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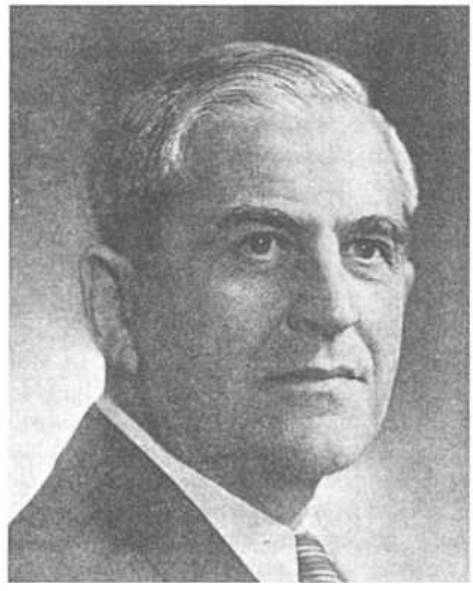
PUBLISHING ON THE HARMFUL EFFECTS OF FLUORIDE EXPOSURE

ABSTRACT: With evidence now showing that fluoride, in combination with aluminium, can affect diverse molecules and biological processes, it is very appropriate that the opportunities for publishing on the harmful effects of fluoride exposure have greatly improved in the 65 years since Dr George Waldbott had difficulty publishing, in 1954, his review on "Medical evidence against fluoridation of public water supplies."

Key words: Fluoride-induced adverse effects; Harmful effects of fluoride; Publishing.



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George L Waldbott, M.D.
14 January 1898 –17 July 1982

In 1954, Dr George Waldbott, founder of the International Society for Fluoride Research (ISFR) and the journal *Fluoride*,[1] after having had an article on "Smoker's respiratory syndrome: a clinical entity"[2] published in *JAMA*, the journal of the American Medical Association (AMA), phoned the editor, Dr Austin Smith, to enquire if JAMA might be interested in publishing an extensive review of the literature on fluoridation which included some data that had never been brought to the attention of the medical profession.[3] Dr Smith initially indicated that the journal was always interested in new information but became silent when Dr Waldbott disclosed that the title was "Medical evidence against fluoridation." Dr Smith then explained that the American Medical Association had endorsed fluoridation and that any contribution on the subject therefore needed to clear the policy making body of the organization. However, he reviewed the paper and advised Dr Waldbott that he should not submit it for publication because the review did not include any original research and it had been received too late after the AMA's position was firmly established. Dr Waldbott then asked Dr Joseph Garland, editor of the *New England Journal of Medicine* if he would be interested in an article on "Medical evidence against fluoridation of public water supplies."[3] When Dr Garland replied that "the profession hereabouts (Boston and environs) is pretty well sold on fluoridation ...", Dr Waldbott realized that the subject had already become such a political issue with the medical profession that it would be impossible to have the article published in any American medical journal.

Dr Waldbott responded by printing the article at his own expense and sending copies to his medical society and some Detroit dentists. Dental groups outside the USA were subsequently reached and he was invited to present his data at the national congress of an Argentinian dental organization, Federacion Odontologica, in Mar del Plata on 1–4 October 1958. He was not able to attend because of the expense but his paper was read to the dentists at the congress. The *Australian Journal of Dentistry*

requested the privilege of publishing his article and a revised version was published there in February 1955.[4]

It appears that it was not only in the USA that Dr Waldbott's views received a mixed reception. When I looked, in circa 1989, for a copy of Dr Waldbott's paper in a New Zealand dental library I found a pencilled note, on the first title page in the hard bound volume of the issues for 1955 of the *Australian Journal of Dentistry,* that Dr Waldbott's paper was in the volume but on looking for it I found that the relevant pages were missing.

Along with the holding of a successful conference on fluoride research in Bern, Switzerland, on 15–17 October 1962, the difficulties Dr Waldbott experienced in publishing research on the harmful effects of fluoride contributed to the formation of the ISFR.[5] The ISFR was founded in 1966 at a meeting in Detroit, USA, of the American Society for Fluoride Research to promote the sharing of scientific information on all aspects of inorganic and organic fluorides. This has been done by publication of the peer reviewed quarterly journal *Fluoride* and the holding of international conferences.

In the 65 years since 1954, it has become easier to find journals willing to publish information on the adverse effects of fluoride. Notable among the opportunities is a special issue of the *International Journal of Environmental Research and Public Health* entitled "The harmful effects of fluoride exposure." The guest editors of the special issue are Professor Emeritus Hardy Limeback, Faculty of Dentistry, University of Toronto, Toronto, Canada, an associate editor of *Fluoride*, and Professor Dr William Potter, Department of Chemistry and Biochemistry, University of Tulsa, Tulsa, USA. Manuscript submissions close on 31 July 2019. The guest editors noted, "Although fluoride is widely used for dental and industrial applications, our understanding of chronic and sub-acute mechanisms for fluoride toxicity is incomplete. Nevertheless, environmental exposures to fluoride from a wide range of consumer products and industrial sources are still increasing. New studies support a growing body of evidence that fluoride should be classified as a neurological toxicant and that the interplay between fluoride toxicity depends greatly on other nutritional and immunological factors. Advancing our knowledge of genetic, developmental, and comorbidity susceptibilities to fluoride toxicity is needed. This special issue invites papers to evaluate and monitor the many factors regarding fluoride exposures and mechanisms of toxicity. As at 8 June 2019, six papers had been published in the issue:

(i) *IN VIVO* COMPARISON OF THE PHENOTYPIC ASPECTS AND MOLECULAR MECHANISMS OF TWO NEPHROTOXIC AGENTS, SODIUM FLUORIDE AND URANYL NITRATE[6]

Alice Bontemps, Laurine Conquet, Christelle Elie, Victor Magneron, Céline Gloaguen, Dimitri Kereselidze, Karine Tack, Olivier C. Barbier, Yann Guéguen. Fontenay-aux-Roses, France, and México City, Mexico.

Because of their nephrotoxicity and presence in the environment, uranium (U) and fluoride (F) represent risks to the global population. There is a general lack of knowledge regarding the mechanisms of U and F nephrotoxicity and the underlying molecular pathways. The present study aims to compare the threshold of the appearance of renal impairment and to study apoptosis and inflammation as mechanisms of nephrotoxicity. C57BL/6J male mice were intraperitoneally treated with a single dose of U (0, 2, 4, and 5 mg/kg) or F (0, 2, 5, 7.5, and 10 mg/kg) and

euthanized after 72 hr. Renal phenotypic characteristics and biological mechanisms were evaluated by urine biochemistry, gene/protein expression, enzyme activity, and (immuno)histological analyses. U and F exposures induced nephrotoxicity in a dose-dependent manner, and the highest concentrations induced severe histopathological alterations as well as increased gene expression and urinary excretion of nephrotoxicity biomarkers. KIM-1 gene expression was induced starting at 2 mg/kg U and 7.5 mg/kg F, and this increase in expression was confirmed through *in situ* detection of this biomarker of nephrotoxicity. Both treatments induced inflammation as evidenced by cell adhesion molecule expression and *in situ* levels, whereas caspase 3/7-dependent apoptosis was increased only after U treatment. Overall, a single dose of F or U induced histopathologic evidence of nephrotoxicity renal impairment and inflammation in mice with thresholds under 7.5 mg/kg and 4 mg/kg, respectively.

(ii) OLD AND NEW THREATS—TRACE METALS AND FLUORIDE CONTAMINATION IN SOILS AT DEFUNCT SMITHY SITES[7]

Michał Kupiec, Paweł Pieńkowski, Beata Bosiacka, Izabela Gutowska, Patrycja Kupnicka, Adam Prokopowicz, Dariusz Chlubek, Irena Baranowska-Bosiacka. Szczecin and Sosnowiec, Poland.

The aim of this study was to investigate soil contamination with trace elements and fluoride at sites in Szczecin (NW Poland) where economic activity was historically associated with the use of trace metals. As the Polish legislation does not recognize the lasting impact of historical pollution on soils, land developers are not obliged to determine soil pollution in the new residential areas, including parks and playgrounds for children. Therefore, in this study, at the locations of defunct metalwork enterprises (smithies, foundries, chemical plants, and small metal production plants), which were closed down after World War II, we determined lead (Pb), chromium (Cr), copper (Cu), zinc (Zn), iron (Fe), manganese (Mn), nickel (Ni), mercury (Hg), cadmium (Cd), and cobalt (Co) levels in the soil. In addition, we also determined fluoride (F) levels due to the contemporary fluoride pollution in the area generated by a large chemical plant with a post-production phosphogypsum waste landfill and a power plant complex. Our results show that soil at the sites of now-defunct smithies can still act as a significant source of trace metals. Pb concentration in the surface (0–20 cm) and subsurface (20–40 cm) layers exceeded concentration thresholds for soils with first-degree pollution. The concentrations of Zn and Cu also exceeded their natural background limits. Furthermore, our research indicates an increased concentration of fluoride in surface layers of the soil; however, not exceeding the fluoride content threshold. These observations have important consequences for public health and safety because, presently, the studied sites function as housing estates and other public facilities. Therefore, contaminated soil at these sites may pose a threat to the health of local residents and should be closely monitored for trace metal contamination levels.

(iii) INFLUENCE OF ACETYLCHOLINESTERASE INHIBITORS USED IN ALZHEIMER'S DISEASE TREATMENT ON THE ACTIVITY OF ANTIOXIDANT ENZYMES AND THE CONCENTRATION OF GLUTATHIONE IN THP-1 MACROPHAGES UNDER FLUORIDE-INDUCED OXIDATIVE STRESS[8]

Marta Goschorska, Izabela Gutowska, Irena Baranowska-Bosiacka, Katarzyna Piotrowska, Emilia Metryka, Krzysztof Safranow, Dariusz Chlubek. Szczecin, Poland

It has been reported that donepezil and rivastigmine, the acetylcholinesterase (AChE) inhibitors commonly used in the treatment of Alzheimer's disease (AD), do not only inhibit AChE but also have antioxidant properties. As oxidative stress is involved in AD pathogenesis, in our study we attempted to examine the influence of

donepezil and rivastigmine on the activity of antioxidant enzymes and glutathione concentration in macrophages—an important source of reactive oxygen species and crucial for oxidative stress progression. The macrophages were exposed to sodium fluoride-induced oxidative stress. The antioxidant enzymes activity and concentration of glutathione were measured spectrophotometrically. The generation of reactive oxygen species was visualized by confocal microscopy. The results of our study showed that donepezil and rivastigmine had a stimulating effect on catalase activity. However, when exposed to fluoride-induced oxidative stress, the drugs reduced the activity of some antioxidant enzymes (Cat, SOD, GR). These observations suggest that the fluoride-induced oxidative stress may suppress the antioxidant action of AChE inhibitors. Our results may have significance in the clinical practice of treatment of AD and other dementia diseases.

(iv) FLUORIDE EXPOSURE INDUCES INHIBITION OF SODIUM-AND POTASSIUM-ACTIVATED ADENOSINE TRIPHOSPHATASE (Na^+, K^+-ATPASE) ENZYME ACTIVITY: MOLECULAR MECHANISMS AND IMPLICATIONS FOR PUBLIC HEALTH[9]

Declan Timothy Waugh. Bandon, County Cork, Ireland.

In this study, several lines of evidence are provided to show that Na^+, K+ -ATPase activity exerts vital roles in normal brain development and function and that loss of enzyme activity is implicated in neurodevelopmental, neuropsychiatric, and neurodegenerative disorders, as well as an increased risk of cancer, metabolic, pulmonary, and cardiovascular disease. Evidence is presented to show that fluoride (F) inhibits Na^+, K^+-ATPase activity by altering biological pathways through modifying the expression of genes and the activity of glycolytic enzymes, metalloenzymes, hormones, proteins, neuropeptides, and cytokines, as well as biological interface interactions that rely on the bioavailability of the chemical elements magnesium and manganese to modulate ATP and Na^+, K^+-ATPase enzyme activity. Taken together, the findings of this study provide unprecedented insights into the molecular mechanisms and biological pathways by which F inhibits Na^+, K+ -ATPase activity and contributes to the etiology and pathophysiology of diseases associated with impairment of this essential enzyme. Moreover, the findings of this study further suggest that there are windows of susceptibility over the life course where chronic F exposure in pregnancy and early infancy may impair Na^+, K^+-ATPase activity with both short- and long-term implications for disease and inequalities in health. These findings warrant considerable attention and potential intervention, not to mention additional research on the potential effects of F intake in contributing to chronic disease.

(v) FLUORIDE EXPOSURE INDUCES INHIBITION OF SODIUM/IODIDE SYMPORTER (NIS) CONTRIBUTING TO IMPAIRED IODINE ABSORPTION AND IODINE DEFICIENCY: MOLECULAR MECHANISMS OF INHIBITION AND IMPLICATIONS FOR PUBLIC HEALTH[10]

Declan Timothy Waugh. Bandon, County Cork, Ireland.

The sodium iodide symporter (NIS) is the plasma membrane glycoprotein that mediates active iodide transport in the thyroid and other tissues, such as the salivary, gastric mucosa, rectal mucosa, bronchial mucosa, placenta, and mammary glands. In the thyroid, NIS mediates the uptake and accumulation of iodine and its activity is crucial for the development of the central nervous system and disease prevention. Since the discovery of the NIS in 1996, research has further shown that NIS functionality and iodine transport is dependent on the activity of the sodium potassium activated adenosine 5'-triphosphatase pump (Na^+, K^+-ATPase). In this

article, I review the molecular mechanisms by which F inhibits NIS expression and functionality which in turn contributes to impaired iodide absorption, diminished iodide-concentrating ability, and iodine deficiency disorders. I discuss how NIS expression and activity are inhibited by thyroglobulin (Tg), tumour necrosis factor alpha (TNF-α), transforming growth factor beta 1 (TGF-β1), interleukin 6 (IL-6), Interleukin 1 beta (IL-1β), interferon-γ (IFN-γ), insulin like growth factor 1 (IGF-1), and phosphoinositide 3-kinase (PI3K) and how fluoride upregulates the expression and activity of these biomarkers. I further describe the crucial role of prolactin and megalin in the regulation of NIS expression and iodine homeostasis and the effect of fluoride in down regulating prolactin and megalin expression. Among many other issues, I discuss the potential conflict between public health policies such as water fluoridation and its contribution to iodine deficiency, neurodevelopmental disorders, and pathological disorders. Further studies are warranted to examine these associations.

(vi) THE CONTRIBUTION OF FLUORIDE TO THE PATHOGENESIS OF EYE DISEASES: MOLECULAR MECHANISMS AND IMPLICATIONS FOR PUBLIC HEALTH[11]

Declan Timothy Waugh. Bandon, County Cork, Ireland.

This study provides diverse lines of evidence demonstrating that fluoride (F) exposure contributes to degenerative eye diseases by stimulating or inhibiting biological pathways associated with the pathogenesis of cataract, age-related macular degeneration, and glaucoma. As elucidated in this study, F exerts this effect by inhibiting enolase, τ-crystallin, Hsp40, Na^+, K^+-ATPase, Nrf2, γ-GCS, HO-1, Bcl-2, FoxO1, SOD, PON-1, and glutathione activity, and upregulating NF-κB, IL-6, AGEs, HsP27, and Hsp70 expression. Moreover, F exposure leads to enhanced oxidative stress and impaired antioxidant activity. Based on the evidence presented in this study, it can be concluded that F exposure may be added to the list of identifiable risk factors associated with the pathogenesis of degenerative eye diseases. The broader impact of these findings suggests that reducing F intake may lead to an overall reduction in the modifiable risk factors associated with degenerative eye diseases. Further studies are required to examine this association and determine the differences in the prevalence rates amongst fluoridated and non-fluoridated communities, taking into consideration other dietary sources of F such as tea. Finally, the findings of this study elucidate molecular pathways associated with F exposure that may suggest a possible association between F exposure and other inflammatory diseases. Further studies are also warranted to examine these associations.

These articles in the special issue of the *International Journal of Environmental Research and Public Health* are of high quality and they refer to widespread effects of fluoride on enzyme function and gene expression, e.g., the ability of fluoride to inhibit Na^+, K^+-ATPase activity by altering biological pathways through modifying the expression of genes and the activity of glycolytic enzymes.

Strunecka et al. have described a mechanism, involving the formation of soluble aluminofluoride complexes—fluoroaluminate (AlF_x)—whereby fluoride is able to affect various enzyme activities and cell signalling cascades.[12] The fluoroaluminate complexes are able to simulate phosphate groups in many biochemical reactions and exacerbate many pathological and clinical problems by interfering with a great number of G-protein-dependent cellular mechanisms. The action of aluminium in the presence of fluoride is not restricted to G proteins and the phosphate analogue model

can apply to free phosphates and nucleotide phosphates. The effects of AlF_x may be amplified during the process of signal transduction and thus potentiate AlF_x-mediated deleterious actions. including immunoexcitability.

With evidence now showing that fluoride, in combination with aluminium, can affect diverse molecules and biological processes,[13] it is very appropriate that the opportunities for publishing on the harmful effects of fluoride exposure have greatly improved in the 65 years since Dr George Waldbott had difficulty publishing his review on "Medical evidence against fluoridation of public water supplies."

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