

## ALLERGY AND HYPERSENSITIVITY TO FLUORIDE

Bruce Spittle  
Dunedin, New Zealand

**SUMMARY:** A review of the literature was undertaken in response to four recent reviews which found that the evidence that fluoride was an allergen was unconvincing. Reports were found of urticaria, contact dermatitis and stomatitis occurring in response to fluoride, settling on the withdrawal of fluoride and recurring with appropriate challenges. It is concluded that the four reviews were seriously incomplete in their coverage of the literature, and that when a more complete examination is made there are reasonable grounds for concluding that there are individuals in whom allergy or hypersensitivity to fluoride has been demonstrated. The sources of fluoride included those used in the fluoridation of community water supplies.

**Keywords:** Allergy; Contact dermatitis; Fluoridation; Fluoride; Hypersensitivity; Stomatitis; Urticaria.

### Introduction

Four recent reviews, from the United States of America (1,2), Australia (3) and New Zealand (4), have concluded that claims that fluoride is an allergen could not be supported from studies undertaken to date, and that the weight of evidence shows that fluoride is unlikely to produce hypersensitivity and other immunological effects. Although the two US subcommittees involved were different, the sections dealing with the effects of fluoride on hypersensitivity and the immune system are almost the same. Thus although all four reports reached a similar conclusion that fluoride was unlikely to produce allergic or hypersensitivity effects, the 1993 reports (2,4) refer to those published in 1991 (1,3) and are not completely independent. The present review was undertaken to see if the same conclusion was reached.

### Literature Review

In dismissing the occurrence of allergic reactions to fluoride, the New Zealand report (4) refers to the earlier United States (1) and Australian (3) reviews both of which in turn cite a statement by Austen *et al* (5) on behalf of the American Academy of Allergy. The Academy reviewed reports of fluoride allergy and found no evidence of allergy or intolerance to fluorides as used in the fluoridation of community water supplies (5).

Waldbott made a rebuttal of the findings of Austen *et al* in 1971 (6) and noted that in 1978 this was still unrefuted (7). He observed that the statement by Austen *et al* cited only seven references, of which only five referred to fluoride (6). He commented that the committee had referred to a book of his, *A Struggle with Titans* (8), which was written for lay persons, but had apparently not given attention to 19 articles of his in scientific journals (6).

Austen *et al* conclude that in the review of the cases reported there was insufficient evidence to state that true syndromes of fluoride allergy or intolerance existed (5). This included the cases reported by Feltman and Kosel (9). They had reported that 1% of their cases reacted adversely to fluoride tablets (9). Atopic dermatitis and urticaria occurred with the use of fluoride tablets, disappeared with the use of placebo tablets, and recurred when the fluoride tablets were, unknowingly to the patient, given again (9). Kaplan (10) notes that when an urticarial drug reaction is suspected, this diagnosis may be tested by eliminating the agent. If it is correct, gradual resolution of the urticaria is anticipated. He notes that all medications should be considered a potential cause of urticaria. Except for penicillin, it is stated that no routine tests are available that can reliably confirm or refute the diagnosis of drug-induced urticaria or angioedema, and an empirical approach is therefore indicated (10). The empirical approach adopted by Feltman and Kosel of withdrawal of the fluoride tablets, substitution with placebo tablets and later a blind challenge with fluoride tablets (9) appears to be in keeping with the guidelines of Kaplan (10). Contrary to the view of Austen *et al*, the results suggest that there is clinical evidence that a syndrome of fluoride allergy exists.

Another paper reviewed by Austen *et al*, by Shea, Gillespie and Waldbott (11), reported allergy to fluoride in toothpaste and drops. In one case, involving a 48-year-old man with giant urticaria, double-blind testing was used to confirm the aetiological relationship with fluoride (11). The lesions had involved mainly the hands and feet but sometimes the entire body surface. They usually occurred about one hour after breakfast. He had been using a fluoridated toothpaste at the time. Six days after discontinuing this he was completely free of symptoms. Three years later he experienced another episode of generalized urticaria. This occurred within an hour of his inadvertently brushing his teeth with a fluoridated toothpaste. The double-blind testing involved taking a tablespoonful of water each morning from three bottles labelled 1, 2 and 3 with each bottle being used in turn for a week at a time. Bottle 2 contained 1 mg of fluoride per tablespoonful, this code being known only by the pharmacist who prepared the bottles. On the fourth day on bottle 2 he developed generalized pruritis and oedema in the distal joints of his extremities. Nevertheless he continued taking the water from bottle 2 for another three days during which time he developed hives on the right elbow and pains in the lumbo-sacral area followed by an outbreak of generalized urticaria. These symptoms disappeared 2 days after the patient discontinued the use of bottle 2 (11).

In a second case the aetiological role of fluoride was confirmed using a patch test (11). The patient, a 9-year-old female, had frequent urticaria, allergic conjunctivitis and minor asthmatic attacks. There had been constant episodes of ulcers distributed throughout the oral cavity. Slight abdominal tenderness was present. A fluoridated toothpaste had been used since the onset of the oral lesions. A patch test gave a two plus reaction to the fluoride toothpaste but not to chewing gum, Lifesavers, or a non-fluoride toothpaste. During the development of the positive patch test reaction the patient experienced a flare-up of the oral lesions associated with severe abdominal pain. After changing to a non-fluoride toothpaste the oral lesions as well as the

abdominal pains subsided completely. One year later a recurrence of the stomatitis occurred within 15 minutes of inadvertently brushing her teeth with a fluoridated toothpaste. Severe abdominal pain also occurred (11). Again in this case the guidelines of Kaplan (10) appear to have been followed and indicate that there is clinical evidence to show that a syndrome of fluoride allergy exists. Although the above cases refer to the use of fluoride tablets and toothpaste in contrast to the mention in the statement by Austen *et al* of fluorides as used in the fluoridation of community water supplies, this qualification is not mentioned earlier in the article by Austen *et al* (5). There it is stated that there is not sufficient clinical evidence to state that a true syndrome of fluoride allergy exists (5).

Urticaria is characterized by the appearance of pruritic, erythematous, cutaneous elevations that blanch with pressure, indicating the presence of dilated blood vessels and oedema (10). Urticaria, both local and generalized, was described with acute sodium fluoride poisoning by Lidbeck, Hill and Beeman (13). In 1959 Waldbott described six cases of urticaria due to fluoridated water (13). In one case, Mrs PO aged 40 years, the relation of the urticaria to fluoride in water was substantiated by a double-blind test (14). The patient was required to take a tablespoonful of water daily from three bottles labelled 1, 2 and 3, using each for a week at a time. One bottle contained 1 mg of fluoride per tablespoonful but neither the patient nor her attending physician knew which one it was. The urticaria reappeared on the third day of using the fluoride solution. Another patient, Mrs HP aged 48 years, had generalized urticaria which began three weeks after moving to a fluoridated area. On using water with a low amount of fluoride in hospital (0.1 ppm) the urticaria subsided. Within 24 hours of resuming using fluoridated water the urticaria recurred. An intradermal skin test with a 1:100 dilution of a 1% aqueous solution of sodium fluoride gave a 3-plus wheal reaction. This was followed by a generalized outbreak of urticaria within ten minutes. Control tests with a 1% solution of sodium bromide and sodium iodide were negative. With double-blind testing involving three bottles of water only one of which contained fluoride, urticaria recurred within two days of taking the water from the fluoride-containing bottle (14).

Contact dermatitis is a term used to describe any rash resulting from a substance touching the skin and as a synonym for allergic contact dermatitis (15). Allergic contact dermatitis is the result of a substance contacting skin that has undergone an acquired specific alteration in its reactivity (15). This altered reactivity is the result of prior exposure of the skin to the material eliciting the dermatitis or a chemically closely related substance (15). The patch test, whereby the suspected substance is applied to the skin under an occlusive dressing for one to two days and the test site observed after removal, remains the only practical test for demonstrating contact dermatitis (15). In 1948 Abelson reported a typical contact dermatitis with vesiculopapular pruritic lesions on the hand of a dentist occurring immediately upon application of a 2% solution of sodium fluoride to a patient's teeth (16). Waldbott reports observing repeatedly the same pattern of dermatitis in dentists with confirmation by patch testing (17). Waldbott (14) also described a scaly erythematous pruritic lesion on the thighs of a woman aged 20 years which subsided after moving for observation

to a nonfluoridated area. After she had been symptom-free the dermatitis recurred at the same site with papulous, vesicular lesions and intense pruritis within an hour of receiving a test dose of 6.8 mg of fluoride in 300 ml of water. A placebo test with 300 ml of distilled water produced no ill effect (14).

Aphthous stomatitis and ulcers of the mouth have been described as being not uncommon in persons using fluoride toothpaste and in children who have had topical fluoride applications applied to their teeth (14). Douglas (18) has described 133 cases of stomatitis from fluoride containing toothpaste. All the lesions were refractory to antibiotic therapy and local medication. The lesions cleared up with changing to a nonfluoride toothpaste. In 32 patients the stomatitis was reproduced by applying the fluoride toothpaste, in some as often as six times (18). Waldbott (14) records the case of Mrs LCH aged 62 years who developed a mouth ulcer within three days of starting the use of a fluoride toothpaste. Elimination of the fluoride toothpaste caused the condition to gradually disappear. Application of a saline solution with a cotton swab beneath her tongue produced no ill effect. When a 1% aqueous solution of sodium fluoride was applied, there developed, within five minutes, a hyperæmic œdematous intensely pruritic lesion in the test area which extended into a large portion of the oral mucosa. A smear of the mucus from the area showed marked eosinophilia (14).

Waldbott (19) also reported the case of Mrs WEA aged 62 years who developed the allergic symptoms of rhinitis, allergic sinus disease and urticaria within hours of using fluoridated water with an intake of 1 to 2 mg a day. A typical allergic appearance of the nasal mucosa, eosinophilia and an allergic wheal followed the intradermal injection of 0.1 mg of sodium fluoride. Control injections with horse serum, saline solution and weaker aqueous dilutions of sodium fluoride had no adverse effect (19). Zanfagna (20) has reported on Mrs MET aged 48 years who developed acute generalized urticaria after drinking fluoridated water. A further attack was also traced to fluoridated water. It was stated that sensitivity to fluoride was confirmed by positive challenge tests (20).

### Discussion

Currently allergy is considered to be synonymous with hypersensitivity in meaning (21). They usually refer to type 1 immediate hypersensitivity, mediated by specific IgE antibodies in genetically predisposed individuals and resulting in symptoms characteristic of eczema, urticaria, rhinitis, asthma and anaphylaxis, although it is noted that several types of allergic states encompass all the mechanisms described by Gell and Coombs (21).

Waldbott (14) saw a difference between reactions to fluoride due to the toxic action of the fluoride ion and allergic sensitivity. He pointed out that the degree of tissue damage from the toxic action of the fluoride ion has been seen to depend on numerous factors including the dose of the fluoride ion, the duration of the contact with the involved tissue, the pH of the intracellular and extracellular fluids, and the presence of calcium, magnesium and other metals. When in contact with fluids in an acid medium such as gastric juice, fluoride compounds tend to induce undissociated hydrofluoric acid which has a corrosive action. True allergic reactions, on the other

hand, can result from relatively insignificant doses and from short exposures. The presence of such allergic symptoms as urticaria, vasomotor rhinitis, dermatitis and eosinophilia, a prompt response to adrenaline, and occasionally positive skin and patch test reactions, point to allergy (14). As an example of the difference between allergy or hypersensitivity to a drug and intolerance to it, reactions to aspirin can be considered (7). Intolerance to aspirin is characterized by hæmorrhages in the stomach whereas allergy to aspirin results in such symptoms as hives, asthma, allergic nasal and sinus disease or even anaphylactic shock (7).

To establish the existence of allergy to fluoride, community studies which are prone to the ecological fallacy (22) are insufficient and stronger evidence based on the studies of individuals is required. Although in the above discussion reference is made to cases of allergy related to fluoride tablets and toothpaste, there are included cases (Mrs PO, Mrs HP, Mrs WEA, Mrs MET) in which the reaction of allergy has been to fluorides as used in the fluoridation of community water supplies.

Although Waldbott found that allergic reactions to fluoride could occur, it was not considered that this was the only mechanism whereby adverse reactions to fluoride were experienced (7). Intolerance to fluoride was seen to occur for example through the formation of corrosive undissociated hydrofluoric acid when fluoride ions were in contact with acidic gastric secretions.

This potential mechanism for fluoride damaging the gastroduodenal mucosa has been supported by Susheela *et al* (23) along with other potential mechanisms such as enzyme system inhibition. By studying patients intensively, including by endoscopy and biopsy for histopathological and scanning electron microscope examination, they found that the gastroduodenal mucosa could be severely damaged by the toxic effects of fluoride resulting in dyspeptic symptoms. The changes found included surface abrasions with loss of microvilli in the gastric antrum and duodenum, and a 'cracked-clay' appearance of the duodenal mucosa. Gastrointestinal discomfort, in the form of dyspeptic symptoms was thus seen to be an important diagnostic feature in identifying persons affected by fluoride and it was considered that such symptoms should not be dismissed as non-specific (23).

Moolenburgh (24) described abdominal discomfort occurring on a double-blind basis with exposure to fluoride. He found in his Dutch general practice patients with illnesses similar to those described by Waldbott. He considered that far from having exaggerated the side-effects, Waldbott had, on the contrary, been inclined to understatement. Although Moolenburgh expected to find an allergic basis for the adverse effects associated with fluoride, he considered that the symptoms represented poisoning with inhibition of the immune system by a toxic substance in sensitive persons. Where an exacerbation of illnesses with an allergic component such as eczema and asthma occurred, his view was that immune system inhibition by fluoride had resulted in a loss of the ability to cope with the allergy (24). The work by Moolenburgh and his colleagues has been described by Grimbergen (25). By double-blind testing with 60 patients he showed that certain individuals were intolerant to fluoride and that exposure to this could reproduce gastrointestinal symptoms,

DIETARY MODULATION OF THE SYMPTOMS OF CADMIUM TOXICITY IN RATS: EFFECTS OF VITAMIN-A, VITAMIN-C, VITAMIN-D, VITAMIN-D HORMONE, AND FLUORIDE E W Pleasants, C Waslien and B A Naughton, USA .....	283-284
PLASMA INORGANIC FLUORIDE LEVELS WITH SEVOFLURANE ANESTHESIA IN MORBIDLY OBESE AND NONOBESE PATIENTS E J Frink, T P Malan, E A Brown <i>et al</i> , USA .....	284
EVIDENCE THAT FLUORIDE THERAPY INCREASES TRABECULAR BONE DENSITY IN A PERIPHERAL SKELETAL SITE H Resch, C Libanati, S Farley <i>et al</i> , USA .....	285
BIOAVAILABILITY AND PHARMACOKINETICS OF FLUORIDE FROM 2 GLUTAMINE MONOFLUOROPHOSPHATE PREPARATIONS G Warneke and I Setnikar, Italy .....	285
EFFECTS OF MEAL ON THE PHARMACOKINETICS OF FLUORIDE FROM ORAL MONOFLUOROPHOSPHATE G Warneke, I Setnikar, Italy .....	286
HIP FRACTURE RATES IN HONG KONG AND THE UNITED STATES, 1988 THROUGH 1989 S C Ho, E Bacon, T Harris <i>et al</i> , USA .....	286
THE FLUORIDATION OF DRINKING WATER AND HIP FRACTURE HOSPITALIZATION RATES IN 2 CANADIAN COMMUNITIES M E Suarezalmazor, G Flowerdew, L D Saunders <i>et al</i> , Canada .....	287
HIP FRACTURE INCIDENCE BEFORE AND AFTER THE FLUORIDATION OF THE PUBLIC WATER SUPPLY, ROCHESTER, MINNESOTA S J Jacobsen, W M Ofallon and L J Melton, USA .....	287-288
EVALUATION OF THE USE OF TOPICAL FLUORIDE GEL S H Y Wei and C K Y Yiu, Hong Kong .....	288
SYSTEMIC FLUORIDES - DROPS AND TABLETS K W Stephen, Scotland .....	288
ROLE OF FLUORIDE TOOTHPASTES IN A CARIES-PREVENTIVE STRATEGY K G Konig, Netherlands .....	289
FLUORIDE MOUTHRINSES AND FLUORIDE VARNISHES L G Petersson, Switzerland .....	289
<i>INSITU</i> REMINERALIZATION OF SUBSURFACE ENAMEL LESION AFTER THE USE OF A FLUORIDE CHEWING GUM W J Lamb, R E Corpron, F G More <i>et al</i> , USA .....	290
CALCIUM FLUORIDE FORMATION IN ENAMEL FROM SEMI-CONCENTRATED OR LOW-CONCENTRATED-F AGENTS <i>INVITRO</i> C Bruun and H Givskov, Denmark .....	290
INFLUENCE OF CONSTANT FLUORIDE LEVELS IN SOLUTION ON ROOT HARD TISSUE DEMINERALIZATION AND REMINERALIZATION MEASURED BY I-125 ABSORPTIOMETRY H Almqvist and F Lagerlof, Sweden .....	291
FLUORIDE AND MINERAL CONTENT IN HYPER-REMINERALIZED CORONAL BOVINE DENTINE <i>INVITRO</i> AFTER AN ACID CHALLENGE Y Iijima, J L Ruben, T G M Zuidgeest and J Arends, Japan and Netherlands .....	291-292
LONG-TERM FLUORIDE RELEASE OF VISIBLE LIGHT-ACTIVATED COMPOSITES <i>INVITRO</i> : A CORRELATION WITH <i>INSITU</i> DEMINERALISATION DATA G E H M Dijkman, J Devries, A Lodding and J Arends, Netherlands .....	292
SLOW-RELEASE FLUORIDE K J Toumba and M E J Curzon, England .....	292
1993 AUTHOR INDEX .....	293-295
XXth ISFR CONFERENCE, BEIJING, October 10-13 1994 .....	295
1993 SUBJECT INDEX .....	296-298

stomatitis, joint pains, polydipsia, headaches and visual disturbances. Grimbergen noted that Young had found that intracutaneous injections of sodium fluoride gave positive reactions in four persons with urticaria associated with the use of fluoridated water but no such reactions in four persons without urticaria (25).

Petraborg (26,27) similarly described a wide spectrum of symptoms in 27 persons exposed to fluoridated water. He considered that since none of the persons were aware that their drinking water was fluoridated or were familiar with the manifestations of fluoride toxicity, that the accounts of their illnesses were equivalent in validity to those associated with double-blind procedures. He noted that several patients were not convinced that something in their drinking water was causing their illness and resumed drinking fluoridated water. Relapses of their illnesses followed. The symptoms included extreme chronic fatigue, polydipsia, general pruritis, headaches and gastrointestinal symptoms (26,27).

Another adverse effect of fluoride, described by Lee (28), involved an elevation of the serum bilirubin level in six patients with Gilbert's disease. Long-term testing and studying the effect of fluoride tablets in one patient gave evidence that the hyperbilirubinemia was due solely to fluoride and not to some other ingredient of the water supply. An enzyme-inhibiting action by fluoride was considered to be the most likely mechanism involved (28).

It is concluded, on the basis of the above examination, that the recent North American, Australian and New Zealand reviews (1-4) were seriously incomplete in their coverage of the literature. There are some individuals in whom allergy or hypersensitivity to fluoride has been demonstrated by appropriate challenge tests. This is seen to be just one of a number of mechanisms whereby adverse reactions to fluoride occur. It is considered that intolerance to fluoride may also follow the formation of corrosive hydrofluoric acid or through enzyme inhibition.

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