Current Practice

PRACTICAL PROBLEMS

Fluoridation of Water-supplies

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Fluoridation of water-supplies is the official policy of the Ministry of Health, the British Medical Association, and the British Dental Association. Yet at present only four out of 204 local health authorities in Britain fluoridate their water, and opposition to this measure is strong. In order to assist doctors who may be questioned on the subject, we invited Dr. R. Duckworth to review the scientific evidence on its effectiveness and safety.

Fluoridation of water entails the adjustment of its fluoride content to levels which reduce the prevalence of dental caries without causing damage to teeth or other organs. Fluoridation aims to reproduce the natural situation where some drinking-water contains fluoride in quantities which are sufficient to confer relative resistance to caries.

Epidemiological Studies

Field investigations first revealed the important role of fluoride in the control of dental caries. During the early part of this century epidemiologists in the United States investigated a brownish mottling of dental enamel which proved to have a geographical distribution and was therefore thought to be due to a water-borne chemical. After this had been identified as fluoride (Churchill, 1931) Dean (1938) demonstrated a quantitative relationship between mottling and the fluoride content of water, and he went on to show that teeth with mottled enamel were less susceptible to dental caries than unmottled teeth (Dean *et al.*, 1939). Later surveys revealed that the prevalence of dental caries decreased as the fluoride content of drinking-water increased (Dean *et al.*, 1942) and that almost maximum protection, without enamel-mottling, was obtained when fluoride was present in the water in a concentration of about 1 part per million (p.p.m.).

These findings have since been confirmed by workers in many countries, including Forrest (1956) in the United Kingdom. Under a variety of conditions of diet and climate, epidemiological surveys have repeatedly shown that the presence of approximately 1 p.p.m. of fluoride in public water-supplies is associated with a reduction in the mean D.M.F. (an index of caries severity based upon the number of decayed, missing, and filled teeth per subject), children drinking such water having a D.M.F. usually less than half the D.M.F. in children reared in communities where the drinking-water is virtually free of fluoride. The benefits are not limited to children, for where adults have been continuously exposed to a water-supply containing about 1 p.p.m. of fluoride their caries rate has also been halved (Russell and Elvove, 1951 ; Englander *et al.*, 1964).

Controlled Trials of Fluoridation

After the demonstration of the inverse relationship between caries prevalence and the fluoride content of drinking-water, controlled trials were carried out to determine the effects of adding fluoride, in a concentration of 1 p.p.m., to water containing insignificant amounts. The long-term effects have been shown by the results of several trials, but the two of longest duration started in 1945.

In the first, where the water-supply to Grand Rapids, U.S.A., was fluoridated, the number of D.M.F. permanent teeth in children aged 12–14 years, born after fluoridation began and continuously resident in the town, was 50–60% less than the D.M.F. of children of the same age, from the same town, prior to fluoridation. After fluoridation the D.M.F. in Grand Rapids remained close to the D.M.F. in another town, where the water had a naturally acquired fluoride content of 1.2 p.p.m. (Arnold *et al.*, 1962), and during the early stages of the study the D.M.F. was less than in the control low-fluoride town. Comparison, over a longer period, of the D.M.F. in Grand Rapids with the D.M.F. in the control town was not possible because the water of the latter was fluoridated in 1951. However, this trial provided further evidence of the ability of the fluoride ion to prevent caries, and it showed that when the fluoride content of a water-supply was adjusted to 1 p.p.m. its effect was equivalent to that of water with naturally acquired fluoride at a similar concentration.

In the second long-term study children aged 16–17 years in Brantford, Canada—as yet the oldest children to be investigated after drinking fluoridated water since birth—had a caries rate equivalent to that in a town with a naturally fluoridated water and much less than the rate in the control town with a water-supply low in fluoride (Brown and Poplove, 1965).

The results of many similar controlled trials carried out in different parts of the world have now confirmed the findings obtained in these early fluoridation studies. Among these trials is the United Kingdom investigation, which, after five years of fluoridation in three centres, showed that, under British conditions of water intake, fluoridation reduced by a half or more the incidence of dental caries in the deciduous teeth of children born after fluoridation began (*Reports on Public Health and Medical Subjects*, 1962).

Mode of Action of Fluoride in Preventing Dental Caries

Caries-susceptible surfaces of the teeth are covered by films of adherent bacterial plaque. It is in this plaque that glycolysis leads to the formation of acids which are responsible for

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solution of the enamel and for the initial lesion of dental caries. Fluoride may control caries by increasing the resistance of the enamel to this acid decalcification or it may inhibit the bacterial enzymes active in the formation of acids in the plaque.

Support for the first hypothesis has been obtained in the laboratory, where enamel, consisting largely of hydroxyapatite, reacts with fluoride to produce the more stable fluorapatite (Leach, 1959), which is less soluble in acid. Similarly, enamel from teeth developed in regions where the water-supplies contained 2 p.p.m. of fluoride was less acid-soluble than enamel formed in low-fluoride areas (Jenkins *et al.*, 1952).

Until recently the concentration of fluoride in the bacterial plaque has been considered inadequate for the inhibition of glycolytic enzymes. However, Hardwick (1963) has reported the presence of relatively large amounts of fluoride in the plaque, and he has suggested that this is concentrated and stored in an organic form until it is released as the *p*H falls. The ionic fluoride thus released inhibits further acid production and hence enamel solution, and the development of a carious lesion is avoided.

Intake, Absorption, and Distribution of Fluoride

Fluoridation is effective in the control of dental caries because it adds to the normal intake of fluoride. Most foods and prepared drinks contain less than 1 p.p.m. of fluoride (Longwell, 1957), with the exception of tea infusion, which contains a little more (Longwell, 1963). From analyses of food and drinking-water and surveys of total dietary intake, the amounts of fluoride ingested in different communities have been calculated. In temperate climates the daily intake ranges from 0.25 to 0.55 mg. in the United States (McClure, 1949) to a maximum of 2.74 mg. in Newfoundland (Elliott and Smith, 1960). The intake of adults in the United Kingdom is 1.3 to 1.8 mg. per day (Longwell, 1962).

Although fluoride intake depends partly upon the nature of the diet, the fluoride concentration in drinking-water and the amounts of water consumed are more important. Where the fluoride content of water is high and the climate hot, as in parts of India (Singh *et al.*, 1962), the daily intake of fluoride may reach 10 mg. or more, but in the United Kingdom the additional intake from fluoridated water is only about 1 mg. per day.

Alternative methods of supplementing fluoride intake are the distribution of fluoride-containing milk and the use of fluoride tablets (Held, 1965) or fluoridated salt (Wespi, 1964). These methods of administration are effective in controlling dental caries if they are used conscientiously, but therein lies their chief disadvantage. In comparison with water fluoridation these alternative measures depend upon the efforts of individuals and therefore often fail through lack of cooperation. However, fluoride tablets and fluoridated salt are of value in regions without piped water-supplies.

Animal experiments have shown that relatively large amounts of calcium in the diet reduce the absorption of fluoride (Wagner and Muhler, 1960), probably by precipitating calcium fluoride, which is poorly soluble, or by the formation in the gut of calcium phosphate, which binds fluoride. In man this action of dietary calcium could reduce the amount of fluoride absorbed from drinking-water and foods containing fluoride, but the effectiveness of fluoridated milk in preventing dental caries suggests the calcium has no significant effect.

It has also been suggested that calcium and magnesium in hard waters could bind fluoride and reduce its absorption. However, the administration to rats of fluoride in tap-water and in distilled water produced no significant differences in the fluoride retained by the two groups of animals (Wagner and Muhler, 1957); nor did the addition to water of 160 p.p.m. of magnesium reduce the storage of fluoride in the rat (Wagner and Muhler, 1958). Thus drinking-water appears to be compatible chemically with fluoride and is therefore a suitable vehicle for its administration.

Controlled absorption depending upon the concentration gradient, sequestration in calcified tissues, and excretion via the kidney all play a part in maintaining the level of plasma fluoride. Individuals using communal water containing 0.15–2.5 p.p.m. of fluoride had relatively stable plasma fluoride levels, varying between 0.14 and 0.19 p.p.m. Not until subjects were exposed to 5.4 p.p.m. of fluoride in drinking-water did their plasma contain detectably greater amounts of fluoride (Singer and Armstrong, 1960). However, to permit the storage of fluoride which occurs in both teeth and bone, even at the lower levels of fluoride intake, there must be minor increases in plasma fluoride concentration.

With the exception of the kidney, and the stomach during absorption, fluoride in the soft tissues is in equilibrium with plasma fluoride and does not exceed a concentration of 0.5 p.p.m. Because analyses of fluoride in thyroid tissue have given slightly higher values, it has been suggested that the thyroid is halogen-blind, storing fluoride at the expense of iodine. However, experiments with radioactive fluoride have shown that the thyroid does not concentrate fluoride (Hein *et al.*, 1956).

Calcified foci in soft tissues, such as those which occur in the placenta at term, may trap fluoride in amounts in excess of those in the soft tissues. The amounts of fluoride contained in placentae from women drinking water low in fluoride and women drinking water containing 1 p.p.m. of fluoride (Gardner *et al.*, 1952), or taking sodium fluoride tablets (Feltman and Kosel, 1961) have been compared. When fluoride supplements are taken the placenta has been shown to contain up to 40% more fluoride, only some of which enters foetal blood. Animal experiments have demonstrated that the permeability of the placenta to fluoride is limited (Buttner and Muhler, 1958; Maplesden *et al.*, 1960), and measurements during delivery have shown that the concentration of radiofluorine in human foetal blood is only a quarter of that in maternal blood (Ericsson and Malmnäs, 1962). These results are in keeping with clinical findings, for enamel-mottling, due to the intake of too much fluoride, is uncommon in deciduous teeth developing during pregnancy. However, as these teeth are less susceptible to dental caries if developed in the presence of a fluoridated water-supply, sufficient fluoride must cross the placenta to confer some protection.

Deposition of Fluoride in Teeth

The calcified dental tissues incorporate fluoride during accretion of mineral and absorb it by ion exchange. However, these tissues have limited opportunity for fluoride uptake because of their short period of contact with fluoride-containing tissue fluid. It is the mineralized tissues at the interfaces with tissue fluid which contain the most fluoride; thus enamel is relatively rich in fluoride at the surface, the amount, which increases with age (Brudevold *et al.*, 1956), being related to the concentration of fluoride in the drinking-water (Isaac *et al.*, 1958). Brudevold *et al.* (1956) have postulated that fluoride enters enamel during three different stages in its development: during mineralization; prior to eruption, when the completed enamel absorbs further fluoride from the tissue fluid; and after eruption, when the fluoride content of surface enamel is augmented by absorption from water and food.

In appropriate amounts fluoride incorporated into enamel increases resistance to dental caries, and in greater quantities it may cause mottling of the enamel. This mottling, or enamel fluorosis, is the most sensitive indicator of the amount of fluoride being absorbed, although the most delicate physiological

effect of fluoride is its ability to reduce the prevalence of dental caries.

Enamel fluorosis of the permanent teeth results from the drinking of water containing more than 1 p.p.m. fluoride during the first ten years of life. Once enamel formation is completed fluoride cannot cause mottling. This varies from tiny opaque white spots, over which the surface glaze is preserved, to gross, dark brown, disfiguring lesions with a pitted, unglazed surface. The severity of individual lesions, the number of teeth affected in any one mouth, and the number of affected individuals in a community depend upon the fluoride content of the water-supply (Dean, 1938). Although a trained observer may find slight changes in a few teeth in some individuals drinking water containing 1–2 p.p.m. of fluoride, aesthetically objectionable mottling has not been reported at this concentration. Indeed, the community index of hypoplastic defects in enamel is at its minimum when the fluoride concentration in water is 1 p.p.m. (Forrest and James, 1965). Staining does not occur until a concentration of about 3 or 4 p.p.m. is reached, and numerous gross lesions appear only when the drinking-water contains 5 or 6 p.p.m. of fluoride.

Deposition of Fluoride in Bone

The hard tissues of the teeth are not the only mineralized tissues to react with fluoride. The facility with which the fluoride ion exchanges with the hydroxyl ion of hydroxyapatite makes fluoride the most avid of bone-seeking elements. It is rapidly taken up by existing bone and incorporated into forming bone, a reaction which is protective because it aids the kidney in fluoride homoeostasis. Data from studies of fluoride balance in man show that, when extra fluoride is ingested, up to half is bound by bone and the remainder is excreted in the urine. If the raised intake continues the skeleton approaches saturation and the proportion of absorbed fluoride excreted in the urine rises (Largent, 1954).

Increases in bone fluoride with age have been found in subjects from communities with water-supplies containing less than 0.5, 0.8, and 1.9 p.p.m. of fluoride (Smith *et al.*, 1953 ; Jackson and Weidmann, 1958), the increase continuing to middle and old age. In these studies the higher the fluoride concentration in the drinking-water the higher was the level of bone fluoride at any given age.

The effects of larger intakes of fluoride upon human bone have been studied in regions where there are naturally high concentrations of fluoride in the water, and where workers engaged in aluminium-smelting, rock-crushing, or fertilizer manufacture have in the past absorbed vast amounts of fluoride. For many years the water of Bartlett, U.S.A., contained 8 p.p.m. of fluoride, but neither clinical nor significant radiological changes were found in the bones. Above this level of intake skeletal fluorosis may appear as a symptomless diffuse osteosclerosis (Singh *et al.*, 1962) ; not until very large amounts of fluoride (20 mg. per day or more) had been absorbed over many years did cryolite workers in Denmark complain of bone pain and joint stiffness due to severe osteosclerosis and calcification of ligaments and tendons (Roholm, 1937). These high levels of intake will not be achieved with fluoridated water.

Safety of Fluoridation

Accidental or suicidal swallowing of inorganic fluoride has enabled estimates to be made of its acute lethal dose ; these vary from 2.5 to 5 g. of fluoride or about 50 mg. per kilogram of body-weight. Clearly, if only 1 p.p.m. of fluoride (1 mg. per litre) is added to water it would be impossible to drink at once sufficient to cause death. Although the earliest symptoms of acute fluoride poisoning, such as nausea, vomiting, and sweating, can be caused by an intake of as little as 125 mg. of sodium fluoride, the equivalent volume of fluoridated water, 60 litres, could not be drunk at one time. Therefore there is no danger of fluoridated water causing symptoms of acute fluoride intoxication.

Chronic fluoride poisoning, showing itself in childhood as enamel fluorosis and in later life as skeletal fluorosis, does not occur when water contains 1 p.p.m. of fluoride. Cosmetically objectionable mottling of enamel appears in some subjects when the communal water contains 3 p.p.m. fluoride or over, and skeletal fluorosis may be apparent radiologically when the water contains about 8 p.p.m. of fluoride ; even then the changes observed are symptomless.

Because much of the excreted fluoride passes through the kidney, this organ could be in a position of special risk from any toxic actions which fluoride might have. A high concentration of fluoride (125 p.p.m.) in the diet of rats caused renal tubular necrosis (Pindborg, 1957), but there is no epidemiological evidence that renal disease in man has resulted from drinking water containing only 1 p.p.m. of fluoride. Conversely, experimetal renal disease (acute chemical nephritis) has not been shown to be associated with fluoride retention, and there is no clinical evidence to show that impaired renal function in subjects drinking fluoridated water could limit fluoride excretion sufficiently to produce skeletal fluorosis. Indeed, it is probable that a degree of renal failure, incompatible with life, occurs before there is significant fluoride retention.

In numerous epidemiological surveys, in regions where the fluoride content of water varied from 1 to 8 p.p.m., data upon disease prevalence and mortality have been collected and compared with similar data from low-fluoride regions. Examples of these surveys are the Newburgh-Kingston study reported by Schlesinger *et al.* (1956) and the Bartlett-Cameron investigation (Leone *et al.*, 1955). At the end of ten years there were no differences of medical significance between the children drinking fluoridated water in Newburgh and children not doing so in Kingston. In Bartlett the effects of prolonged exposure to water containing 8 p.p.m. of fluoride were assessed by comparing the health of its residents with the health of the people of Cameron, a town with a water-supply low in fluoride. Medical, dental, and radiological examinations of the inhabitants of Bartlett revealed that the only significant effect of their high intake of fluoride was, as would be expected, fairly severe enamel fluorosis. Further evidence of the safety of fluoridation was provided by Hagan (1959), who reviewed mortality statistics in relation to fluoridation in Illinois and concluded that there was no relationship between mortality and the presence of fluoride in drinking-water. These are but a few of the many studies which have demonstrated that traces of fluoride in drinking-water do not have adverse effects upon health.

Conclusion

Judgement upon the desirability of fluoridating communal water must be based upon an evaluation of data that have been obtained in epidemiological studies which first revealed the dental importance of fluoride, in controlled trials of fluoridation which have demonstrated its preventive action, and in laboratory and other experiments designed to elucidate the physiological properties of the fluoride ion and its possible toxic effects. If this evaluation is made it will be seen that fluoridation is not a new and untried procedure, for in certain parts of the world naturally fluoridated water has been drunk for decades ; and in the United States, where over 58 million people now drink water containing significant amounts of fluoride, there is 20 years' experience with fluoridation. Indeed, the available data suggest that probably no other procedure in the whole field of preventive medicine has had its effectiveness and safety so thoroughly established ; yet, in spite of this, and our ample knowledge of the physiological actions of fluoride, we in this country still await the widespread introduction of fluoridation.

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ANY QUESTIONS?

We publish below a selection of questions and answers of general interest.

Parenteral Iron Therapy

Q.—*Can iron be given parenterally without risk of side-effects (particularly carcinogenic) in patients who are unable to take iron orally?*

A.—Parenteral iron therapy, whether by the intramuscular or intravenous route, is usually given without any risk of untoward side-effects. Occasionally local or general reactions can occur.[1]

Saccharated iron oxide causes a painful inflammatory reaction when it is inadvertently given outside the vein. Intramuscular iron dextran usually gives some local discomfort after injection, and occasionally tenderness may persist for months. Staining of the skin may occur and persist for a very long time. Rarely, painful enlargement of regional lymph nodes may occur after the injection, and this is usually associated with pyrexia. Thrombosis of the vein is not uncommon, and local soreness and inflammation not obviously associated with extravasation of iron may occur.

Systemic reactions when they occur are more frequent after intravenous administration, but may also occur with intramuscular treatment. Very shortly after starting administration there may be faintness, tachycardia, sweating, nausea, vomiting, bronchospasm, headache, and pain in muscles and joints. Indeed, death due to circulatory collapse has been reported. Later reactions include pyrexia, rigor, urticaria, headache, and generalized body aches. Patients with urinary tract infections may show an increased urinary excretion of white cells after iron-sorbitol-citrate.[2]

The administration of relatively massive doses of iron dextran to rats has induced sarcomata in these animals.[3] There is no evidence that this compound is carcinogenic to man. Nevertheless, many workers have refrained from the intramuscular use of iron dextran in younger subjects, although it is widely used by the intravenous route, particularly since large amounts of iron can be given as a single infusion.

These reactions are rarely seen when adequate care is taken in giving the iron preparation. Skin discoloration can be avoided by using a deep intramuscular injection. Intravenous therapy should be preceded by the administration of a small "test dose," and vasovagal collapse can be avoided by giving the intravenous injection very slowly and diluting the dose of iron with the patient's own blood by drawing back the syringe. Reaction to infusion of iron dextran can be avoided by starting the infusion with the contents of only one ampoule of iron dextran in 500 ml. of saline and running the drip extremely slowly. If no reaction occurs after 20 minutes the rest of the dose can be added to the saline and the rate of flow increased.

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Prognosis in Ovarian Carcinoma

Q.—*Is a favourable prognosis justifiable in the case of a woman aged 35 who four and a half years ago had a papillary ovarian cyst (histology: undifferentiated pleomorphic carcinoma) removed and x-ray therapy afterwards? There is no clinical evidence of recurrence.*

A.—The longer a patient survives after treatment of an ovarian carcinoma without recurrence the more favourable the outlook, since the majority of women who are going to die of the disease do so within a year or two.[1]

Ovarian carcinoma is a notoriously unpredictable tumour, but most authorities agree that the less the histological differentiation the worse the prognosis.[2,3] The overall five-year cure rate for all types of malignant ovarian tumour is in the order of 20 to 30%. No mention is made of the degree of spread at the time of operation in this patient, but if the tumour had not obviously broken through the capsule of the ovary, and particularly if it was unilateral,[4] the prognosis would be much more favourable.

Since this woman has survived so far without recurrence there is reasonable justification for being optimistic, but it is unfortunately necessary to accept the fact that the future for those who have had an ovarian carcinoma is always likely to be uncertain.

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