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The International Society for Fluoride Research will hold its Sixth Conference in historic Williamsburg, Virginia, November 7 to 9, 1974. This town is easily accessible by air to foreign and U.S. participants. It offers an unusual opportunity to observe, at first hand, the way of life experienced during the early years of our nation. For reservations contact The Motor House, Reservations Manager, Colonial Williamsburg Visitor Accomodations Services, P.O. Drawer B., Williamsburg, Virginia 23185.

EDITORIAL

THE PRE-SKELETAL PHASE OF CHRONIC FLUORIDE INTOXICATION

The two widely acknowledged characteristics of chronic fluoride poisoning in humans and animals are dental fluorosis (mottling of teeth) and skeletal fluorosis. Mottled teeth - an enamel defect consisting of a disturbance of the enamel building cells, the ameloblasts, and absence of cementing substance - develop only if excess fluoride intake occurs during the first 10 to 12 years of life while the teeth are being formed. Skeletal fluorosis, which is characterized by increased bone density and abnormal bone growth, is not likely to occur unless the subject has consumed excess fluoride for 10 to 30 years.

Similarly, chronic poisoning by many other toxic substances is characterized by one or two major features. For instance, the lead line or wrist drop are characteristic of lead poisoning; granulomatous lesions, of beryllium poisoning; keratosis of the skin, of arsenic poisoning; brownish acne-like lesions of the skin, of poisoning by biphenyl chlorides. In all the above-mentioned types of poisoning as well as in chronic fluoride poisoning, however, the action of the toxic agent is not confined to one or two target organs after its entry into the human body. Thus many additional manifestations accompany the above-described principal lesions.

In his classical description of fluoride intoxication, Roholm (1) has outlined a number of manifestations which are associated with skeletal fluorosis, mainly gastrointestinal and neuromuscular symptoms as well as such features as tachycardia, polydipsia, and allergic skin lesions. Yet, only a few subsequent investigators have paid attention to the systemic effects of fluoride in chronic poisoning.

In this issue Gründer (page 135) elucidates the fact that, in domestic animals, fluoride intoxication accounts for a wide variety of manifestations. They are dependent mainly on the kind of compound involved, its dose and the channels by which it enters the system. Long-term uptake of fluoroacetate, for instance, induces changes in the brains and heart. This condition is at variance with the generally recognized features of fluorosis.

In humans, Fradà et al. (2) reported gastrointestinal symptoms, gastroduodenitis, colitis, and acute abdominal episodes associated with liver disorders in 70% of the population of an area where the water contained fluoride naturally at a level of 5.2 ppm. He also noted a high incidence of degenerative arthritis and calcification of arteries. Rich (3) reported involvement of the gastrointestinal tract in conjunction with arthritis and visual disturbances in patients who received large therapeutic doses of fluoride for osteoporosis over extended periods of time. The

literature on the fluoride-containing anesthetic methoxyflurane is concerned particularly with its effect on the kidneys. Polyuria and polydipsia have been recorded in hydrofluorosis (4-6), a condition on which Taves (7, 8) has elaborated in several publications.

In infants, who are notably less resistent to toxic insults, administration of fluoride tablets has led to ulcers in the stomach and upper bowel (9).

Fluoride tablets administered to pregnant women and to young children caused stomach and bowel upsets as well as allergic skin lesions (10).

Duffy et al. (11) observed giant cells in the bone marrow of three patients who received large doses (16 to 150 mg daily for 1 to 36 months) of sodium fluoride for treatment of osteoporosis. These authors considered these cells suggestive of bone malignancy.

The significance of the non-skeletal phase of chronic fluoride poisoning which was originally brought into focus by Waldbott (12, 13) and more recently by Petraborg (14) is corroborated in the current issue of FLUORIDE (page 146) by Grimbergen in a preliminary study. These authors observed a typical syndrome early in the development of fluoride poisoning from such minute amounts of fluoride as are contained in fluoridated drinking water at the so-called optimal concentration. In this phase of the disease neither the teeth nor the bones are involved.

In contrast to acute fluoride intoxication from large doses of fluoride, such trace amounts can have a sustained effect on the gastrointestinal tract - the usual portal of entry of fluoride - in persons who are susceptible to poisoning by it. Symptoms such as nausea, vomiting, and bowel disturbances of the kind often described as "irritable colon" and frequent ulcers of the mouth (stomatitis) appear to be the most common feature. Excessive dryness in the mouth and throat are undoubtedly related to polydipsia and polyuria, which are indicative of an excess requirement of fluids due to damage to the kidneys by fluoride (8).

Of special interest are the neurological symptoms, mainly headaches, vertigo, ataxia and damage to the retina. Since these manifestations also occur in such diseases as multiple sclerosis, neurosyphilis and cerebral tumor a distinction must be made between them and fluoride poisoning in differential diagnosis. In this connection the recent observation by Franke et al. (page 168) acquires special significance. In a case of skeletal fluorosis these authors observed, for the first time, involvement of the cells of the anterior horn of the spinal cord. In their autopsied case they demonstrated incontrovertibly that damage to the ganglion cells of the spinal cord is not associated with pressure upon peripheral nerves nor upon the spinal cord due to proliferation of bone sub-

stance in the vertebral column. Direct involvement of nerve substance by fluoride can, therefore, not be excluded. Such a possibility would also explain the frequent findings of mental disturbances such as slow cerebration, inability to concentrate, loss of memory and mental depression described by Waldbott (12).

Another important feature in the case described by Franke et al. was the damage to muscle cells of the kind originally reported by Fasske in 1964 (15) who found similar changes in the musculature of the heart. Because this is the first and only report on a single individual, no final conclusion can be reached at this time. However, the unusual degree of muscular weakness and the pains in muscle frequently observed in such cases is suggestive of pathology in muscle tissue.

Arthritis of the spinal column develops early in the disease with or without demonstrable radiological changes. It often affects the small joints of the hands and fingers, not unlike the involvement of the metaphalangeal joints in fluorosis in cattle as shown by Gründer.

Lower urinary tract involvement is not uncommon in the more advanced stage of the pre-skeletal phase of fluoride poisoning. Muscular fibrillation, pains and paresthesias in arms and legs and even convulsions have been described during the course of the disease (16). Recently Waldbott and Cecilioni have pointed to the frequency of "Chizzola" Maculae, skin lesions attributed to fluoride in the early thirties in Italy (17) and encountered again in the same Italian area (18). The frequency of the occurrence of this condition in fluoridated communities or near fluoride-emitting industrial facilities is noteworthy. Yet, because of its close resemblance to traumatic suffusions which are often encountered, especially in children, this common skin disease is rarely recognized by physicians. Since the skin lesions constitute the first clue of intolerance to fluoride, they often lead to the detection of the systemic disease which might otherwise remain unrecognized.

It thus appears that fluorosis cannot be considered a disease of teeth or bones. It is a systemic disease liable to involve many, or perhaps all, organs of the system.

The development of clinical research on fluoride is relatively recent. It dates back to 1939 when Roholm presented the first comprehensive study on the subject. With the expanding role of fluoride in industry, with its special significance as an air pollutant and its increasing occurrence in food and drinks, an awakening to the clinical aspect of chronic fluoride poisoning is bound to occur in the not too distant future.

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FLUORIDE AND THE ENVIRONMENT

by

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I am honored to be invited to give this Opening Lecture at the 5th Annual Conference of the International Society for Fluoride Research, at Magdalen College, Oxford; especially so as I am not myself engaged in fluoride research, my specialty being in the field of the ecology of soil fungi. I have been concerned about the environment and its pollution for many years with the result that I have been forced to read, think and write a good deal about fluorides in the environment: As a teacher and consultant in plant and forest pathology for several decades, I find myself increasingly consulted on this subject.

Moreover, some years ago I took up lichenology as a pleasant field study and an escape from the pressing problems of the day. This also led me straight back to the pollution question, since lichens happen to be excellent monitors for air pollution.

Let me start by reminding you of the limitations of our much-vaunted 'scientific method'. Because the real world is too complex for our minds, we scientists take small bits of it and use them to set up our own little 'universes' in the laboratory which we then simplify to the point at which we think we can understand them. In epidemiology and ecology we set up, not a laboratory 'universe' but a statistical one which is even cruder and further from reality, since this involves substituting non-existent and imaginary, identical units which are convenient to handle.

The trouble comes, of course, when we apply our bits of fragmented, and sometimes imaginary, information to the complex reality of the world around us, often with an effect which is itself literally shattering, i.e. it breaks up the ecological balance. Most technological pollution problems are of this nature. Since therefore this Society has an interest in one particular substance in the environment, and this Conference will concern itself with a succession of most absorbing papers on particular aspects of the behavior of this one substance, it is appropriate to start by sketching in its broad background against which all these special considerations have to be set.

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Presented at the Fifth Annual Conference of I. S. F. R., Oxford, England, 4/8-10

The Fluoride Cycle

We might start by considering the fluorine cycle between sea and land on this planet. The most useful paper I could find on this aspect was by R. Carpenter (1) whose conclusions are based mainly on investigations into marine geochemistry and the behavior of fluorine in the major sedimentary cycle. Recent determinations have shown the dissolved fluoride content of sea water to be in the range 1.2 to 1.4 mg/l regardless of ocean location. According to Livingstone (2) the average dissolved fluoride content of the major rivers of the world is fairly well defined at 0.1 - 0.2 ppm. In fact the world average appears to be nearer to 0.1 than 0.2 ppm. Despite the occurrence, therefore, of high-fluoride waters in many scattered localities, the great bulk of the surface waters which supply the rivers cannot exceed the concentration of fluoride found in them. Moreover, the contribution of dissolved fluoride from the rocks, plus soil and dust, to the total delivered by the rivers to the sea, was found to be small, since most of the fluorine weathered from the rocks is carried in the form of largely insoluble detritus.

Thus most of the dissolved fluoride in surface waters and rivers must come from atmospheric precipitation, which, in turn, could derive it from three sources: 1. volcanic activity, 2. industrial pollution, and 3. the sea. Some rough estimates of the order of size of the first two sources seemed to show that at present they would not account for more than 10-20 percent of the amounts commonly found in rain and snow in which, also, the F/Cl ratios are very much higher (10 to 1000 times) than those found in sea water. The rate at which fluorine is being removed in the sea by calcium carbonate and phosphate precipitation was found to be only about one fifth to one eighth of the rate at which it is being delivered by the rivers. Therefore, some 80 to 90 percent of the dissolved fluoride in river waters is cyclic, derived by precipitation from the atmosphere which in turn received it from the sea by a process which is not described but, presumably, would be mainly by fractation at the sea surface in the formation of aerosol from wind-whipped spray.

Whereas it may be unwise, at this stage, to accept the quantitative conclusions, which are based largely on deduction, as more than speculative, there seems to be little doubt among oceanographers whom I have consulted that there is a massive sea/air/land fluorine cycle on this planet, and it would be even more unwise to adopt the common assumption that the sea is a one-way sink for fluorine into which we can pour it indefinitely without getting it back.

It seems certain that the entire terrestrial part of the biosphere - the whole vast complex of living organisms, including man, which live on the land and rely for their existence upon water, of which their bodies consist to the extent of 60 to 90 percent, have existed, in

recent geological time, in relation to a fresh water supply with a fluoride content which can not have averages more than 0.1 - 0.2 ppm fluoride. It is necessary to assert this elementary fact because some misconceptions now current about it have even appeared in some quite respectable semi-popular reference books. Also, it is not without significance that the human body fluids, such as blood plasma and milk, are regulated at a fluoride content of about 0.1 ppm even in the presence of higher fluoride levels in food and drinking water.

Let me now quote from The Penguin Medical Encyclopedia (1972) p. 169, which states, unequivocally, under the heading fluorine: -

> "In most regions there is enough fluorine in drinking water, about 1 part per million."

It then goes on to refer to the remainder of the world's water in terms of deficiency or excess of fluorine. These terms: optimal (i.e. about 1 ppm fluoride) excessive, and deficient, first proposed by H. T. Dean in his '21 Cities' Study (3) related only to the diseases of caries and fluorotic mottling in the teeth of school children. Of these terms, only 'excessive' is justifiable, insofar as fluoride has been identified as the causative agent in this type of dental mottling; but there can be little doubt that the widespread use of the term 'deficient', as referring to the fluoride level in all water supplies below 1 ppm, has misled many people, including Dr. Peter Wingate, the author of this encyclopedia, into assuming that this could refer only to a minority of water supplies, since it would not be credible that the bulk of the world's fresh water could be designated in this way.

In case the reference is intended mainly for British water supplies it should be mentioned that, according to Heasman and Martin (4), during the 1950's about 1/4 million people in Britain (i.e. about 1/2 percent of the population) were drinking waters naturally containing from 1.0 to 5.8 ppm fluoride (i.e. Dean's 'optimal' and 'excessive' together).

The sulphur oxides are well-known natural atmospheric pollutants in volcanic regions, as well as widespread industrial pollutants. Like the fluorides, they are both phytotoxic and fungitoxic, and can inhibit the development of some important fungal diseases of economic crops, such as rusts and mildews, at a concentration slightly below that at which they visibly damage the crop plant. I will not for a moment concede that these plant diseases are of any less importance to mankind than dental caries; for what is the use of having good teeth if there is no food to eat with them! Let us suppose, therefore, that the plant pathologists, taking their cue from the dentists, designate the plant-damage level of SO_2 pollution as 'excessive', the level of fungal suppression without plant damage as 'optimal', and the entire rest of the earth's atmosphere as 'deficient' in SO_2. How then shall we fare in our struggle against air pollution?

Indeed, the case here is even stronger, and far from 'academic', since sulphur is an important micronutrient, which has been stripped from many of our soils by excessive cropping or grazing, with the use of NPK fertilizers. The point has been noted by the New Scientist (2 July 1970) which carried a headline: "Our Grasslands may Depend on SO_2 Pollution". Perhaps they may, but the answer is to rectify the deficiency, not to attribute it to the atmosphere!

Fluoride Essential

Another widespread misconception concerns the alleged 'essential' nature of fluorine or the fluoride ion. I quote from a well-known paperback on pesticides and pollution by one of our leading conservationists (5):

> "Fluorine occurs in minute quantities in all plants and animals and it is one of the essential elements of protoplasm. If the nature level falls below a minimum, and this occurs in nature, harmful effects may be seen."

The only justification so far offered (in correspondence) for this statement has been a reference to some recent work on laboratory mice. The work with laboratory rodents on low-fluoride diets has been summarized recently in an editorial in 'Fluoride' (6). The evidence at present seems inconclusive; but if it should eventually be clearly shown that fluoride, in trace quantities, has some essential function in the laboratory rodent, this is still far from showing it is similarly essential for the natural or wild rodent; should this be so, it is still a long way from showing that it is generally essential in the mammalian, or human, metabolism; and if this should be proved, it is an even longer way from justifying the description of fluorine as an essential element of protoplasm; and finally, should this also prove to be true, it is still quite irrelevant to the 'natural level' mentioned in the quotation, since I have searched the literature in vain for evidence that, anywhere in the world, there is a natural deficiency of fluorine causing harmful effects to any organism whatever. It is notoriously difficult to produce a fluorine-free diet which is not deficient in other respects, and highly unlikely that such a situation could arise in nature, or in the human context. In fact, the whole question of the 'essentiality' of fluorine as demonstrated at experimental levels of purification is largely a matter of academic interest.

Nevertheless, I have heard this 'essentiality' confidently quoted at a public inquiry by the scientific consultant of a smelter company, who supported his claim with the quotation given above, and used it to maintain that the inhalation of the fluorine emission from the proposed smelter would not even meet the minimum 24-hour maintenance requirement of the average human being for this essential element. No such

24-hour maintenance requirement for fluoride can be found reported, or even suggested in the literature; but it is extremely serious that such pseudo-scientific mythology should be allowed to grow unchallenged, and should be used in defense of fluoride pollution.

Fluoride in Air

In contrast to this, there can be no doubt whatever about the toxicity of the soluble inorganic fluorides and their natural occurrence in harmful amounts in many places; but to this we now have to add a massive addition of man-made pollution with fluorine compounds from industrial processes: - superphosphate works, aluminum smelters, steel, glass, brick, ceramic, ironstone and cryolite works. Many forms of welding using fluoride as a flux, and the burning of some coals, have all long been known as sources of fluoride pollution, but since the Second World War there has been a further expansion in fluorine chemistry and industrial use. Elemental fluorine is now used as a rocket fuel and in the purification of uranium. Hydrogen fluoride is utilized for many purposes including refining high-octane petrol, alkylation reactions, and for the production of detergents and of many organic fluoride compounds, including refrigerant and propellant gases. Teflon, and the highly toxic organofluorides are replacing the older inorganic fluoride poisons as pesticides. There is also a whole range of fluoride-containing drugs and anaesthetics and of proprietory fluorine supplements, toothpastes etc. It would require a massive treatise to cover the recent and growing applications of fluorine chemistry in industry. What is wholly unknown is the total extent of the pollution of air, water and food caused by the vast expansion of the use of fluorine and its compounds in recent years. One thing is certain: fluoride pollution is increasing and is expected to continue to do so. At a symposium on Air Pollution Damage to Plants in 1968, it was concluded by F. A. Wood (7) that, even though we may expect some reduction in SO_2 levels by 2000 A. D. or shortly thereafter, by that time the fluoride pollution problem will probably be worse. Treshow (8) reported that estimated emissions of fluoride are expected to double between 1971 and 1980, even assuming 90 percent containment.

In fact, it has been the plant pathologists who have been most concerned with extensive, rather than intensive, air pollution, and have pointed out the importance of the airshed, which quite often corresponds broadly with the watershed, in considering its effects on the environment. As Treshow (9) has stated: "Proximity decreases in significance as the extent of pollution increases or the airshed increases." In the general preoccupation with local and acute effects, there is a tendency to forget that damage to the vegetation cover of this planet is also damage to our means of existence, and to a vital regulator of the composition of our oxygenated atmosphere. Extensive damage to forest cover may be not only of direct economic importance,

but may also affect the local climate. Long-distance effects are now appearing such as, for instance, the elimination, by fluoride pollution, of ponderosa pine over an area of 50 square miles near Spokane, Washington, U.S.A.

Often plants give the first signs of air pollution. Sensitive plants, such as varieties of gladiolus, can be useful indicators for airborne fluorides. Lichens can be particularly useful. But great as may be the economic, environmental, and indicator importance of direct and visible damage to sensitive plants, the more subtle, and indirect, deterioration in the composition of the vegetation, the more serious it is. Close to a local source of pollution these changes may be obvious - the sensitive species die, only a few resistant species survive. Further away, the effects may be undetectable without careful vegetational surveys, carried out before as well as after the onset of the pollution. Nevertheless, they may be important. As Bleasdale (10) has pointed out, in a pasture the higher-yielding and finer strains of grasses (such as Aberystwyth strains of rye-grass) can be eliminated in favor of coarser, less sensitive and more competitive strains. As long ago as 1952, he estimated the cost of damage from air pollution to farmers in East Lancashire, England, at £2.6 million annually.

Unfortunately, usually we do not know how much damage has already been done. It is already too late in many areas to do the detailed ecological baseline studies necessary to establish the state of the vegetation before pollution has set in. The tendency is always to concentrate on those places where the damage is worst, and then usually fluoride monitoring is done by chemists who are not competent to make an ecological study. It is urgent that such baseline studies should be made before pollution has started, or, failing that, before it has had time to cause serious effect. Furthermore, the monitoring of fluoride is itself quite inadequate, being undertaken only around known sources of fluoride pollution, whereas smoke and SO_2 are monitored in Britain by the Warren Spring Laboratory at a range of sites throughout the country, including some in open country without local sources of pollution. Thus we have no idea of the extent of long-distance fluoride pollution, nor of its possible additive and synergistic effects with SO_2 and other pollutants. Rarely indeed do atmospheric pollutants act in isolation, such effects may well be the rule rather than the exception. However, I need not stress this point here because J. R. Marier in his Opending Address to the 4th Conference of this Society a year ago (11) dealt with the question of synergism.

Lichens as Fluoride Monitors

Mention has been made of lichens, which are not, strictly speaking, plants, since they are symbiotic associations between two very different organisms: - a fungus, in most cases an ascomycete,

and a green or blue-green alga. Some of these associations surpass every other form of life in their extraordinary resistance to adverse conditions of drought, moisture and temperature changes, and absolutely minimal nutrition, mostly derived from the air, including dust, and rain, snow and dew. Some of them are very slow-growing. Under extreme conditions in the Arctic some lichen thalli have been estimated to be more than 4000 years old. Most of them consist of a simple thallus of densely woven fungal hyphae, protecting a layer of algae under the upper surface. This simple, slowly expanding thallus behaves like a piece of blotting paper absorbing anything which comes in contact with it. Since it has no excretory mechanism, these substances might accumulate. It can also absorb and accumulate substances from the substrate, especially soil or rock (e.g. in extreme cases as much as 13,000 ppm of zinc or 3000 ppm of lead). Geologists are now beginning to appreciate this in looking for minerals, including those which are radioactive.

Thus, despite their extreme hardness in withstanding adverse conditions, lichens in general are noticeably absent from our industrial and urban areas, except for a few, mostly inconspicuous, pollution-resistant species, of which the common greenish-grey granular crust on trees in many urban parks and gardens, Lecanora conizaeoides, is probably the best known. In the center of the great metropolises, such as London and New York, even this is absent and only one lichen, Lecanora dispersa, which looks like a smudge of dirt on cement or concrete or calcareous building stone, is found.

Many studies have now been made, showing the progressive reduction in size, fertility, and the final disappearance of the common foliose and fruticose lichens along a gradient of increasing pollution approaching the center of a large city. These are not simple studies. The substrate is extremely important, especially where an acid pollutant such as SO_2 is concerned, since base-rich substrates will carry far more lichens than base-poor ones. But we have now reached a stage, in Britain, where we already have two biological scales whereby annual average levels of SO_2 pollution can be estimated. O. L. Gilbert's scale (12) uses bryophytes as well as lichens on various substrates and was worked out in connection with his study of the 'lichen desert' surrounding the city of Newcastle-upon-Tyne. It is thus useful in the the estimation of the higher levels of urban and industrial pollution. In contrast, the scale of Hawksworth and Rose (13) uses epiphytic lichens on trees only, is applicable to a wider area in England and Wales, and is more useful in the less heavily polluted areas. It specifically excludes areas polluted with HF. A book on air pollution and lichens has recently been published by the University of London Athlone Press (14).

With fluorides, the lichenologists are a long way from having any such scales worked out; but much current work and interest has been stimulated owing to the recent establishment, since 1968, of an

aluminum smelter industry in Great Britain, consisting of three large smelters of about 100,000 tons annual production each. Before that, the only aluminum smelter was in Scotland at Fort William (about 20,000 tons); Gilbert (15) has made a brief study of the 'lichen desert' surrounding it.

Gilbert studied the lichens and bryophytes on three substrates: fence posts; boulders of acid rock, which were quite bare near the smelter; trees, most of which had been killed near and downwind to the smelter. He found a lichen and bryophyte 'desert' extending about 2 miles downwind, but undamaged conifers and fence posts covered with lichens only 300 yards to one side of it, in a direction rarely reached by the wind. Thus the vegetation and lichens were useful also in averaging out wind directions. The rock lichens were most affected, then those on posts and trees; those on the ground least. The lichens in general appeared to be more sensitive than the mosses. Suitable lichens were analysed for their fluoride content, and it was found that at their inner limit of survival they had only 20-48 ppm fluoride, compared to leaves of adjacent surviving trees which had 1140-1830 ppm. In contrast, a common lichen, Parmelia saxatilis, at its inner limit of toleration of SO_2 in Newcastle had 2870-3290 ppm S, and the thalli seemed to have accumulated sulphur for many miles around Newcastle, whereas at Fort William, the fluoride levels, starting off very much lower, fell off rapidly and became zero or undetectable at 7 1/2 miles, downwind. These amounts were in thalli which had been washed to remove external particles. In most cases fluoride pollution is so mixed with SO_2 and other pollutants that it is impossible to distinguish its effects with certainty, even in the case of notorious smog disasters such as those at Donora and the Meuse Valley. Hence the scarcity of papers dealing with it, which depend upon the study of isolated pollution sources in rural areas.

Two papers one by Nash (16) the other by LeBlanc et al (17) were published in 1971 on such isolated fluoride pollution sources: Nash used the lichen transplant technique to study the effects of fluoride pollution from a chemical factory in rural Pennsylvania. Two species of Cladonia (fruticose, terricolous lichens) and one of Parmelia (P. plittii, a foliose, saxicolous species) were transplanted to within 100 m. of the factory, with controls transplanted to similar sites 6000 m. away where these lichens grew naturally. Samples of these were periodically examined for injury, fluoride content was estimated spectrophotometrically. They were also checked for content of chlorophylls and their degradation products. Moreover, limed filter papers were exposed and monitored for fluoride. A further check was carried out with transplants of the lichens in fumigation chambers with controlled fluoride concentrations at different humidities. All the nearer transplants were visibly damaged after 3 months exposure, showing chlorosis of the thallus. In fact at the end of the 3 months (July to September) most of the thalli had disintegrated, showing flu-

oride values of 100 to 220 ppm, whereas the controls at 6000 m. showed 8-28 ppm. In the fumigation chambers, comparable results were shown after 9 days at 4 μg F/m^3, with fluoride levels at 85-115 ppm, and those in control chambers at 14-25 ppm. However this occurred in the chambers only at the higher humidities (r.h. 87% or more). At the lower humidities the lichens dried out, and did not accumulate fluoride or become chlorotic.

The other paper, by LeBlanc et al (17), who also used the transplant method, was concerned with an aluminum smelter at Arvida, Quebec. Epiphytic lichens were removed from trees on bark discs which were mounted on wooden boards and exposed at 15 sites, near and far away from the smelter. Thorough analyses were carried out, including standardized color photography which was used to make up triple comparison slides. These authors described more fully the color and other visual changes which occur in foliose lichens damaged by exposure to fluoride. Changes varied with the species, usually from green-grey to yellow or brownish; the authors also noticed the suppression of soredia (vegetative reproductive structures) and a curling away and upturning of the thallus margins, with cracks on their upper surfaces, which corresponds to some extent with the 'crisping' of the leaves seen in some plants. After 12 months' exposure, this thallus detachment was detectable up to 9.5 km. from the smelter. Some observations which have been made around the Anglesey smelter show that in foliose lichens such as Parmelia saxatilis there is a tendency for the patches of chlorosis and necrosis to be marginal, resembling in this respect the marginal and terminal leaf necrosis in plants described by Garber (18). LeBlanc et al. showed that, in lichens within 1 km of the smelter, chlorophylls a and b, and xanthophyll (but not carotene) had been wholly destroyed, and that these effects were more severe in lichens than in mosses at the same exposure, which also had lower fluoride levels when analysed.

One more short paper should be mentioned, not on a lichen but, on the common green alga Chlorella, reported and listed (but probably mistakenly) among the lichen algae.

Sargent and Taylor (19) re-investigated and confirmed a report by Hassall (20) that when this alga is subjected to concentrations of fluoride and copper ions, neither of which was sufficient to suppress its respiration appreciably, the combination halted its respiration completely. Thus $CuSO_4$ at 2×10^{-3} M gave 100 percent of control respiration, and NaF at 5×10^{-2} M, 93 percent of control, but together, respiration was zero. These authors claimed that, on evidence from endogenously respiring Chlorella, the mechanism of this effect is different from that put forward by Hassall, who thought that alternative metabolic paths were blocked, one by fluoride, the other by copper, whereas Sargent and Taylor consider that, while one pathway is blocked

by fluoride alone, the other is not blocked by copper unless accompanied by fluoride.

Fluoride Synergism

We simply do not know how common such markedly synergistic effects may be; but in any case seldom is it safe to assume that additive effects are absent. It must be rare indeed in this urbanized and industrialized age to find one pathogenic factor acting in isolation, especially in a populated area; yet this seems to be the assumption on which the concept of the 'toxic threshold' or 'safe level' of a pollutant is based. Whereas we now have the tools for multiple factor analysis, seldom is it applied where it is most needed, in the world outside the laboratory, where multiple factors always operate. The situation is further complicated by the intervention of monetary and legal considerations!

The law is concerned only with crude cases of pollution injury, where the damage can be clearly proved to have been caused by the pollutant - as when one man shoots another. Either he did, or he did not. But with pollution nowadays, rarely is the situation simple. Even in crude cases, such as the 1952 London smog associated with 4000 deaths, pollution was not the only factor. The people adversely affected were mainly cases of bronchitis, asthmatic and cardiac. But why? Lawther (21) who investigated for the British Medical Research Council, distinguished between acute pollution, such as that of the fatal smog, and chronic pollution, which most town dwellers in Britain have to endure throughout the winter, and which, he says, is "strongly suspect as an etiological factor in the production of chronic bronchitis and lung cancer." The sudden catastrophe resulted in action, in the form of the Clean Air Act, but it was surely of minor importance in comparison with the widespread, low-level chronic conditions without which no single smog incident could have caused a catastrophe.

Where, as in this Society, we are concerned with one particular type of pollutant chemical, it is essential to carry Lawther's division further. In a given pollutant situation one factor, e.g. fluoride, may be at a level which makes it the predominant factor. If so, we may say that it is at the predominant factor level (P.F.L.). But if it is not at the P.F.L., unless we are quite certain that its effect is negligible, we must assume it is a contributory factor to any harm which is being done (i.e. it is at the C.F.L.). The use of these terms will at least start people thinking in realistic terms about a real situation instead of an imaginary, simplified one in which 'harm' and 'no harm' are alternatives.

We have in this country a remarkable and truly British Institution typically called The Alkali Inspectorate, no doubt because it has to deal mainly with acid pollutants. Of Nineteenth Century origin, we

have every reason to be proud of it, as it has done much to eliminate most of the cruder forms of blatantly damaging local pollution. Unfortunately, as to outlook, it seems to have remained in the Nineteenth Century, since it still concerns itself (so far as my experience goes) with questions of crude, local pollution, insisting that concentrations of pollutants at ground level near a factory, shall be well below levels known to cause visible injury to human beings or animals. If the emission threatens to exceed this level, then the stack must be built higher in order to spread it over a wider area in the neighborhood.

This High Stack Policy, generally adopted by industry and by power stations, transforms intensive into extensive pollution; local and probably provable and remediable pollution into long-distance, low-level, almost unprovable, and therefore irremediable pollution, and will continue to do so until, and unless, we change our mode of thinking. This consideration is especially applicable to the case of fluorides. In Britain we are rightly proud of our Smokeless Zones, where the level of visible smoke and smog has been greatly reduced in recent years; but the level of invisible SO_2 has not. At least we know this, because SO_2 is regularly monitored by the Government's Warren Spring Laboratory at points all over the country. But atmospheric fluorides are not regularly monitored at all, except in the immediate vicinity of a few pollutant sources, and then optionally, and by the commercial firm responsible for the pollution. It is high time that this extremely widespread natural and industrial pollutant was also generally and regularly monitored. The great danger of not doing so is that, by continually transforming intensive into extensive pollution, we continually accept as 'normal' an invisibly escalating pollution level until finally we may be confronted with a catastrophe too widespread to do anything about.

Of course, we must concern ourselves with the acute cases, but they should not be allowed to dominate our thinking; for they are only the tip of the iceberg!

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DIFFERENTIAL DIAGNOSIS OF FLUORIDE POISONING IN CATTLE

by

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SUMMARY: For the clinical recognition and differentiation of fluoride poisoning in cattle, it is necessary to consider the pathogenetic differences in the mechanism of intoxication, particularly between the fluoride compounds which are not metabolically degraded, the hydrogen fluorine ions and the fluorine ion. The differences in the pathogenesis and symptomatology of fluoroacetic poisoning and of acute and chronic fluoride intoxication in cattle are outlined.

The trace element fluorine and its numerous chemical compounds and complexes have frequently led to damage to health in domestic animals. Introduced by our civilization, fluorides exert biological effects upon plants, animals and humans which show extremely wide variations depending upon the compound into which the fluorine ion is incorporated. In order to define fluoride poisoning in cattle clinically, knowledge of these various forms and symptomatology is of practical significance. There are fundamental differences in the toxicity of fluoride compounds namely in those of fluorocarbons (CF) and that of hydrogen fluoride (HF) and of elemental fluorine ions (F) depending upon whether or not the ions dissociate in the animal metabolism.

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1. Organic Fluoride Poisoning

In the organic fluoride compounds the fluoride toxicoses are elicited by the derivatives which cannot be metabolized as fluorine ions in the organism (1). These organic compounds reveal great differences in toxicity. Several are completely non-toxic whereas others, designated as war gases such as fluorophosphate esters (2, 3), are extremely toxic.

In cattle we encountered occasional substances employed as pesticides, such as sodium fluoroacetate (FCH_2COONa) and fluoroacetamide (FCH_2CONH_2). We also observed that fluoroacetic and fluoride oleic acid is contained in tropical poison plants such as the species of Dichapetalum, Acacia georginae, Palicourea marcgravii, Gastrolobium grandiflorum. After the fluoroacetates are metabolized in the body to fluorocitrates they block the tricarbonacid cycle which is essential to life by retarding aconitase. Because they act as powerful heart and nerve poisons (4, 5, 6) they lead to acute fatalities. They do not accumulate in the body and are partially eliminated unaltered with urine and fecal matter. The minimal lethal dose for a single oral administration in cattle is approximately 0.9 mg/kg body weight (7, 8). From this dose, death occurs 2 to 3 days following uptake of the poison whereas larger dosages are lethal within a few hours. Thus fluoroacetate is about 100 times more toxic in cattle than sodium fluoride.

The acute form of intoxication is accompanied by relatively few significant morbid manifestations namely, cessation of food uptake, restlessness, uncoordinated movements, muscular fibrillation, markedly increased heart rate (140 to 160 beats per minute) increased respiratory frequency, frequent defecation and urination. In the terminal stage the animals collapse suddenly, fail to rise from a lying position and expire with generalized clonic convulsions. Following a sublethal dose of fluoroacetate, a chronic clinical picture develops characterized by submaxillary edema and edema of the brisket and by polypnea and tachycardia. Gradually, progressive emaciation and reduction in productivity occurs in the animals (8, 9).

The autopsies of cattle poisoned by fluoroacetate reveal no diagnostic macroscopic or histological changes. This kind of poisoning can only be diagnosed by chemical assays of the rumen content, of the urine or feces for fluoroacetate. A simpler means of diagnosis is the animal experiment of feeding specimens of the poisoned organs to dogs or rats or of injecting urine of the poisoned animal or extracts of its organs into guinea pigs. Another diagnostic approach is the determination of citric acid in the tissues of poisoned animals or of the experimental animals. All tissues of poisoned animals contain a high level of citric acid. Because of the instability of the citric acid the organ sam-

ples must be taken and frozen within a few hours following death. More recently Bogin and Egyed (10) described a method for direct determination of the inhibition of aconitase by extracts of kidney and muscle tissue. This test produces positive results even if the samples are taken up to 40 hours after the death of the animal.

2. Inorganic Fluoride Toxicoses

With respect to intoxication due to inorganic fluoride compounds, the effect of hydrogen fluoride must be distinguished from that of the fluorine ions. Gaseous fluorine (F_2), hydrogen fluoride (HF) and silico tetrafluoride (SiF_4) as well as the hydrolitic compounds - hydrofluoric acid and fluosilicic acid - constituted severe respiratory poisons when taken into the body by inhalation with an LD_{50} of 10-200 ppm in the inhaled air depending on the duration of the exposure. In higher concentrations, the watery solutions are highly corrosive and destructive to tissue. In plants, necroses resulting from fluoride emission are common. However, they are practically unknown in domestic animals. They are of practical significance in occupational medicine exclusively when they occur as the result of accidents.

The most important form of damage by fluoride in cattle occurs following resorptive intoxication through short-term or long lasting uptake of fluorides by mouth. The essential feature of acute fluoride intoxication consists of inondation of blood and tissue with large amounts of fluoride which are absorbed within hours or days. The fluoride cannot be eliminated or otherwise rendered innocuous promptly enough in spite of increased excretion and in spite of uptake of fluoride in hard tissue. At the concentrations which occur in this manner in the tissue, the fluorine ion inhibits various enzyme systems such as enolases, lipases, esterases and dehydrogenases by formation of metabolically inactive complexes particularly with calcium, phosphorus, magnesium and iron (11). According to our current knowledge, the specific interference of the carbohydrate metabolism of cells (glycolysis) through blocking of glucose -6-phosphate dehydrogenase is of special significance (12-15). The cells which have a very active metabolism such as that of the heart muscle, the liver, and the kidneys can thus be irreversibly damaged within a short time. Paradoxically, the fluorine ion simultaneously stimulates the contraction of the heart muscle (positive inotropic action) probably by facilitating the transport of calcium ions (16).

Acute fluoride intoxication occurs in cattle occasionally because of erroneous or intentional feeding of fluorides, mostly sodium fluoride, through careless use of certain plant pesticides such as sodium silicofluoride and following improper use of fluoride-containing agents for the protection of wood (17-23). Recent intoxications have occurred in cattle on pasture, especially through licking or gnawing wooden electric poles. The animals have previously eaten the non-poisonous

protective cuffs which are made of cardboard or plastic. These poles have been processed with pastes containing sodium fluoride or impregnated with solutions containing fluoride. Other cases of poisoning have occurred when cattle was fed hay which had been stored in barns, the wood floor of which had been treated with protective agents containing fluoride.

The minimal acute toxic dose for readily soluble fluoride in cattle lies between 6 and 20 mg/kilogram body weight per day following oral uptake for several days. These values vary according to conditions of absorption. This is equivalent to 250 to 1000 ppm of dry matter. The mean lethal dose for ruminants following a single oral administration is 50 to 70 mg/kg/body weight which corresponds to the amount taken up and the rate of absorption of the various compounds. Sublethal poisoning exhibits the clinical picture of acute to subacute febrile digestive disturbances with cessation of food uptake, decreased motility of the rumen, bloating, as well as diarrhea, "indigestion" according to Goetze (24). Following repeated intake of such sublethal doses, the animals become emaciated. They expire within one to two weeks with signs of general cachexia or they have to be slaughtered because of increasing cardiac insufficiency.

In severe and subacute fatal cases of poisoning, however, the clinical signs of damage to the central nervous system predominate. The animals lay down and get up frequently as though they had colics; they show spastic mastication and crepitation of teeth, excess salivation, widening of pupils, fibrillation and spasms of muscles accompanied by disturbances in equilibrium which cause them to fall down. Simultaneously, within a few hours, increasing circulatory disturbances develop such as hypotension, cardiac arrythmias and syncope. They show respiration disturbances and, occasionally, pulmonary edema. The digestive function may cease completely with arrest of the mobility of the stomach and with constipation. Death occurs after a short period with agonizing convulsions and cardiac arrest.

Therapeutic measures such as prompt withholding of the fluoride-containing forage, forced lavage of the stomach, laxatives and infusions of calcium salts provide only limited benefit.

Macroscopic and histological changes in organs may be completely absent in acute poisoning. When the course of the illness is more protracted such changes may not be conspicuous: Catarrhal inflammation of the mucosa of the stomach and bowels with vascular congestion or degeneration of the parenchyma of the large organs are found.

Acute fluoride poisoning can be established through the chemical assays exclusively. In differential diagnosis, meningitis, brain

disease of various etiologies, rabies, acute lead poisoning and hypomagnesemic tetany have to be ruled out since the clinical picture of fluoride poisoning is dominated by disorders of the central nervous system similar to those in many other diseases. In addition to the suspected food items such as waste flour, mineral mixtures, hay or such objects as electric poles which are consumed by the animals, the content of the rumen, blood and portions of such organs as liver and heart should be analyzed for fluoride. The diagnosis of acute fluoride poisoning can be considered established if the stomach content contains more than 250 ppm, the blood more than 1.5 ppm, and soft tissues more than 20 ppm of fluoride (22). Assays for fluoride in urine and kidney tissue are less suitable for establishing the diagnosis of acute fluoride poisoning because they may have increased fluoride levels in chronically poisoned cattle likewise.

In chronic fluoride poisoning, which is designated fluorosis, fluoride accumulates in the hard tissue of the body i.e. teeth, bones, and cartilage whereas the other organs and body fluids contain relatively little fluoride (25) except for the excreta i.e. urine or fecal matter. Absorption of excess amounts of fluoride during months or years leads to a small rise of fluoride in blood and a limited increase in the renal excretion of fluoride as well as to structural changes in the hard tissue associated with dental and skeletal fluorosis. It appears that the function of other organs or of the microbiotic digestive processes are not directly affected by the slightly increased fluoride level of blood and soft tissues (26, 27).

Chronic fluoride poisoning in cattle is of great economic significance. It prevails in all parts of the world, mainly because of industrial emissions from metallurgic, ceramic, and chemical industries; damage due to water high in fluoride or to fluoride present in phosphate rocks and other minerals involves only locally limited regions (28). The maximum threshold for chronic toxicity ranges between 1.2 to 1.5 mg F/kg body weight which corresponds to 50 - 60 ppm in dry substance for readily soluble fluoride or for contaminated forage. However even lesser amounts in the range of 0.7 to 1.2 mgF/kg body weight can induce dental fluorosis without other toxic manifestations.

The significant clinical signs of fluorosis in cattle consist of structural changes of the incisors and molars as well as skeletal alterations with recurrent painful disturbances in motion and with a trend to spontaneous fractures. Uptake of toxic amounts of fluoride, furthermore, leads to reduction of food consumption.

For the clinical definition and recognition of fluorosis in cattle, the dental and skeletal changes are of practical importance. Since the deposition of fluoride occurs nearly exclusively during the develop-

ment of teeth and during their mineralization, the damage to teeth due to fluorosis varies with the age of the animal. The developing intrauterine decidual denture usually remains unaffected because of the placental barrier and because of the postnatal nutrition with milk which contains little fluoride, with the exception of some cases described by Obel and Erne (29) which remain pathogenetically unexplained. The permanent internal pair of incisors I_1 and I_2 and the molars P_1-3, M_2+3 during the first two years of life and the two external incisors I_3 and I_4 are affected by chronic fluorosis during the first two lactations. Diagnostically significant are the symmetrical involvement of the defects of dentine and their abnormal attrition which is always present in the incisors in varying degree.

From the differential diagnostic viewpoint, we must consider coating of teeth due to dental deposits related to feeding. They can be scratched off and show a uniform discoloration of all pairs of incisors.

The clinical manifestations of skeletal fluorosis which are useful for the diagnosis consist of the periosteal hyperostosis, especially on the metatarsals which can be recognized by palpation; the cumulative occurrence of intermittent or recurrent disturbances in movements and of gait, various grades of palsy of the anterior extremities and an unusual accumulation of fractures especially on ribs, pedal and pelvic bones. Bone appositions which are clinically recognizable, however, develop only after damage by fluoride which extends over several years. The differentiation of the manifestations induced by skeletal fluorosis from similar skeletal changes due to trauma, faulty nutrition or to infection is often difficult in cattle and requires careful clinical studies. In addition, we must exclude diseases of hoofs, joints and muscles which occur frequently as well as neurological palsies and their sequelae.

The very important practical differentiation between the innocuous dental fluorosis which is not accompanied by diminished productivity and the damaging dental or skeletal fluorosis associated with emaciation and decrease of productivity requires regular chemical assays for fluoride of green and raw forage with calculation of the mean daily doses per kg of body weight and the determination of the bone fluoride content in the vertebrae of the tail or in portions of the ribs. Because of the very complex conditions related to the development of chronic fluoride poisoning, especially of those caused by industrial emissions we must continuously review the changing circumstances associated with time and place in order to establish the diagnosis.

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HUMAN FREE IONIZED PLASMA FLUORIDE CONCENTRATIONS DURING PREGNANCY, TOXEMIA, AND LACTATION

by

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SUMMARY: Inorganic fluoride concentrations of plasma were measured by an electrometric method in women with normal pregnancy, with toxemia, and during lactation.

Women with normal pregnancy showed a significant negative correlation between the week of pregnancy and the concentration of plasma ionized fluoride ($p<0.001$). During lactation the correlation coefficient was positive; this correlation was also statistically significant ($p<0.001$). The mean inorganic plasma fluoride concentration during mild toxemia was almost significantly higher than during normal pregnancy ($p<0.05$).

As an indirect conclusion it can be stated that more fluoride is available to the fetus through the placenta than through maternal milk, because during pregnancy the plasma fluoride concentration of the mother decreases whereas it returns to normal level during lactation.

It has been known for many years that the mineralizing fetal tissues retain fluoride (1). This accumulation of fluoride is believed to result in increased resistance of caries in developing teeth of the fetus (2). Naturally all fluoride is acquired from the mother through the placenta. Although the fetal fluorides have been an object of great interest, and much data has been collected on the subject, the effects of the retention of fetal fluoride on the fluoride metabolism of the mother has not been studied. Only one investigation (3) reports the significant decrease of maternal urinary fluoride concentrations during the course of pregnancy, which is at its lowest in the latter part of pregnancy. This phenomenon is explained by accumulation of fluoride in the fetal bone.

The purpose of our study is to find out whether pregnancy has any effect on the fluoride concentrations of the plasma in pregnant and lactating women.

Material and Method

The test group consisted of 79 pregnant healthy women, 15 nurs-

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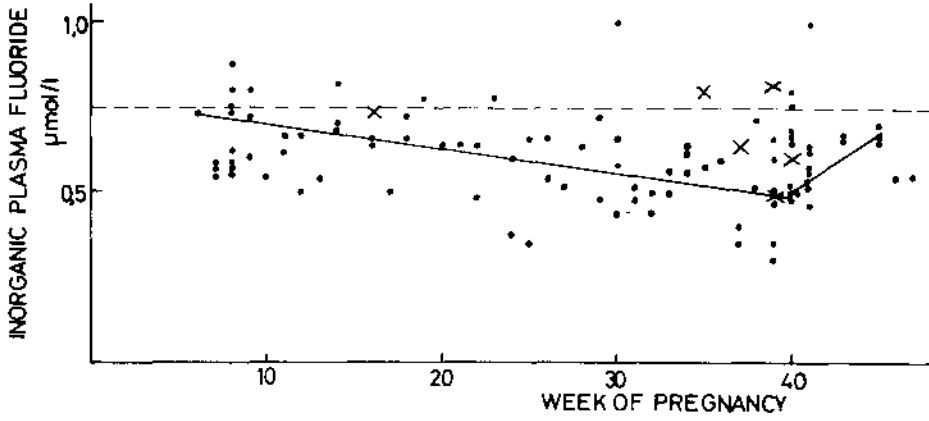
ing mothers and 6 toxemic pregnant women from the Maternity Hospital of Turku City. All women lived in the same district in which the normal mean fluoride excretion is approximately 0.5 mg per day. The control group consisted of 57 women. Since age has a clear effect on the concentrations of ionized fluoride in plasma we selected the cases so that their mean age was about the same (4). The blood samples were withdrawn into heparinized polyethylene tubes and centrifuged. The concentrations of inorganic plasma fluoride were measured by a slight modification of the electrometric method of Fry and Taves (5, 6). Because the calibration curve turns near vertical when the fluoride concentration of the sample is below 0.3 µmol/liter, it is very difficult to obtain reliable results below this limit. The recovery percent of our modification is at least 90 to the level of 9.0 µmol/l. At the level of 0.5 µmol/l the recovery percent is still at least 80, but when the concentration of fluoride of the sample is 0.3 µmol/l, it is only 70. The accuracy of the double measurements is never less than ± 0.05 µmol.

Results

The stage of pregnancy and the concentration of ionized plasma fluoride of all pregnant and lactating women are presented in Figure 1. A very significant correlation ($p < 0.001$) was found between the week of pregnancy and the concentration of ionized fluoride in the plasma in these women. The mean fluoride concentration of the plasma in the

Fig. 1

Inorganic Plasma Fluoride
Related to Duration of Pregnancy



——— Correlation between the week of pregnancy (4 = ⁻0.317), or lactation (r = 0.210) and inorganic plasma fluoride concentration.

— — — The mean plasma inorganic fluoride concentration of the control group of the same age.

• Woman with normal pregnancy.

× Toxemic patient.

toxemic patients, 0.70±0.041 (S.E.M.) µmol/l, differed statistically ($p<0.05$) from the mean value of plasma fluorides of those women whose pregnancy had lasted as long (0.58±0.018 µmol/l). During lactation the ionized fluoride concentrations of the plasma begin to regain their normal level, which causes the correlation coefficient to become controversial. This correlation is also statistically highly significant ($p<0.001$).

Discussion

Our results support earlier assumptions of Gedalia et al. (1). The levels of plasma fluoride in pregnant mothers begin to decrease when the fetal hard tissues begin to mineralize. Thereafter the decrease is rather steady until the birth of the baby. Not even the increase of 20-40% in the mother's plasma volume during 26-33 weeks of pregnancy (7) makes this smooth decrease more pronounced.

Although fluorides are lost also during lactation (8), the plasma levels of the lactating mother return to normal within a few weeks. This probably means that considerably more fluoride is retained in the fetal bone than excreted into the milk. This leads also to the conclusion that there probably is a definite decrease in the availability of fluoride for the infant's teeth during lactation, because the amount of fluoride going through the placenta seems to be bigger than later into the milk.

The renal blood flow during toxemia of pregnancy decreases about 20 percent. The six cases with toxemia in our study were mild ones and the increase in plasma fluorides was probably therefore slight.

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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	1.40 " " 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.

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

Complaints	Number	Percent	Remarks
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.

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FURTHER OBSERVATIONS ON CANCER IN A STEEL CITY

by

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SUMMARY: This paper represents an extension of a previous study concerned with the incidence of cancer in the steel city of Ontario. A review of the mortality rates for cancer for the years 1966 to 1970 in Hamilton reveals a considerably higher death rate from cancer in Hamilton than in the less industrialized city of Ottawa. The highest rate (65 per 100,000) occurred in the proximity of the steel mills, compared with the death rates (23 and 12 per 100,000) farther distant. Admission records at two large Hamilton Hospitals showed a close correlation between respiratory disease and the daily pollution indes. The role of fluoride, as a major pollutant derived from manufacture of steel, is discussed.

In a previous study (1) a significant correlation between atmospheric pollution and mortality rates for respiratory diseases, as well as for certain kinds of non-respiratory cancers in Hamilton, Ontario was reported. This study extended over the years 1966 to 1968. Airborne fluoride was found to be a major contaminant.

The current study covering the two years 1969 and 1970 is designed to supplement the earlier observations.

Two procedures were carried out:

1. The official mortality records for cancer in the city of Hamilton were reviewed and classified according to the areas which had the highest and the lowest degrees of pollution.

2. The admission records of two Hamilton hospitals were charted and related to the daily pollution index.

1. Mortality from Cancer

Cancer of the respiratory organs, the trachea, bronchus and

From the Hamilton General Hospital, Hamilton, Ontario

* * * * * * *

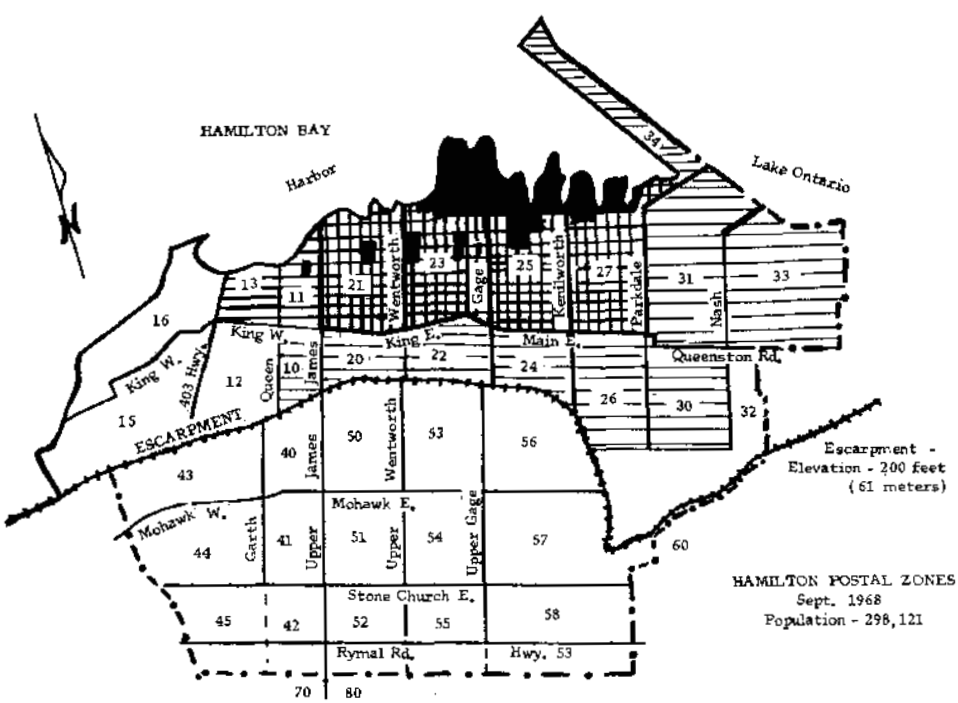
Presented at the Fifth Annual Conference of I.S.F.R., April 8-11, 1973.

lungs accounted for 225 deaths in Hamilton, 106 in 1969 and 119 in 1970. The annual death rates for the same years were more than 35 and 39 respectively per 100,000 population. Of the 225 deaths from lung cancer during 1969 and 1970, 190 were males and 35 females. The overall male to female ratio for the city for the same years was 5.4 to1 compared with 8.4 to 1 for the three previous years, 1966 through 1968. In the northeastern industrial section of Hamilton the male to female ratio was also lower in 1969 and 1970, namely 10.3 to 1, compared to 14.7 to 1, for the three previous years.

In the previous survey the death rate from lung cancer ranged from 12 to 65 per 100,000 population compared with an overall cancer mortality in Ontario of 25 and of 23 in Canada. The incidence of cancer of the larynx, trachea,bronchus, lung, stomach, bladder and prostate gland was about one-third higher in Hamilton than in Ottawa for the five years, 1966 through 1970 (Table 1).

Fig. 1

Zonal Distribution of 300 Primary Lung Cancer Deaths in Hamilton for 3 Years - 1966, 1967, and 1968



FLUORIDE

These data reveal a clear pattern. The highest death rate from primary lung cancer, 65 per 100,000, occurred among the older or retired steel-workers, mostly men, who resided in or had recently moved away from, the industrial northeast section of the city. Because of expropriation by industry of many homes in this area and because of the city's urban renewal projects during the past few years, it was necessary to check carefully into the patients' former place of employment and residence. This was especially important in the case of many retired steel-workers who had moved to less polluted zones within the city or into the homes of their children and of other close relatives or into nursing homes.

TABLE 1

Comparison of the Mean Cancer Death Rate in the "Steel City" Hamilton with that in Less Industrialized Ottawa During 1966 to 1971*

	Hamilton	Ottawa
Larynx	21	14
Trachea, Bronchus and Lungs	502	353
Stomach	215	148
Bladder	117	77
Prostate	113	85

*Population - Hamilton 298,121, Ottawa 290,741 (1966-1968)
Compiled from the vital statistics of the Province of Ontario

Variations in individual susceptibility were again apparent in the deaths from lung cancer during 1969 and 1970. The population of the city of Hamilton can be roughly divided into three approximately equal-sized segments, namely British-born immigrants, Canadians (born in Canada), and a large ethnic group born in other European or Asiatic countries. The British immigrants led again with 44% of the total number of cases whereas Canadians made up 36%, and the remaining 20% came from an ethnic group of immigrants.

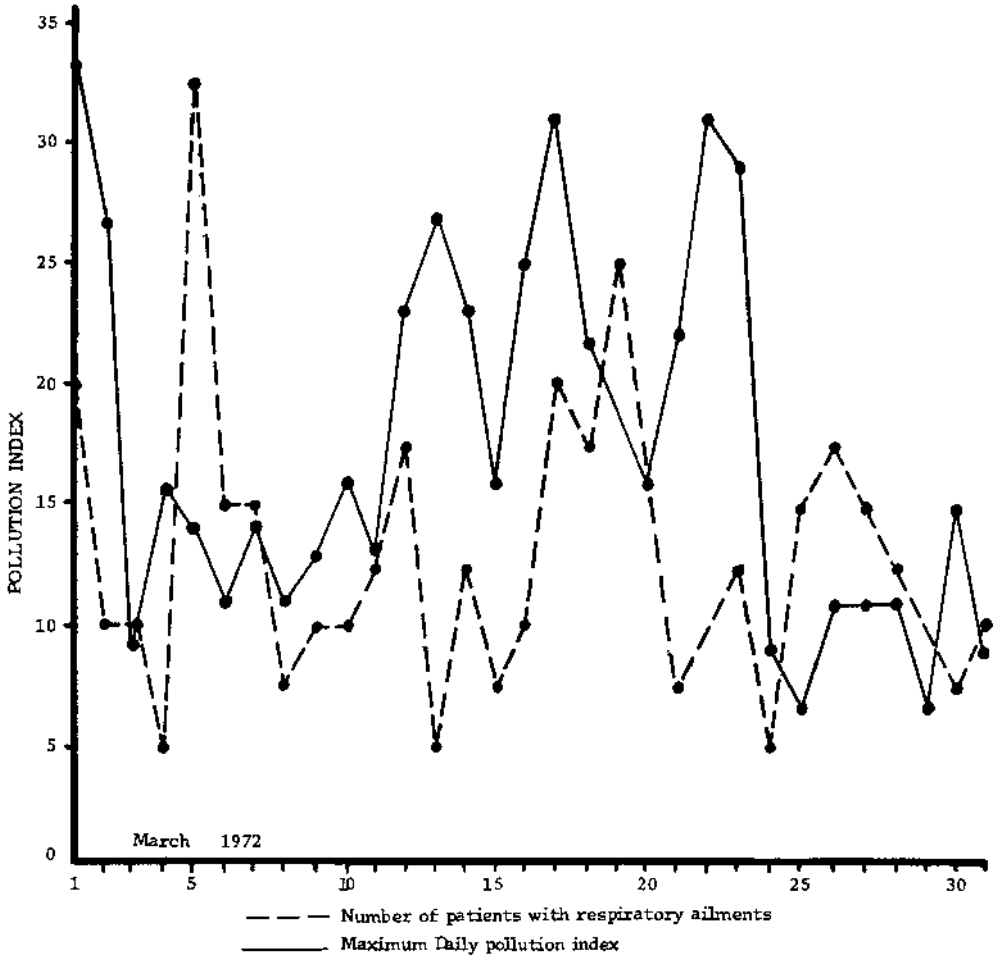
Biopsies and histological examination of 90% of the lung cancers during 1969 and 1970 showed again that a large number of the cases (48 percent) from the industrial area were of the undifferentiated small cells (oat cell) type; 40% were of the epidermoid or squamous cell variety; and about 12% were of the undifferentiated large cell and alveolar, adeno-carcinoma type.

2. Respiratory Diseases and Hospital Admission

In order to gain further knowledge regarding the possible cor-

Fig. 2

Daily Pollution Index and Number of Patients Treated for Respiratory Diseases in Hamilton General Hospital in March 1972

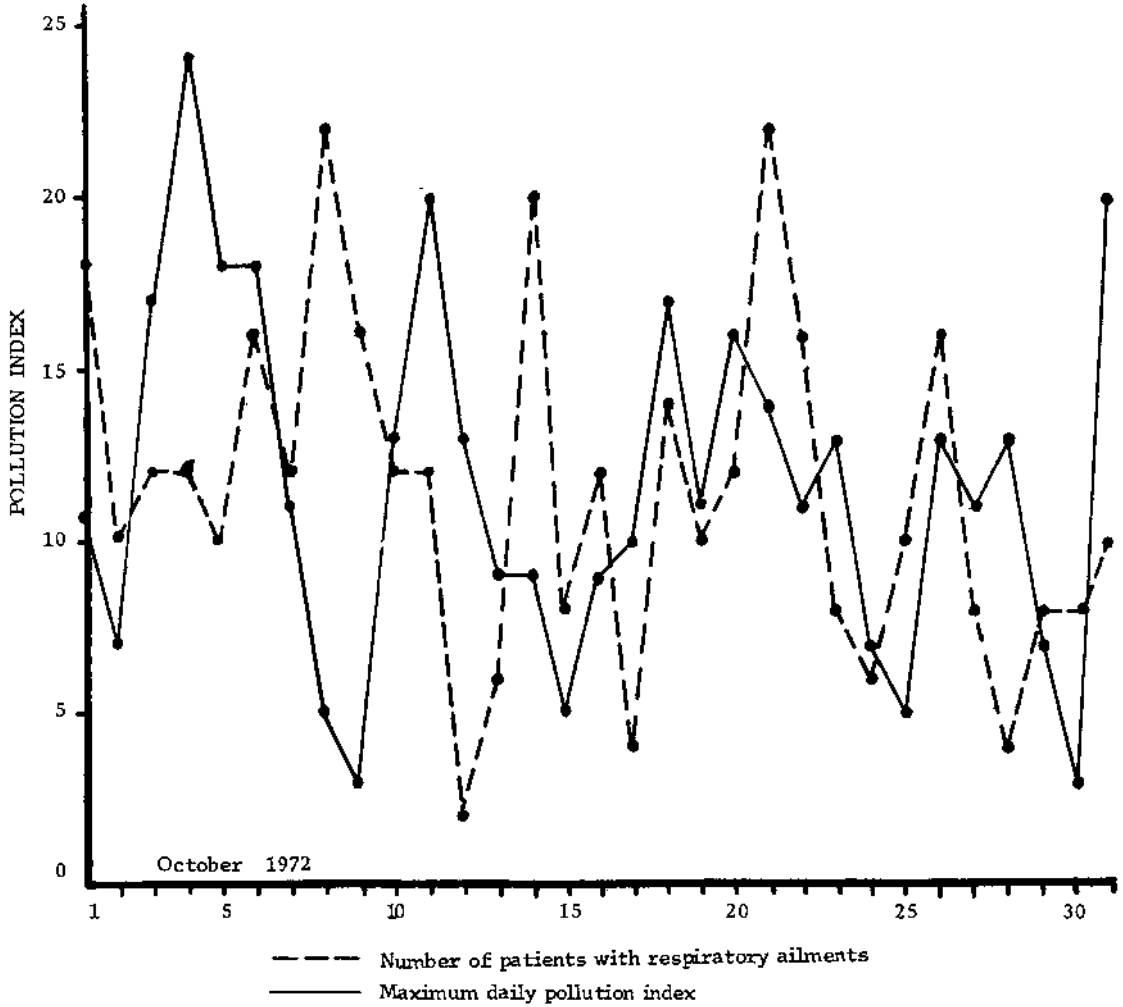


Of a total of 166 patients with respiratory diseases, 118 attended the emergency room, 48 were admitted to the hospital.

FLUORIDE

Fig. 3

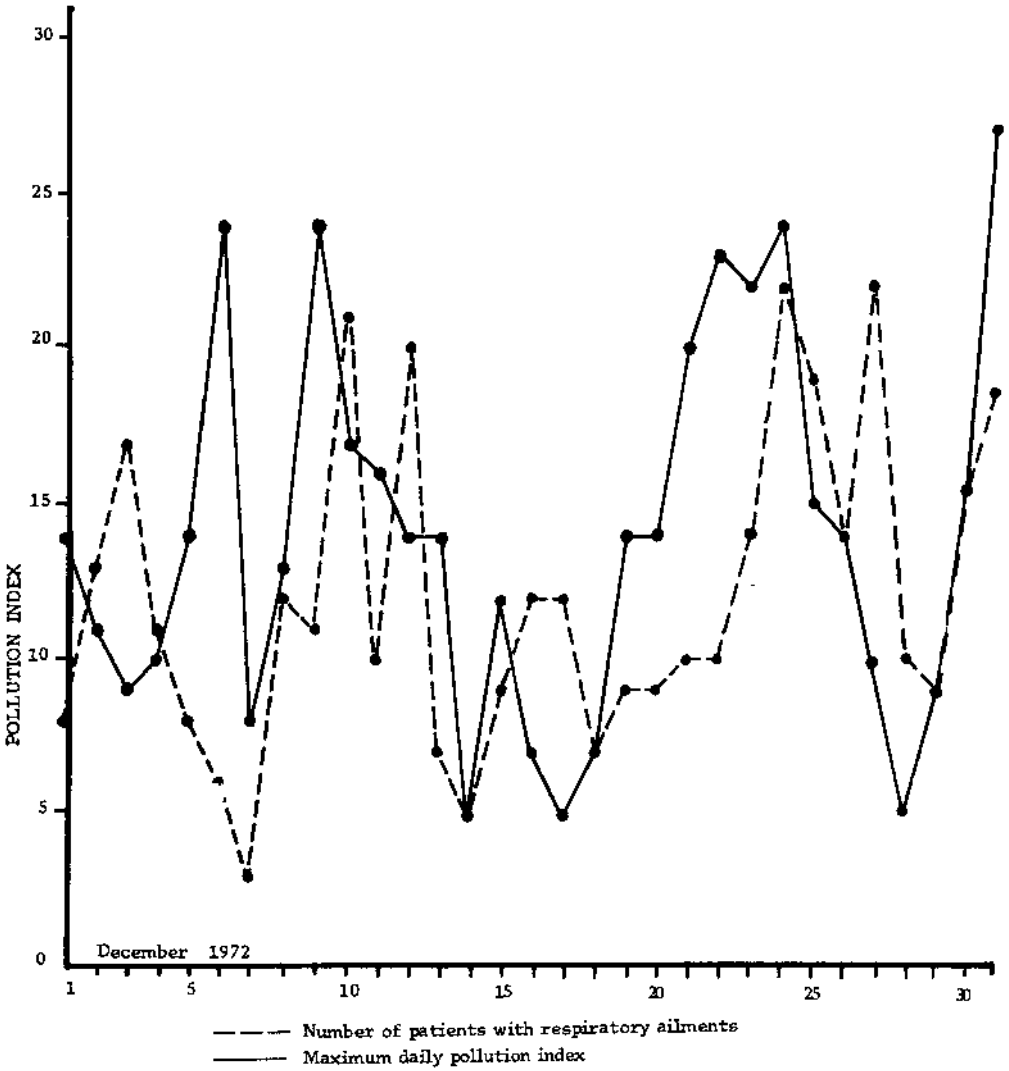
Daily Pollution Index and Number of Patients Treated for Respiratory Illness in the Emergency Room of Hamilton General Hospital During October, 1972



Of 2,642 patients treated, 177 patients had respiratory diseases.

Fig. 4

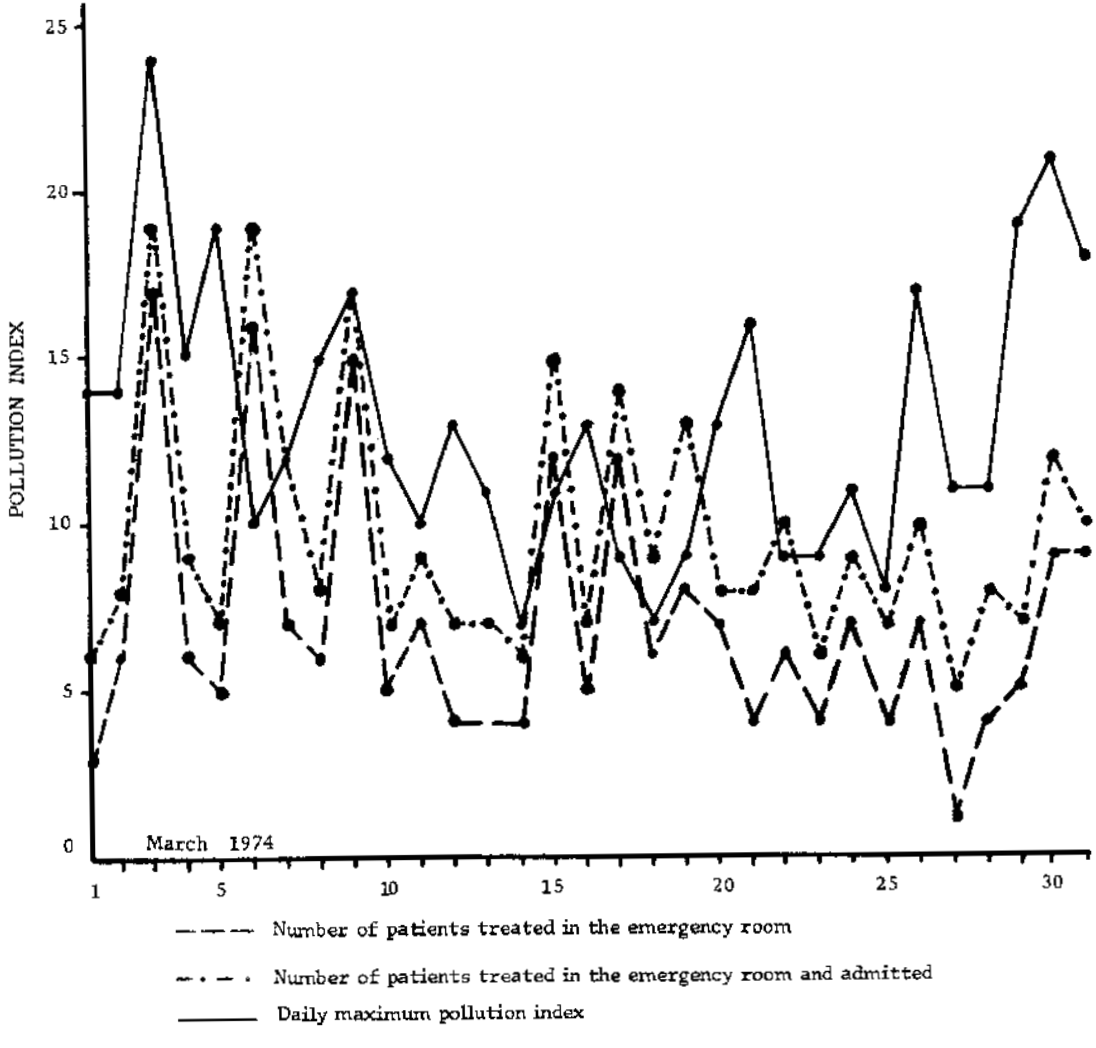
Daily Pollution Levels and Number of Patients with Respiratory Illness at Hamilton General Hospital During the Month of December, 1972



Of 4,029 patients treated, 264 patients with respiratory diseases attended the emergency room and 92 were admitted to the hospital.

Fig. 5

Daily Pollution Index and Number of Patients Treated for Respiratory Illness in March, 1974 at Hamilton General Hospital



Of a total of 4,408 patients, 299 had respiratory diseases (215 in the emergency room, 84 admitted to the hospital).

relation between pollution, respiratory disease and mortality, the daily number of patients treated in the emergency room and admitted to the Hamilton General Hospital* during March, October, and December, 1972 and March, 1974 (Fig. 2-5), were tabulated and compared with the maximum daily pollution index levels. Most of the acute upper respiratory infections, such as 'croup' in infants and young children as well as asthmatic attacks, occurred during or shortly after the peaks in the pollution index. On the other hand, the majority of the lower respiratory diseases such as bronchitis, bronchiolitis, lobar and bronchopneumonia were not manifest until 2 to 4 days after the peaks of the Pollution Index Level.

Seventy percent of all patients tr ated in the Emergency Room of the hospital and 75% of those admitted, resided in the industrial eastern section of the city. A similar study, by Dr. M. Newhouse at St. Joseph's Hospital, Hamilton, which is located in the southern, residential area of the city, confirms the relationship. During a six month period, 54% of their patients admitted for respiratory disease came from the east-end of Hamilton, which is the more polluted section of the city.

In both children and adults in Hamilton, the incidence of respiratory illness rises with the increase in the level of air pollution. Even though the pollution index level is based on varying amounts of sulphur dioxide and suspended particulates in the atmosphere, this figure serves also as a rough guide to the relative amount of other pollutants such as fluorides, hydrocarbons, carbon monoxide and dioxide, oxides of nitrogen, ozone, etc.

Fluoride in Air

In 1970, the air management branch, Ministry of the Environment, Ontario (2), reported atmospheric fluoride levels in Hamilton to be 8 times those considered damaging to vegetation.

A report by the Environment Department, Ottawa, Canada (3) named the industrial north-end of Hamilton as one of Canada's worst polluted areas. It stated that the maximum acceptable level for suspended particles which causes damage to the lungs, including sulfur dioxide and five other pollutants (including fluorides)** was exceeded throughout the years 1970 and 1971.

*Hamilton General is the city's largest hospital for acute and chronic respiratory ailments.

** The standard maximum levels for contaminants in September 1972 were carbon monoxide - 5 ppm, fluoride 5 ppb, iron 10 mg/m^3, lead - 20 $\mu g/m^3$, nitrogen oxide - .25 ppm, sulfur dioxide - .3 ppm, suspended particles - 100 per m^3.

Continuous monitoring at several stations in the industrial area (4) disclosed that the levels of these pollutants increased to 15 times above the average of the province of Ontario. In 1971-1972, the atmospheric fluoride levels were up to 20 times higher (5) than the average value for Ontario as a whole which is 40 mgm F/100 cm^2/30 days. One monitoring station recorded 1180 mgm F/100cm^2/30 days during February 1972, approximately 30 times higher than average. Because of these progressively increasing fluoride levels Stelco, Hamilton's and Canada's largest steel producer, began in March 1973 to employ a substitute for fluorspar for an eight month trial period. Fluorspar, utilized as a flux in the steel-making process, constitutes the greatest source of fluoride emissions.

Fluoride in the Biosphere

Further data on the magnitude of pollution by fluoride was obtained by analyses of dust, plants, leaves and garden vegetables grown in the vicinity, within 5 kilometers downwind from the steel mills (Table 2). Some of the samples revealed that in this area the fluoride content ranged from 17 to 130 times above the maximum permissable levels (by dry weight). One sample of lettuce, grown and eaten by a family, contained 74 ppm of fluoride (Table 2).

TABLE 2

Comparison of Fluoride Levels in Hamilton Food With Those of Tobacco Analysis for Fluoride and Sulfur (Dry Weight)

Food *			Tobacco **	
	Fluoride	Sulfur		Fluoride
Endive (Escarole)	269	9,300	Grobglockener	21.7
Swiss Chard	146	8,500	Falk	22.1
Lettuce	74		Erntekrone	19.2
Celery Leaves	35.8		Ernte 23	17.0
Red Rose (6 tea bags)	91.0		H B	24.2
Nestle's Instant Tea	371.0		Roth - Handle	26.8
			#3 La Pal	21.0*
			2 samples of cigarette rice paper	5.8 and 6.8*

* The analyses were made by the Wisconsin Alumnae Research Institute
** Analysis by Dr. W. Oelschläger

Okamura and Matsuhisa (6) found a correlation between the fluoride content of rice and excess death rates for gastric cancer. This increase in deaths over an eight year period corresponded to the increasing amounts of phosphate fertilizer applied each year to the paddy fields. They also found excess fluoride in other common foods, as well as in tea and tobacco.

The question arises whether or not the elevated levels of fluoride in locally grown and imported vegetables, food-stuffs and liquids, especially those which are artificially fluoridated, may be a contributing factor to the excess cancer deaths in a steel city.

Discussion

In 1969 and 1970 the number of deaths from primary lung cancer in the city of Hamilton and in the industrial north-east area has risen over those for the previous three years, even though the population remained much the same.

In the steel plants themselves, some departments such as the open hearth, sintering, galvanizing, coke ovens, blast furnace, foundry, have higher concentrations of toxic or irritating gaseous and particulate pollutants than in other areas of the facility. However it was impossible to obtain sufficient data to determine the effect in these different departments upon the mortality from cancer.

During the past few years the already excessive fluoride emissions from steel mills, iron foundries, and other industries in the north-east section of Hamilton, have been further increasing steadily in direct relation with the rate of iron and steel production. It cannot be considered proven that the effects of gaseous and particulate fluorides, when inhaled alone or together with other toxic or irritating fumes and minute particulates, are responsible for the high rate of cancer of the respiratory system among steel workers and other persons (mostly male), living in or near such a polluted industrial area.

A comparison with the non-industrial city of Ottawa, Ontario, which has much less atmospheric pollution, was made on the basis of the data obtained from the Vital Statistics for the Province of Ontario (7).* Here too a breakdown of these cancer deaths shows,as in the case of deaths for lung cancer, that nearly one-half of the affected subjects worked and/or resided in the east and northeastern zones of Hamilton. Deaths from cancer of the prostate, the only exception, were more evenly distributed throughout the city.

Over 80% of the individuals with cancer or cancer of the prostate were or had been moderate to heavy smokers. It was therefore of interest to learn that the fluoride content of 7 brands of tobacco, and 2 brands of cigarette paper ranged from 5.8 to 26.8 ppm of fluoride (dry weight) (Table 2). Several Japanese studies (8) of domestic and imported cigarette tobacco and paper showed much higher fluorine content

*The population of Hamilton at that time, 1966, was only slightly higher than that of Ottawa.

than in U.S.A. namely from 7.3 to 5469.5 ppm fluoride, in 35 samples.

The environmental difference appears to be more important than smoking in producing the high death rates from cancer of the respiratory, gastrointestinal and genito-urinary cancer deaths in the steel city of Hamilton.

This difference is quite apparent when comparing cancer deaths in the two Ontario cities of Hamilton and Ottawa (see Table 1). It is further brought out in a comparison of the deaths from cancer in two other Ontario cities, London and Windsor with about equal population, 194,416 and 192,544 respectively. In industrialized Windsor, deaths from cancer of the mouth, esophagus, respiratory tract and bladder were significantly higher than those in London where there is much less industry (Table 3).

TABLE 3

London and Windsor During Five Years - 1966 to 1971*

	London	Windsor
Buccal Cavity (Mouth)	25	44
Esophagus	25	43
Trachea, Bronchus, and Lung	236	312
Bladder	52	74

Deaths from cancer of the larynx, stomach and prostate were also higher in Windsor than in London, during this five year period.

*Population - London 194,416 Windsor 192,544 (1970)

Many other factories which are concentrated in this industrial section of Hamilton contribute to the overall pollution problem. Table 4 records the approximate output of soluble emissions into the U.S. atmosphere in various industries. It is therefore not unexpected that workmen

TABLE 4

Sources of Soluble Fluoride Emissions (9)

	thousands of tons F/yr. in the U.S. atmosphere	Approx. % of total
Iron and Steel:		
Open hearth steel	25	
Iron ore sintering	18	
Iron ore pelletizing	18	
Blast furnace	2.8	
Group total:	63.8	41
Coal Burning:	27	17
Phosphorus-Phosphate:		
Wet process phosphoric acid	6.4	
Normal superphosphate	5.0	
Electrothermal phosphorus	4.1	
Triple superphosphate	3.8	
Defluorinated phosphate rock	1.8	
Group total:	21.1	14
Aluminum Production:	16	10
Clay:		
Clay products	10	
Expanded clay aggregates	5.3	
Group total:	15.3	10
HF Alkylation:	5.8	44
Opal Glass Production:	3.3	2
		98

Minor additional sources amounting to about 2% are HF production, Enamel frit production, Cement manufacture, and Copper, Lead, or Zinc smelting and refining.

in the polluted areas have a much higher incidence of chronic respiratory diseases and lung cancer, as well as cancer of the gastrointestinal tract and genito-urinary system.

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FLUORIDE LEVELS IN THE SURFACE ENAMEL OF DIFFERENT TYPES OF HUMAN TEETH

by

R. Aasenden, E. C. Moreno, and F. Brudevold
Boston, Massachusetts

(Abstracted from Archs. Oral Biol., 18:1403-1410, 1973)

Little information is available on the fluoride content of the enamel of the different types of permanent teeth. Fluoride uptake in the enamel is expected to occur prior to, rather than following, the eruption of teeth since the rate of deposition of fluoride in the surface of the enamel is much slower after eruption than during the pre-eruptive period.

The authors studied the relationship of the fluoride content of the upper anterior teeth in low fluoride Boston (less than 0.1 ppm in drinking water) to that in Danvers, Massachusetts (1 ppm) and in Midland, Texas (5 to 7 ppm). In eight groups of 12 to 16 year-old school children, who were lifelong residents of their respective communities, two of three upper anterior teeth on each individual were biopsied. The authors employed a recently described method by Aasenden et al. which makes it possible to compare fluoride levels in teeth in vivo.

In all three areas, the central incisors showed significantly less fluoride than the lateral incisors and the canines. In Boston, the low fluoride area, this difference amounted to 28% for the canines and 19% for the lateral incisors. This pattern was similar in Danvers, the fluoridated area, and in Midland, the high fluoride area. There were also definite, but less significant, differences between the lateral incisors and the canines in Boston and Danvers. In all three areas, the differences in the mean fluoride concentrations between the compared teeth were statistically significant ($p < 0.01$), except for those between the canines and the lateral incisors in the Midland children.

The observed differences in the fluoride concentration of the enamel in the three areas persisted up to a depth in the enamel surface of at least 3 to 4 μm.

The authors concluded that the observed differences in the concentration of enamel fluoride developed prior to the eruption of the

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From the Forsyth Dental Center, Boston, Massachusetts.

teeth. Their studies suggested that the rate of incorporation of fluoride into the tooth enamel increases with decreasing fluoride present in teeth.

GLW

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VERHOOGD FLUORIDEGEHALTE VAN LEIDINGWATER TE ANTWERPEN DOOR EEN FLUORIDELOZING IN DE MAAS

by

R. Verheyden, V. Van Craenenbroeck, and J. Meheus
Antwerp, Holland

(Abstracted from Rev. Belge Med. Dent., 28:125-138, 1973)

The Belgian province of Antwerp receives its water supply through the Albert Canal, the water of which is derived from the Meuse River in the vicinity of the city of Liège. Because fluoride is present in the effluents from a fertilizer factory near Liège, the drinking water of the province of Antwerp shows wide fluctuations in its fluoride content throughout the year, a situation of which the Belgian authorities have been aware since 1970. In 1971, an exceptionally dry year with 74% of the normal precipitation, the fluoride level of the Meuse river reached a maximum of 9 ppm at one location; the maximum in the Albert Canal was 7 ppm. The so-called "optimal" concentration recommended by the World Health Organization is 1 ppm.

After measures were instituted to reduce these high levels in 1972, the fluoride content in the Meuse river continued to fluctuate markedly. It ranged between 0.24 ppm at Jambes and 1.6 ppm in Luik, a difference of 1.36. The authors state that the contamination of rivers by fluoride through industrial pollution is a new phenomenon with the cause and control of which they are concerning themselves.

From the Provinciaal Instituut voor Hygiëne, Antwerpen, and Werkzaam in de laboratoria van de Antwerpse Waterwerken.

GLW

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BEITRAG ZUR NEUROLOGISCHEN SYMPTOMATIK DER FLUOROSE ZUFALLSBEFUND ODER AUSDRUCK EINER ORGANMANIFESTATION?

by

J. Franke, R. Lahl, F. Fengler, and H. D. Hempel
Halle/Saale, GDR

(Das deutsche Gesundheitswesen, 28:120-124, 1973)

Neurological complications of skeletal fluorosis have been described in endemic areas, especially in India. They consist of radiculomyelopathy which may lead to spastic tetraplegia. The authors present a case of such complications in a 60 year-old male who had been working for 10 years in an aluminum smelter. Following a fall on his back in November, 1970, the patient complained of increasing weakness in the right leg, pains in the lumbar spine and vertigo.

Clinically, the authors observed limited mobility of the vertebral column, bilateral protrusion of bulbi, atactic gait, absence of reflexes on arms and legs, and tetraparesis which was most noticeable on the legs, especially on the right side. The patient also manifested loss of mental acuity, mental depression and a limited ability of orientation. X-ray examination revealed evidence of fluorosis, degree one to two according to Roholm's classification. The patient expired on May 30th, 1971.

Autopsy Findings: A large 4x4 cm globlastoma was found in the left parietal portion of the cerebrum, a pathobiosis of the ganglion cells of the anterior horn of the spine where the size of the cells was decreased, a reduction in the horns number of ganglion cells on the anterior horns and to a lesser degree in the medial posterior and lateral areas. The skeletal musculature revealed focal necrosis of muscle fibers with fibrosis and proliferation of fibroblasts and sarcoblasts. Depositions of calcium were noted at the sites of periosteal attachments. The bones showed periosteal apposition of bone substance with widened and spongiosed compacta.

Additional findings included a scar of an old cardiac infarct at the left ventricle and evidence of a generalized arteriosclerosis of a moderate degree. No fluoride-related damage was found in the parenchymatous organs, particularly on liver and kidneys. The fluoride content of the iliac crest was 0.74% (7400 ppm) ashed, compared to normal values which range from 0.05 to 0.1%.

Discussion: The pareses of the extremities were attributable

From the Orthopedic Hospital of the Martin-Luther-University.

to the lesions of the cells of the motor anterior horns (myelopathy) and the changes in the cells of the muscles (myopathies). Whereas the simultaneous occurrence of the cerebral tumor and fluorosis must be considered coincidental, the structural changes of the anterior motor cells and the skeletal musculature are etiologically related to the existing fluorosis. Significantly, the authors found no evidence of a narrowing of the spinal canal nor of the foramina intervertebralia to which damage to the cells of the pyramidal column is usually attributed in skeletal fluorosis. These spinal cord lesions and the associated muscular damage are, therefore, likely to be due to direct action of the fluoride ion on the cells of the anterior horn and the muscle.

JF

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FLUORIDE-INDUCED DIURESIS: RENAL-TISSUE SOLUTE CONCENTRATIONS, FUNCTIONAL, HEMODYNAMIC, AND HISTOLOGIC CORRELATES IN THE RAT

by

G. M. Whitford and D. R. Taves
Rochester, New York

(Abstracted from Anesthesiology, 39:416-427, 1973).

Whereas there is considerable literature which pertains to the effect of inorganic fluorides on the structure and function of kidneys, the exact mechanism of the action of fluoride on the kidneys - which is not a prominent feature in fluoride toxicity - has not been explored. The authors sought to determine whether or not the fluoride which is released from the anesthetic methoxyflurane, $CH_3OCF_2CHCl_2$, is responsible for the renal failure associated with a high output of urine occasionally encountered after anesthesia. They also wanted to learn whether or not fluoride concentrations in plasma encountered in clinical medicine could produce comparable renal effects in animals when no other methoxyflurane metabolites are present.

In a previous publication Taves et al. had noted that, in a patient with high-output renal failure, plasma concentrations of fluoride were

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much higher (275 μM or 5.2 ppm) than in two others who had no nephrotoxic symptoms (30 μM or .57 ppm). The current experiments concentrate on the fluoride levels in blood plasma encountered in clinical medicine and on the possible associated changes in the appearance of kidney tissue, their function, hemodynamics and histology.

Methods

Seven experiments were performed on female, 200-g Sprague-Dawley rats who were infused with 0, 100, 500, and 1000 nanomoles/min. (0, .0019, .0095, and .019 ppm). All infusates were isotonic containing 145 mM (2,755 ppm) sodium and various concentrations of chloride. Additional trace solutes were hydroxymethol, ^{14}C-inulin and ^{131}I-hippuran in some of the experiments. The rate of the infusion was 20 microliters per minute into the left iliac vein. Catheterized urine was usually obtained at half-hour periods; blood was drawn from the tail tips at the mid-points of the urine-collection periods but terminally from the tail tip or from the heart depending on the experiment. After the final urine collection both kidneys were removed simultaneously and each kidney divided along its longitudinal axis. A second longitudinal cut was made so that a wedge from the center of the kidney remained. This wedge was divided into cortex, outer medulla, inner medulla, and papilla in one experiment, whereas in two others the inner medulla included the papilla.

Results

Urinary Flow Rate: In six out of the seven experiments the urinary flow rates of the fluoride infusion groups were significantly elevated after the second half hour of the infusion. The control group showed a fluoride concentration of less than 2 μM (.04 ppm). The group of 50 showed a 64 per cent increase over the control. In the groups of 100 and 500 the increase of the urinary flow rate was 121 and 253 per cent, respectively.

Sodium, Potassium and Fluoride in Renal Tissue: The sodium concentration of the inner medulla and of the papilla showed an inverse relationship to the concentrations of fluoride. The potassium concentrations were generally reduced in all renal sections of the fluoride groups. The fluoride concentrations in the kidney tissue ranged from 92 μM (1.75 ppm) in the cortex of the F (50) group to 5.8 mM (110.2 ppm) in the papilla of the F (1000) group.

Rate of Sodium and Potassium Excretion: The graded increases in urinary flow rate were not accompanied by increased excretion of sodium and potassium or osmolal clearance. In each of the fluoride infusion groups, urinary osmolality showed a consistent and nearly linear decline with time. The lowest mean urinary osmolality of 580 mOsm occurred in the eighth period for the F (500) group. Mean plasma osmolality was

299 in Ogm for each group.

Glomerular Filtration Rate and ^{131}I-Hippuran Clearance: Glomerular filtration rates were 80 and 50 per cent of the control values in the F (100) and F (500) groups, respectively. F (450) infusion for 3 1/2 hours had essentially no effect on ^{131}I-hippuran clearance. Differences between group means were not statistically significant.

Microscopic Appearance of the Kidney: There was no evidence of cellular damage in kidney sections from rats which had received F (0) and F (500) for three hours. However the glomeruli of the sections from F (500) group contained less than half the quantity of red blood cells than those in the glomeruli of the F (0) group. The vessels of the outer medulla of the F (500) group appeared to be hyperemic compared with those in F (0) group and there was slight but consistent dilatation of the distal tubules in the cortex and in the intermediate juxtamedullary zone.

Discussion

The authors concluded that the elevated fluoride concentrations in these experiments are consistent with the hypothesis that fluoride is responsible for the nephrotoxicity in patients following methoxyflurane anesthesia. A statistically significant increase in urinary flow rate of 64 per cent was already noticeable in rats which showed plasma fluoride concentrations of only 32 μM (.61 ppm). This increase in urinary flow rate was not accompanied by increased excretion of potassium and sodium. The constant reduction in urinary osmolality is also similar for man (1, 2) and the rat. These studies therefore indicate a concentrating defect of the kidneys as previously pointed out in experiments by Fascino (3) in dogs and by Mazze, et al. in rats (2) and that fluoride is the probable cause of the concentrating defect.

Most striking and consistent was the reduction of the sodium concentration of the inner medullary portion of the kidney. The authors consider it possible that the failure of fluoride to promote increased excretion of sodium can be attributed to reduced reabsorption of sodium. They consider it possible that increased blood flow in the medullary portion of the kidney is the primary event respondible for reduced capacity of this portion to concentrate sodium. They postulate a direct effect of fluoride on the medullary vasculature since single large doses of fluoride cause peripheral dilatation of capillaries (4).

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GLW

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EYE DAMAGE IN WORKERS WITH FLUORINE INTOXICATION

by

V. A. Maltseva

(Abstracted from Vestn. Oftalmol., 2:71-74, 1973)

The examination of eighty workers exposed to fluorine compounds revealed a high incidence of abnormalities affecting the external parts of the eye. They consisted of inflammatory and dystrophic changes of the mucosa and cornea, varying degrees of retinal angiopathy, and interference with vision. The intensity of these changes appeared to be related to the duration of the employment and the severity of other manifestations of fluorosis. The author advises that fluorosis should be included in the category of occupational diseases.

GLW

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ACUTE FLUORIDE POISONING

by

R. Clarke, J. Welch, G. Leiby, W. Y. Cobb, and J. N. MacCormack
Atlanta, Georgia

(Abstracted from the Morbidity and Mortality Weekly Report,* 23:199, 1974)

On April 16, 1974, 213 individuals, namely 12 adults and 201 students at a rural school in Stanly County, North Carolina experienced nausea and vomiting, two to five minutes after drinking orange juice during the morning recess. The illness lasted 15 to 60 minutes. None of the 126 students who did not drink orange juice became ill. The orange juice had been prepared by diluting a commercial frozen concentrate with water and ice obtained at the school between 8:00 and 8:30 a.m. A survey of nearby schools during the next few days, revealed no other cases of illness among those who drank orange juice made from the same lot of frozen concentrate.

While the school was closed for the Easter holiday the fluoride pump, which was feeding the solution of sodium fluoride into the water supply had malfunctioned. The sodium fluoride solution was being fed into the water system continuously whereas the water pump was not operating. The laboratory analysis of the orange juice showed a fluoride content of 270 mg/liter; a water sample, obtained at the school on April 16, a concentration of 125 mg/liter.

This is the second reported outbreak of waterborne fluoride poisoning since 1966 when the Food and Waterborne Disease Surveillance System was initiated at the U.S.P.H.S. Communicable Disease Center.

*From the Communicable Disease Center, U.S.P.H.S., Atlanta, Georgia.

GLW

Editorial Note: Another similar outbreak occurred in 1965 in Hungary, see Fluoride, 1:123, 1968.

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CORRECTION

On page 116, paragraph 7 (volume 7) "1.3" should read "1/3".

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