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Professor Guan's group of researchers at Guiyang have been the first to describe and investigate coal-burning endemic fluoride and to identify the possible role of oxidative stress in the pathophysiology of fluorosis. Both of these findings have opened important new areas of research and increased our understanding of the development of endemic fluorosis.

Professor Guan has a large group of researchers in Guizhou, PR of China, who have been investigating the epidemiology, pathology, pathogenesis, drug therapy, and prevention of chronic fluorosis. The province of Guizhou, in South-Western China, has a total population of 37 million of whom 15 million live in the area of coal-burning endemic fluorosis. Approximately 10 million people suffer from dental fluorosis and 1 million from skeletal fluorosis. Endemic fluorosis was first reported in Guizhou by Dr Oliver Lyth in 1946 (Lyth O. Endemic fluorosis in Kweichow, China. Lancet 1946 Feb 16; 1(6390):233-5). He

considered that it was caused by a high content of fluoride in drinking water. However further research in Guizhou in the 1970s found the this was not the case and a new type of fluorosis, coal-burning endemic fluorosis or non-drinking water endemic fluorosis, was described (Wei ZL, Zhou LY, Bao RC et al. Endemic foodborne fluorosis in Guizhou, China. Fluoride 1981;14(2):91-3; Daijei H. X-ray analysis of 34 cases of foodborne skeletal fluorosis. Fluoride 1981;14(2):51-5; Waldbott GL. Food-induced skeletal fluorosis [editorial]. Fluoride 1981;14(2):49-50).

Professor Guan's group has continued to investigate the nature of fluorosis including epidemiological studies and laboratory animal research.

Non-drinking water endemic fluorosis is now recognized as occurring in more than five provinces in China and in other parts of the world.

Professor Guan's team on the research of fluorosis have worked on the pathogenesis of fluorosis and were the first to propose the hypothesis involving oxidative stress and free radicals) in the pathogenesis of the disease (Guan ZZ, Yang PS, Yu ND, Zhuang ZJ. An experimental study of blood biochemical diagnostic indices for chronic fluorosis. Fluoride 1989;22(3):112-8). This work has since been cited in approximately 30 papers.

Professor Guan's group has also published many further papers which have supported their hypothesis (Guan ZZ, Wang YN, Xiao KQ, Dai DY, Chen YH, Liu JL, Sindelar P, Dallner G. Influence of chronic fluorosis on membrane lipids in rat brain. Neurotoxicol Teratol. 1998 Sep-Oct;20(5):537-42;

Wang YN, Xiao KQ, Liu JL, Dallner G, Guan ZZ. Effect of long term fluoride exposure on lipid composition in rat liver. Toxicology 2000 May 5;146(2-3):161-9;

Guan ZZ, Xiao KQ, Zeng XY, Long YG, Cheng YH, Jiang SF, Wang YN. Changed cellular membrane lipid composition and lipid peroxidation of kidney in rats with chronic fluorosis. Arch Toxicol. 2000 Dec;74(10):602-8;

Long YG, Wang YN, Chen J, Jiang SF, Nordberg A, Guan ZZ. Chronic fluoride toxicity decreases the number of nicotinic acetylcholine receptors in rat brain. Neurotoxicol Teratol. 2002 Nov-Dec;24(6):751-7.

Chen J, Shan KR, Long YG, Wang YN, Nordberg A, Guan ZZ. Selective decreases of nicotinic acetylcholine receptors in PC12 cells exposed to fluoride. Toxicology. 2003 Feb 1;183(1-3):235-42.

Shan KR, Qi XL, Long YG, Nordberg A, Guan ZZ. Decreased nicotinic receptors in PC12 cells and rat brains influenced by fluoride toxicity--a mechanism relating to a damage at the level in post-transcription of the receptor genes. Toxicology. 2004 Aug 5;200(2-3):169-77.

Gao Q, Liu YJ, Guan ZZ. Oxidative stress might be a mechanism connected with the decreased alpha 7 nicotinic receptor influenced by high-concentration of fluoride in SH-SY5Y neuroblastoma cells. Toxicol *In Vitro*. 2008 Jun;22(4):837-43. doi: 10.1016/j.tiv.2007.12.017. Epub 2008 Jan 15. Erratum in: Toxicol In Vitro. 2008 Oct;22(7):1814.

Zhang T, Shan KR, Tu X, He Y, Pei JJ, Guan ZZ. Myeloperoxidase activity and its corresponding mRNA expression as well as gene polymorphism in the population living in the coal-burning endemic fluorosis area in Guizhou of China. Biol Trace Elem Res. 2013 Jun;152(3):379-86. doi: 10.1007/s12011-013-9632-9. Epub 2013 Feb 26.;

Lou DD, Guan ZZ, Liu YJ, Liu YF, Zhang KL, Pan JG, Pei JJ. The influence of chronic fluorosis on mitochondrial dynamics morphology and distribution in cortical neurons of the rat brain. Arch Toxicol. 2013 Mar;87(3):449-57. doi: 10.1007/s00204-012-0942-z. Epub 2012 Sep 25.)

Wei N, Li Y, Deng J, Xu SQ, Guan ZZ. The effects of comprehensive control measures on intelligence of school-age children in coal-burning-borne-endemic fluorosis areas. Chin J Endemiol 2014;33(3):320-2.

Li FC, Guan ZZ. Synergistic intoxication with aluminum and fluoride in patients in an area of coal burning endemic fluorosis [review]. Fluoride 2014;47(4):283-6.

Since chronic fluorosis or endemic fluorosis involves damage to many organs and systems, as well as bone and teeth, understanding the pathophysiology of the process is important for developing therapeutic interventions. The hypothesis that a high level of oxidative stress is induced by an excessive amount of fluoride is still a reasonable explanation of the pathogenesis of chronic fluorosis.

From the 1970s to the present, Professor Guan's group in Guizhou have obtained financial support from the National Science Foundation of China, the Ministry of Science and Technology of China, the Ministry of Education of China, the Ministry of Health of China and the foundations of Guizhou province of China. They have produced more than 300 publications including in excess of 30 papers published in the journals covered by the

Thomson Corporation Science Citation Index (SCI). They have trained more than 50 postgraduate students, many of whom are doing leading scientific research.

Professor Guan's group has worked to change the style of coal-burning stoves and improve health education to help eliminate the hazard of coal-burning endemic fluorosis in China. This has been very successful with a significant decrease in the numbers of the patients with dental fluorosis and skeletal fluorosis.