently with respect to fluoridation history. Thus, on the basis of the published evidence, it is virtually impossible to distinguish differences in incidence attributable to fluoridation from those which were assigned to overall yearly increases. The possible origin of the latter was not discussed, although they might have been due, at least in part, to the increases in dietary fluoride levels that have apparently occurred nationwide since the advent of fluoridation (25). Another factor which was not discussed is the impact that the general decline in birth rate during the second half of the study period might have had on the incidence trends.

Although it was reported that "fluoride levels in the water supplies of fluoridated communities were generally near the target range of 1 ppm," there is other evidence cited by Aasenden and Peebles (26) that this was not true in some cases. Moreover, the number of fluoridating compared to nonfluoridating communities was so small as to preclude any statistically significant differences from being found unless the incidence rates were markedly different. Even so, assuming that the reported differences have indeed originated primarily from fluoridation, and also assuming that all the water supplies of the State <u>had</u> been fluoridated, then the increase in incidence of only 1.34 to 1.53 would have produced over 330 <u>additional</u> mongoloid births out of the 1,752,345 total births associated with the cities that were not actually fluoridating. Under these circumstances, even an apparently insignificant increase in the incidence of Down's syndrome has very disturbing implications.

With respect to the question of the true overall incidence of mongolism — which obviously will now have to be viewed differently with the rise in the use of amniocentesis and subsequent abortion of fetuses with chromosome 21 trisomy (27) — Rapaport himself recognized (13) that the rates indicated by his data from the small and large cities in Illinois (0.38 and 0.44 cases per 1,000 total births, respectively) were undoubtedly somewhat low. Nevertheless, the impressive statistical consistency of his correlations strongly suggests that the various official records he consulted and utilized were, in fact, fairly reliable indexes of the actual distribution of cases of Down's syndrome in Illinois. A similar method of ascertainment by Gentry et al. (28) for the State of New York (exclusive of New York City) for the comparable

period 1948-1955 yielded an even lower rate of 0.32 per 1,000 live births. Likewise, Silberg et al. (29) found an incidence of only 0.37 from birth certificates in the State of Missouri for the period 1953-1964.

Other Correlations

In addition to an abnormally high frequency of cataracts (14, 30), a relatively low rate of dental caries during childhood and adolescence (9-13, 15), and delayed eruption of teeth (10, 12, 13, 15, 31), there are many other characteristic clinical and biochemical features of mongolism which bear a striking resemblance to various known effects of fluoride. Thus a peculiar type of deciduous enamel "brown stain" occurs widely among mongoloid children (31, 32). Although it has not been established whether this is a form of dental fluorosis, as it appears to be, Rapaport himself has reported (13) chemical analyses indicating a decidedly elevated fluoride content in the primary teeth of mongoloid children compared to those of epileptics in the same institution where the drinking water contained only 0.1 ppm fluoride.

Another peculiarity of Down's syndrome is an anomalous metabolism of tryptophan (33), which Rapaport (34) correlated with the formation of melanotic tumors in Drosophila having a dietary exposure to fluoride. Elevated serum alkaline phosphatase, which is generally characteristic of skeletal fluorosis (35), is likewise widely observed in the leucocytes of mongols (36). Premature aging and senility with extensive calcific deposits in certain soft-tissue organs is another feature common to both mongolism (37) and chronic fluoride intoxification (38).

Although the evidence for fluoride involvement in thyroid disorders is still debated (39), thyroid disease has come increasingly under suspicion in connection with the etiology of Down's syndrome, especially of the mosaic type (4, 40, 41). Women with a history of thyroid disorders have about a threefold greater risk of giving birth to a mongoloid child (40, 41). Thyroid autoantibodies associated with the production of chromosomal aberrations in the fetus are also significantly increased in the mother as well as the child (41).

Other clinical features of mongolism which suggest the influence of fluoride include disturbances in the growth (42) and pigmentation (12) of the hair and hyperkeratinization of the skin (12). Rapaport (12) observed that the latter was more prevalent among mongols who were admitted to Wisconsin institutions after 1950 when fluoridation had begun to be widely adopted in the State.

The effects of fluoride on bone marrow cells studied by Gileva

et al. (8) raise the question of whether there is fluoride involvement in the comparatively high incidence of leukemia among mongoloid children. Similarly, findings of direct toxicity of fluoride to heart muscle tissue (43) point to a possible connection with the 30 per cent incidence (24) of congenital heart disease among mongols. Clearly, much more work needs to be done before these and other aspects of the bearing of fluoride on the nature and occurrence of Down's syndrome can be satisfactorily understood.

In closing, let it be clearly stated and understood that, although this discussion has dealt primarily with fluoride, there are other agents and factors that also have to be considered in relation to the etiology of Down's syndrome (4). Fluoride is only one of many mutagens in the human environment.

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