

5. Fry, B. and Taves, D. R.: Serum Fluoride Analysis with the Electrode. *J. Lab. Clin. Med.*, 75:1020-1025, 1970.
6. Hanhijärvi, H., Penttilä, I., Pekkarinen, A., and Hakulinen, A.: The Effect of Age on the Free Ionized Plasma Fluoride Concentrations in Patients from Artificially Fluoridated and Non-Fluoridated Drinking Water Communities. In press.
7. Hytten, F. E. and Paintin, D. B.: Increase in Plasma Volume During Normal Pregnancy. *J. Obstet. Gynec. Brit. Commonwealth*, 70: 402-405, 1963.
8. Ericsson, Y.: Fluoride Excretion in Human Saliva and Milk. *Caries Res.*, 3:159-165, 1969.
9. Chesley, L. C. and Duffus, G. M.: Preeclampsia, Posture and Renal Function. *Obstet. Gynec.*, 38:1-5, 1971.

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A DOUBLE BLIND TEST FOR
DETERMINATION OF INTOLERANCE TO FLUORIDATED WATER
(Preliminary Report)

by

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SUMMARY: A double blind test for the detection of untoward effects from fluoridated water is described. Preliminary results with 60 patients out of a group of 300 indicate that certain individuals are intolerant to fluoride and reproducibly develop gastrointestinal symptoms, stomatitis, joint pains, polydipsia, headaches, and visual disturbances.

During recent years a clinical syndrome has been presented in several publications which has been attributed to total fluoride intake from water (1, 2), food (3, 4), tooth-paste (5, 6) and to oral administration of fluoride (7, 8). This syndrome involves mainly the gastrointestinal tract with pains in the epigastric area and in the bowels; nausea; vomiting; diarrhea alternating with constipation; and symptoms attributable to the neuromuscular system, namely headaches, paresthesias, muscular fibrillation, pains in arms and legs, and arthritis in the spinal column. Others have encountered these manifestations in conjunction with skeletal fluorosis induced by fluoride intake through industrial exposure (9, 10) and from fluoride in water naturally (11). In India, on the other hand, where endemic fluorosis is probably more widespread

than anywhere else in the world these manifestations have rarely been recorded (12).

One of the methods, by means of which the relationship of these symptoms to fluoride has been established, is a double blind test (1). Three identical bottles labeled #1, 2, and 3 are prepared by the pharmacist: Two contain plain distilled water, the third 1 mg of fluoride (2.2 mg NaF) per tablespoon of water, the daily dose recommended for prevention of tooth decay. Neither the patient nor the physician knows which bottle contains fluoride. The patient is instructed to take 1/2 tablespoon twice daily in one pint of water (before breakfast and before dinner) from bottle #1 for one week, from bottle #2 the second week and from bottle #3 the third week. Through the recurrence of symptoms the patient is able to identify the fluoride-containing bottle.

Since fluoridation has been introduced in communities of the Netherlands, Dr. E. Young of the University Hospital in Utrecht has observed a case of urticaria which was associated with the use of fluoridated water. Intracutaneous injections with a 1 mg/ml solution of sodium fluoride gave positive reactions in 4 patients with urticaria whereas no such reactions occurred in 4 persons without it. Waldbott (13) has also described urticaria attributable to fluoridated water. The occurrence of urticaria due to fluoride induced us to carry out double blind studies utilizing a modification of the above-described method. The current report is concerned with our preliminary findings on 60 patients.

Method

1. Scope of the Study: In addition to twelve physicians practicing in Haarlem and its surroundings, individuals with such special interests as biology, chemistry, and neurology participated in the study. In order to establish a close control, we obtained the collaboration of a pharmacist and a notary public.

2. Screening of Cases: To determine which individuals should be included in the series, the patients who suspected that they were harmed by fluoridated water were screened in the following manner: They were instructed to discontinue drinking fluoridated water for brief periods of time which varied from patient to patient. Those individuals in whom the symptoms disappeared and recurred upon resumption of fluoridated water were considered eligible for the double blind study.

3. Preparation of the Solution: The pharmacist was asked to prepare solutions of NaF and of Na_2SiF_6 at concentrations which would cause one drop from a dropper* to contain 0.25 mg fluoride. He added

*These dropper bottles are on the market and are legally gauged and registered internationally.

"X" drops from one of the bottles to 1 liter of distilled water. From this solution the concentration of fluoride was determined.

In a closed envelope, under code letter and number, the notary public was informed by the pharmacist how many drops had been added to the water, i. e. the value of "X". Likewise in a closed envelope under the same code letter and number, analysis of the solution, i. e. the chemist's results were recorded. The notary public was informed regarding the percentage of fluoride in the solution as determined by an impartial laboratory.

The notary public certified that "X" was stated to be 20 drops and that the fluoride concentration according to the analysis was 4.3 ppm fluoride. Therefore, the addition of 4 drops from this bottle to 1 liter of unfluoridated water raised the level of fluoride in the water by 0.86 ppm fluoride.

As a second check the drop volume was determined by means of a buret in order to establish as exactly as possible that the 1 ppm fluoride addition was not being exceeded. A preliminary study established exactly the dose per drop as shown in the following table.

TABLE 1

Initial Reading of Buret: 45.93 cc.

1) Added 1 drop	45.89	0.04 cc for 1 drop
2) " 2 drops	45.80	0.09 " " 2 drops
3) " 20 "	44.87	0.93 " " 20 "
4) " 30 "	43.47	1.40 " " 30 "
5) " 20 "	42.54	0.93 " " 20 "
6) " 20 "	41.60	0.94 " " 20 "
7) " 30 "	40.20	<u>1.40</u> " " 30 "
		5.73

Total 123 drops with a volume of 5.73 cc.

Thirty drops from this test bottle had a total volume of 1.40 cc.* Four drops of solution from this bottle added to 1 liter of water resulted in an increase of 0.86 ppm fluoride per liter. This shows there are 21.5 drops per cc.

*At no time in this study did the volume of 30 drops exceed 1.58 cc.

FLUORIDE

4. Coding: In order to further assure complete reliability of the double blind test, code numbers were assigned to both physicians and patients. Each physician received a code letter, and a code number was assigned to each patient. The combination of these two codes provided a simple system:

The first patient of Dr. P. was coded: P-1

The second " " " " " " P-2

The sixth " " " Q. " " Q-6

The physician places an order for a certain number of dropper bottles under a code letter and number through a messenger. The pharmacist receives the order from the messenger and prepares a series of bottles numbered 1 to 8. Several of these bottles contain fluoride with a concentration of 0.25 mg fluoride per drop. The 8 bottles are sent by the messenger in a single container marked with the above-described code system, for instance P-1 or S-3. At the same time, the pharmacist sends a letter to the notary public in a sealed envelope which divulges which bottles contain the fluoride solution. This envelope is marked with the same code letter and number as the package of bottles.

5. The Patient: After the physician receives the bottles from the messenger he gives the package to the patient who now uses bottles 1, 2, 3, up to 8 under the supervision of the physician. The patient is also instructed to avoid tea and seafood which are high in fluoride. To every liter of unfluoridated water he adds four drops out of a dropper bottle which contains either distilled water or the fluoride solution. Thus the original unfluoridated water is either rendered fluoridated or remains unfluoridated. Neither the patient nor the physician are aware which water is fluoridated and which is not. If the patient develops no symptoms he uses bottle #1 for two weeks then bottle #2, etc. On the other hand, if ill-effects occur, he discontinues the use of the water immediately and reports to his physician who then records the number of the bottle which presumably induced the complaints. The test is then discontinued until the symptoms disappear. Following cessation of symptoms, the test is promptly resumed with the following bottle until all 8 bottles are used.

When all eight bottles have been used the physician sends his findings to the notary public in a sealed envelope which is marked on the outside with the code letter and number. The two envelopes with the same number are opened by the notary public and the contents are recorded.

Results

Table 1 presents the symptoms observed in 60 patients, selec-

ted from a group of about 300 individuals who had suspected ill-effect from fluoridated water.

The following case demonstrates a clear relation between the symptoms and the use of fluoridated water:

Case M. R., female, age 28, (Code G-1) had experienced ulcers in the mouth, general pruritus, acneform lesions around the mouth and eyes for 12 days prior to the test. In the preliminary screening, the patient was taken off fluoridated water during which interval he had no complaints. In January 1973 immediately upon disappearance of his illness, the test was initiated. On the 12th day of employing bottle #1, the ulcers in the mouth recurred, whereupon the patient switched to distilled water exclusively. After a 5 day interval the ulcers had subsided and the patient resumed the test. Use of bottle #4 reproduced the symptoms. They recurred on the 8th day and lasted for 14 days. Ten days following the use of bottle #7 the symptoms recurred with general pruritus which lasted for 17 days. The recurrence of these minor symptoms correlated precisely with the intake of the fluoride water in bottles 1, 4, and 7.

TABLE 2

Summary of 60 Selected Patients

<u>Complaints</u>	<u>Number</u>	<u>Percent</u>	<u>Remarks</u>
Stomach and intestinal	30	50	Nausea (4) Pain in epigastrium (5) Abdominal pain (17) Bloating of abdomen (2) Diarrhea (12) Constipation (1)
Stomatitis	18*	30	
Polydipsia	5	8	
Joint pains	3	5	
Migraine-like headaches	3	5	
Visual disturbances	3	5	
Tinnitus	2	3	
Mental depression	2	3	

*Two of these patients had complaints after using fluoride-tablets.

An additional experiment was carried out by a participant of our panel (G. G.) who had not been ill prior to the test.

He consumed four glasses of water each of which contained 1 ppm fluoride (total of 1 mg fluoride per day) without any noticeable effect. Subsequently he drank four glasses of water with 2 ppm (total 2 mg fluoride per day) without experiencing any reaction. The following day he repeated the experiment with 3 ppm fluoride in water and four ppm the next day. At 5 mg of fluoride in water per day he experienced diarrhea and bloating in the abdomen. The day following the disappearance of these symptoms he took a glass of 20 ppm fluoride (total 5 mg per day). This induced a severe stomatitis which disappeared after 10 days. When he reduced the dose to 4 glasses of water each of which contained 4 ppm of fluoride, the intestinal symptoms returned in conjunction with dryness of the oral mucous membranes. After these symptoms disappeared he consumed 4 glasses of water each containing 3 ppm fluoride. Again the symptoms appeared but did not recur after taking 4 glasses containing 2 ppm. This experiment suggests that if fluoride has already been stored in the system, the symptoms recur at a lower concentration than without prior fluoride intake. We name this phenomenon "charging effect".

Comment

Although our observations have been limited to a relatively small number of cases it is evident that, by this method, a definite relationship between the symptoms and the presence of fluoride in drinking water can be established. When employing this method, in order to obtain the equivalent of artificially fluoridated water at the 1 ppm concentration, 4 drops per liter must be added to all nonfluoridated water used for drinking and cooking. In this way it can be assured that the daily amount of ingested fluoride will equal that consumed in communities where the municipal water supply is fluoridated.

Bibliography

1. Waldbott, G. L.: Fluoride in Clinical Medicine. Suppl. 1 ad Vol. 20, Intl. Arch Allergy and Applied Immunology, 1962.
2. Petraborg, H. T.: Chronic Fluoride Intoxication from Drinking Water (Preliminary Report). Fluoride, 7:47-52, 1974.
3. Cook, H. A.: Crippling Arthritis Related to Fluoride Intake (Case Report). Fluoride, 5:209-212, 1972.
4. Waldbott, G. L. and Cecilioni, V. A.: "Neighborhood" Fluorosis. Clinical Toxicology, 2:387-396, 1969.
5. Waldbott, G. L.: Acute Fluoride Intoxication. Suppl. 400, Acta Med. Scand., 1963.
6. Douglas, T. E.: Fluoride Dentifrice and Stomatitis. Northwest Med., 56:1037-38, 1957.
7. Rich, C.: Osteoporosis and Fluoride Therapy. Journ. Am. Med. Assoc., 196:1165, 1966.
8. Shea, J. J., Gillespie, S. M., and Waldbott, G. L.: Allergy to Fluoride. Annals of Allergy, 25:388-391, 1967.
9. Roholm, K.: Fluorine Intoxication. A Clinical Hygienic Study, Arnold Busck, Copenhagen, 1937.
10. Maltseva, V. A.: Eye Damage in Workers with Fluorine Intoxication. Vestn. Oftalmol., 2:71-74, 1973.
11. Frada, G., Mentasana, G., and Nalbone, G.: Research on Endemic Fluorosis. Minerva Medica, 54:45-59, 1963.
12. Singh, A., Jolly, S. S., Bansal, B. C., and Mathur, C. C.: Endemic Fluorosis. Medicine, 42:229, 1963.
13. Waldbott, G. L.: Urticaria Due to Fluoride. Acta Allergologica, 13:456-468, 1959.

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