and Trowell, *Tr. Roy. Soc. Trop. Med. Hyg.* **44,** *756 (1951)*), this view is now less certain, for intensive studies have not revealed any unequivocal dietary, biochemical or pathologic features specific for the condition (Walker, *Ann. N. Y. Acad. Sci.* **69,** *989 (1958)*).

Vesical Stone in Indians

Bladder stone occurs with considerable frequency among the children of Delhi and its environs. Thirty years ago, R. McCarrison concluded that calculus in India was a disease of faulty nutrition, particularly vitamin A deficiency (*Brit. Med. J.* **1,** *1009 (1931)*). Yet recent exhaustive studies in nutrition (and other environmental factors), metabolism, and pathology, have not identified any specific etiological factor or factors (V. Ramalingaswami and A. L. Aurora, *Fed. Proc.* **20,** Suppl. No. 7, 317 (*1961*)). In South Eastern Asia, the foci of occurrence are very restricted. As far as is known, there are no such foci in Central or Southern Africa.

COMMENT

This discussion illustrates that while knowledge is far advanced regarding the predictability of numerous diseases caused or modified by nutrition, such knowledge is far from complete. There are certain diseases which should be more common than they are and certain diseases, whose etiology, formerly ascribed to nutrition, remains unknown. Among local workers such conditions or diseases constitute a serious challenge. They present problems of a type, moreover, in which animal experimentation is likely to give meagre or no help.

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METABOLISM OF FLUORIDES

Ingestion, absorption, and excretion of fluorides vary from individual to individual. Currently there is no convincing evidence to indicate potential fluoride toxicity from the ingestion of water fluoridated at the recommended levels in the United States, because of the presence of an adequate safety factor.

The problems associated with determining the optimal quantity of the trace element fluorine for human consumption have been explored in considerable detail. While these problems have many facets, the over-all relationship of the absorption, excretion, and toxicity of fluorides in man is certainly not particularly complex. Nearly all nutritionists agree that adequate supplies of fluorides in the diet during tooth development result in a major reduction in dental caries incidence. The general acceptance of the benefits of water fluoridation was well reviewed recently by J. M. Dunning (*Nutrition Reviews* **18,** *161 (1960)*). It is true that fluorine is a highly reactive element and that consumption of excessive amounts of its salts by man or by laboratory animals causes serious sequelae. In general there is agreement as to how much fluorine produces toxicity and what the characteristics are of the syndrome of fluorosis. Studies in experimental animals have shown that the renal changes may be related to lower concentrations of fatty acid oxidase (*Ibid.* **18,** *79 (1960)*).

Last year a symposium was published entitled "The Physiologic and Hygienic Aspects of the Absorption of Inorganic Fluorides" (*Arch. Indust. Health* **21,** *303 (1960)*). This symposium included some very interesting observations on various aspects of fluoride metabolism, some of which were reviewed recently (*Nutrition*

Reviews **19,** *198 (1961)*). A particularly thought-provoking hypothesis raised in this symposium was: "Disadvantageous effects on the bone structure of an adult population may be associated with the prolonged use of drinking water that contains an insufficient concentration of fluoride."

In a recent article G. L. Waldbott (*Arch. Environ. Health* **2,** *155 (1961)*) commented on this symposium and presented a lengthy series of references about fluoride toxicosis. In essence he challenges the interpretation of certain data in the symposium. In the light of his interpretations, he believes that the amounts of fluoride available from water fluoridation at recommended levels are toxic for a fraction of the population. Thus, his conclusions are at variance with those in the symposium, which are the generally accepted ones in the scientific community. There are essentially no data presented in Waldbott's article that have not already been used widely by opponents to fluoridation of public water supplies.

Waldbott believes that three major shortcomings have been common to most investigations on fluoride metabolism: 1) a great variability of intake, absorption, and excretion of fluorides from one person to another might mean that detailed studies on a limited number of subjects did not necessarily apply to the entire population; 2) relatively few clinical data are available on how fluorides affect man; 3) fluorine is distributed widely throughout the body and is not confined to bones and teeth.

In discussing the symposium in connection with the subject of variations in fluoride intake from one individual to the next, Waldbott listed numerous examples, such as the following ones, from the literature to point out the potential variability in intake. Tables of food content of fluorine indicate wide variations in fluoride content within individual foodstuffs. For example, the fluoride content of mackerel was stated by one author to range from 0.02 p.p.m. to 84.47 p.p.m. Admittedly, the lower value is difficult to explain other than on the basis of a technical error, for this low level is not expected in any plant or animal tissue. The high level is undoubtedly due to the inclusion of a high percentage of bone in the sample analyzed, for normal muscle meat from animals or fish never contains levels of this order of magnitude.

Boiling food in water containing fluoride may increase the fluoride content of the food significantly. Certain insecticides contain fluorides which may remain on the food which has been sprayed. Some of these fluoride-containing chemicals are organic chemicals in which the fluoride is not available. The author also points out that individual food habits are important determinants of the level of fluoride consumed, for example, whether or not an individual drinks tea, for tea contains some fluorides and may be made with water which contains fluorides. Air ordinarily contains very minute amounts of fluoride. In some parts of the world the levels in the air are greatly increased by contamination from factories, resulting in high fluoride concentrations on the surfaces of the leafy vegetables grown nearby and of milk from neighboring cows which have consumed herbage in these areas. Individuals or cattle in these areas undoubtedly absorb some fluorides as a result of inhalation of the contaminated air.

Waldbott points out that the rate of absorption of fluorides varies widely depending upon the form in which the fluorine is consumed. Fluorine in organic compounds is not released in the body since these compounds do not ionize to release the fluoride ion. Therefore, fluorine consumed in organic insecticides or in drugs is not metabolized by the body as fluoride ion and does not contribute to the fluoride pool of the body. Inorganic salts of fluorine may be absorbed less efficiently when consumed along with food than when simply dissolved in water. Numerous laboratory trials have indicated that increases in dietary fat enhance fluoride

retention and the onset and severity of toxicity.

The author mentions that the rate of intake may also be important. Continuous ingestion of the element results in greater storage than does intermittent dosage with the same quantity. Hard water containing high levels of calcium, magnesium, and phosphates retards the rate of fluoride absorption somewhat.

In the course of a short paragraph, Waldbott records the fact that in a clinical study of 77 cases in which 6.8 mg. of fluoride were given as sodium fluoride, as little as 3.6 or as much as 99.5 per cent was recovered in the urine in 24 hours. These data are not even closely similar to excretion data from other investigators and it would be interesting to know more about his procedures and experimental subjects. No comments were made about the total fluoride consumption of these patients from sources other than the test dose.

Waldbott believes that relatively little is known regarding the toxicity of fluorides in man. Osteosclerosis may occur when more than 5 mg. per liter (or 5 p.p.m. of fluoride) is present in the urine of a patient. Crippling fluorosis may occur when fluorides exceed 20 to 80 mg. per liter of fluid. According to these data, drinking water would have to contain approximately 20 to 30 mg. per liter in order to induce clinical illness. However, the author accumulated data from 22 separate reports which occurred in localities where the fluoride content of the water was less than 16 p.p.m. and in most instances less than 8 p.p.m. It is probably noteworthy that amounts of water consumed, the amounts of fluoride from non-water sources, and the influences of malnutrition, high environmental temperatures, and the like, were not considered by the author as he makes this assertion. Obviously the total amount of fluoride consumed is of greater importance than the strict parts per million of fluoride in the drinking water.

He suggested that in any given case the degree of disability due to fluorides is most difficult to assess and that most reports overemphasize biochemical data and most authors have made little or no reference to the accumulation of fluorides in soft tissues. The only definite characteristics of fluoride intoxication are characteristic bone changes as seen by x-ray and characteristic mottling of teeth.

Waldbott believes that fluoride intoxication may cause arthritic pains, joint stiffness, gastrointestinal disturbances, faulty sight and hearing, parasthesias, paraplegias, convulsions, hypochromic normocytic anemia, splenomegaly, and the like. The author concluded that organs were involved in the following order: upper gastrointestinal tract, kidneys, buccal mucosa, and liver. The way in which he has obtained many of these symptoms from questionnaires with leading questions has been described elsewhere (Hornung, *J. Am. Dent. Assn.* **53,** *325 (1956)*). Waldbott believes that there is serious import to the fact that fluorides concentrate selectively in the diseased soft tissues where calcification is taking place. Abnormally high concentrations have been found in cataracts, atheromatous aortas, diseased kidneys, and even in neoplasms. He believes that it is possible, if not probable, that these high concentrations of fluoride may have an effect on the disease process. In general, storage of fluorides in aortas occurs in rough proportion to the degree of aortic sclerosis even in regions where the fluoride content of the water is not high. The author emphasized that no conclusions can be drawn from these data, partially because of the wide variations in intake, the lack of adequate clinical observations, and the inability at the present time to evaluate the effects of fluoride on various organs.

From Waldbott's discussion of the earlier symposium, one might conclude that nothing but confusion existed in connection with the metabolism of fluorides by man. While it

seemed apparent that some of the investigations reviewed and commented upon regarding fluoride metabolism have lacked not quality but depth, many of the investigations upon which our confidence in the safety of water fluoridation is based are substantial studies worthy of our trust.

The fact that fluorides are related primarily to skeletal metabolism may have distracted investigators from the possibility that this element also may have an important role in the metabolism of other tissues. However, the lack of evidence today of soft tissue pathology at recommended levels for human ingestion seems to indicate that there is no need for concern. Possibly, instead of being concerned about the minute amounts of fluoride in all soft tissues as potential hazards, the evidence may come that fluoride ion in appropriate amounts is an important regulator of enzymatic function in the maintenance of homeostasis to prevent excess activity of certain fluoride-sensitive enzymes. The fact that fluoride increases in tissues where calcification is occurring, such as in aortic sclerosis, is to be expected rather than otherwise. Why should calcification occur anywhere in the body without the incorporation of an amount of fluoride commensurate with what is available in the circulatory system?

REDUCTION OF SERUM CHOLESTEROL CONCENTRATION BY TRIPARANOL

Triparanol, an inhibitor of cholesterol biosynthesis, causes a reduction in serum cholesterol concentration in human subjects.

Cholesterol appears sufficiently implicated in the etiology of atherosclerosis that much effort is being devoted to discovering the factors which affect its concentration in the circulating blood. Numerous reviews in this journal have covered the nutritional and endocrine factors which are known to be involved.

In an attempt to find agents which will lower the level of serum cholesterol, investigators have become interested in various other compounds, *e. g.* thyroxine analogues (*Nutrition Reviews* **18,** *249* (*1960*); **19,** *209* (*1961*)) and synthetic drugs which might interfere with cholesterol synthesis (*Ibid.* **19,** *251* (*1961*)). A number of compounds of this class are appearing for clinical trial.

One of these is triparanol ("MER-29"), a product of pharmaceutic research on which an early symposium has been published (*Progress in Cardiovascular Diseases* **2,** *485 1960*)). This drug apparently acts at a late stage of cholesterol synthesis, by inhibiting a single enzymatic step in the transformation of desmosterol to cholesterol. Two recent clinical studies are reviewed below.

P. Lisan, W. Oaks, and J. H. Moyer studied 45 patients with arteriosclerotic heart disease and serum cholesterol levels above 250 mg. per 100 ml. (*Am. J. Cardiol.* **6,** *246* (*1960*)). The subjects, on several triparanol dosage regimens plus their normal diet, were followed up to eight months. Decreases in cholesterol levels of 75 to 100 mg. per 100 ml. were obtained after three months on doses of 250 mg. per day, sooner with 500 or 1,000 mg. The control cholesterol levels of the groups averaged 324 mg. per 100 ml., with standard deviations as high as 66 mg. per 100 ml. In half the subjects, the final serum cholesterol values were lower than 75 mg. per 100 ml. below pretreatment values.

Two patients developed rashes; three (without cirrhosis) had increased bromsulphalein retention, but their pretreatment values were not known.