THE EFFECT OF ADDITIONS OF FLUORINE TO THE DIET OF THE RAT ON THE QUALITY OF THE TEETH.*

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As a result of special studies in relation to various nutrition problems we have observed the widest possible differences in the quality of the teeth of many of our experimental rats. In some groups where the nutrition was excellent throughout life we have seen teeth which lasted until the animals were advanced in age without showing signs of decay, or disease of the attaching tissues or apical abscesses. They were essentially perfect. In other groups the teeth would be defective and would early show lesions of the kinds mentioned, although the general nutrition of the animals during early life appeared to be satisfactory. The effects of faulty diets on the teeth were always more pronounced in the incisors, which in the rat grow from persistent pulp throughout the life of the animal. It has proven an exceedingly difficult problem to decide in many cases why the teeth of these animals should have been as defective as they were.

Since all investigators who have examined the teeth and bones for fluorine have found considerable amounts of this element, we were led to consider whether perhaps a deficiency of fluorine in the food might lead to the formation of teeth which had poor structure, and consequently possess little power to resist the

* Since this work was reported at the meeting of the National Academy of Sciences at Cambridge, Mass., in November, 1924, the paper of Schulz and Lamb (Schulz, J. A., and Lamb, A. R., Science, 1925, lxi, 93) has appeared in which they report the results of feeding sodium fluoride to rats.
agencies which lead to decay. We have in no instance attempted to control the intake of fluorine in any of our experimental animals, so that the amount of fluorine ingested may have varied over a wide range depending upon the nature and amount of natural foods in the diet. Our diets in many cases consisted in considerable measure of purified foodstuffs, so the amount of fluorine ingested in these diets was very small. The possible beneficial effect of adding small amounts of several inorganic elements which are of widespread occurrence but which have generally been regarded as being accidental constituents of the animal body has been suggested by Osborne and Mendel (1), but their experimental evidence gives no definite information concerning a need by the body for fluorine. We were led, in seeking for an explanation for the cause of defective teeth, to study the effect of adding small amounts of fluorine to certain of our experimental diets used with rats.

In making a decision as to the amount of fluorine which should be included in the food mixtures, we were guided by the data relating to the amounts of this element in natural foods, waters, and the body tissues. The following data relating to the distribution of fluorine will serve to help one to gain an idea as to the importance of the amounts ingested by our rats, in terms of what wild or domesticated animals are likely to secure.

Tammann (2), using a method by means of which 0.1 mg. of fluorine could be detected, found the element to be present in the ash of 114 gm. of egg albumin. He found 11.7 parts per million of fluorine in egg yolk, 7.4 parts per million in calf brains, and detected the element in blood and milk. His results were expressed in terms of fresh material.

Zdarek (3) analyzed the tissues of two men, killed in accidents, and found the following amounts of fluorine: In the heart, 4.6 parts per million; kidney, 15.4 parts per million; brain, 2.7 parts per million; lung, 2.2 and 7.0 parts per million; spleen, 8.2 and 23.5 parts per million; liver, 6.8 and 8.0 parts per million. These results are calculated to a dry basis.

Gautier and Clausmann (4) published analyses of 63 samples of vegetable tissues, mostly of food plants. The extreme values found were 5.9 parts per million and 1,380 parts per million, the average for all samples being 265 parts per million. The fluorine content was highest in leaves of plants, but was not characteristic of any particular order. The skins of apples and bananas were found to contain over ten times as much fluorine as the pulp.

Carlos (5) analyzed 93 samples of mineral waters, including sea water,
and found fluorine in all but five. The values varied from 4.5 to 79.0 parts per million. Vichy contained 6.0 parts per million. Fluorine is reported to be sometimes added to wines. Carles (6) also found 120 parts per million of fluorine in oyster shells. This is about ten times the content of sea water in this element. He found fluorine in the shells of all the molluscs examined.

Carnot (7) found fluorine in fresh human, ox, manati, and elephant bones in amounts ranging from 1,000 to 3,000 parts per million. In fossil bones he found from 4,000 to 19,000 parts per million. In the teeth of elephants and mastodons of the Pliocene and Miocene ages respectively he found 25,000 to 30,000 parts per million. All the fossil bones contained much more fluorine than modern bones.

Wrampelmeyer (8) found 13,600 parts per million in the sound teeth of an adult, and 6,500 parts per million in the sound teeth of a child as compared with 11,400 parts per million in carious adult teeth, and 15,500 parts per million in the diseased teeth of a child.

Harms (9) asserts that the results of Carnot, Wilson, and Gabriel are too high. He described a method by means of which 0.43 mg. of fluorine could be determined and reports the following values for bones: calf, 50; ox, 50; swine, 180; rabbit, 220 parts per million respectively. In teeth he found the following amounts: calf, 50; swine, 180; dog, 90; man, 60 parts per million respectively.

Jodlbauer (10) criticized the analytical technique of Harms and asserts that his results are too low. He found 1,500 and 1,800 parts per million of fluorine in the bones of a child. In a later paper he confirms the results of Carnot and Wilson. He found bones to contain 500 to 3,200 parts per million of fluorine. The bones of new-born animals contained 1,500 to 1,600 parts per million of this element. Human incisors contained 2,600 to 3,200 parts per million. Molars contained 3,300 to 3,500 parts per million. Tooth germs in dogs contained 4,800 parts per million.

Gautier and Clausmann (11) found the fluorine content of human bones to vary from 150 to 560 parts per million. Animal bones contained similar amounts, but the content was greater in old than in young individuals. The dentine of a dog contained 615 parts per million.

Sonntag (12) examined the bones and teeth of normal dogs and of dogs fed sodium fluoride. He found not over 300 parts per million of fluorine in the bones and teeth of normally fed animals. In animals fed sodium fluoride he found 17,300 parts per million in dried bones and 12,900 parts per million in dried teeth.

Gautier (13) found that in artificial media of known fluorine content the addition of fluorine in most cases favored the growth, flowering, and seed production of plants, especially of Sinapis. Its influence was doubtful in rye, wheat, or oats, and in rare cases it was found to be harmful.

Brandl and Tappeiner (14) fed a dog weighing 12.75 kilos varying amounts (0.1 to 1.0 gm.) of sodium fluoride during 647 days. During this time 402.9 gm. of this salt were fed. He found 330.5 gm. in the urine and 72.6 gm. in the feces. No special effects were visible in the dog except a
556 Effect of Fluorine Additions on Teeth

stiffness of the back. The dog was anesthetized and the principal tissues were analyzed. He found the following amounts in different tissues.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>NaF in 100 parts of dry substance</th>
<th>Weight of fresh organ</th>
<th>NaF content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>0.12 per cent</td>
<td>750 gm.</td>
<td>0.14 gm.</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.18 per cent</td>
<td>5,710 gm.</td>
<td>1.84 gm.</td>
</tr>
<tr>
<td>Liver</td>
<td>0.59 per cent</td>
<td>360 gm.</td>
<td>0.51 gm.</td>
</tr>
<tr>
<td>Skin</td>
<td>0.33 per cent</td>
<td>1,450 gm.</td>
<td>1.98 gm.</td>
</tr>
<tr>
<td>Skeleton</td>
<td>5.19 per cent</td>
<td>2,039 gm.</td>
<td>59.94 gm.</td>
</tr>
<tr>
<td>Teeth</td>
<td>1.00 per cent</td>
<td>25 gm.</td>
<td>0.23 gm.</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>64.64 gm.</td>
</tr>
</tbody>
</table>

Pitotti (15) stated that rabbits and guinea pigs endure neutral solutions of sodium fluoride in "considerable amounts" given by mouth for considerable periods. They became accustomed to it so that a partial immunity was established in that they tolerated doses which would have been toxic to animals unaccustomed to the substance. The kidneys are said to have remained sound. In acute poisoning with sodium fluoride there was degeneration of the epithelium of the kidneys in the region of the convoluted tubules and the loops of Henle. The liver suffered from fatty degeneration and cloudy swelling. The nervous system was greatly affected clinically, but there was no histological alteration. The general nutrition became poor and the number of red blood corpuscles was decreased.

Blaiot (16) found that rabbits tolerated undamaged the injection of a 2 per cent solution of sodium fluoride intravenously up to doses of 0.050 gm. per kilo. Doses exceeding 0.08 gm. per kilo caused symptoms of poisoning. After a 0.1 gm. dose there resulted dyspnea, salivation, polyuria, thirst, diarrhea, and fever. 10 to 15 minutes after the injection coma developed which resulted in death.

Sollmann, Schettler, and Wetzel (17) have recently studied the tolerance of albino rats for sodium fluoride. They fed daily doses of 15 to 150 mg. per kilo of body weight. These amounts resulted in progressive impairment of growth and lessened food consumption. The damage was proportional to the dose, and tended to outlast the administration, since the growth of the animals poisoned with sodium fluoride remained permanently below that of normal animals.

EXPERIMENTAL PROCEDURE.

It is evident from these studies that fluorine is found in nearly all food materials and accumulates in the body tissues. The
high content of fluorine in the teeth suggests that it is one of the structural elements of the enamel and perhaps of dentine. We have carried out experiments to see whether, using certain diets with which we had had much experience, the addition of amounts of fluorine comparable to what might be expected to occur in natural foods would favorably influence the teeth in rats. We tried the inclusion of 226 parts per million of this element in the form of sodium fluoride. We report at this time only the results of feeding a diet which produces good teeth, and of feeding the same diet with fluorine addition. The results showed, contrary to our expectations, that the ingestion of fluorine, in amounts but little above those which have been reported to occur in natural foods, markedly disturbs the structure of the teeth.

The diet of Lot 3619 consisted of: wheat, 67.5; casein, 15.0; whole milk powder, 10.0; NaCl, 1.0, CaCO₃, 1.5; and butter fat, 5.0 per cent respectively. The diet of Lot 3623, containing fluorine, had the same composition, except that sodium fluoride was included to the extent of 226 parts per million. For this purpose 0.1 per cent of a mixture of equal parts of dextrin and sodium fluoride replaced an equivalent amount of wheat.

Those rats fed Diet 3619 had excellent teeth. The ages of the animals, when killed, together with other significant data regarding them, are given in the following table.

<table>
<thead>
<tr>
<th>Lot No.</th>
<th>No. of animals and sex</th>
<th>Age at death</th>
<th>On diet</th>
<th>Added fluorine</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>3619</td>
<td>5♀</td>
<td>389</td>
<td>350</td>
<td>0</td>
<td>Animals in good condition.</td>
</tr>
<tr>
<td></td>
<td>5♀</td>
<td>392</td>
<td>362</td>
<td>0</td>
<td>&quot; &quot; &quot; &quot; &quot;</td>
</tr>
<tr>
<td></td>
<td>5♀</td>
<td>473</td>
<td>443</td>
<td>0</td>
<td>Coats somewhat rough.</td>
</tr>
<tr>
<td>3623</td>
<td>△</td>
<td>268</td>
<td>238</td>
<td>+</td>
<td>Overgrown incisors.</td>
</tr>
<tr>
<td></td>
<td>△</td>
<td>107</td>
<td>77</td>
<td>+</td>
<td>&quot; &quot; &quot; &quot; &quot;</td>
</tr>
<tr>
<td></td>
<td>△</td>
<td>290</td>
<td>260</td>
<td>+</td>
<td>&quot; &quot; &quot; &quot; &quot;</td>
</tr>
<tr>
<td></td>
<td>△</td>
<td>127</td>
<td>97</td>
<td>+</td>
<td>&quot; &quot; &quot;</td>
</tr>
<tr>
<td></td>
<td>△</td>
<td>310</td>
<td>280</td>
<td>+</td>
<td>&quot; &quot; &quot;</td>
</tr>
<tr>
<td></td>
<td>△</td>
<td>368</td>
<td>338</td>
<td>+</td>
<td>&quot; &quot; &quot;</td>
</tr>
<tr>
<td>2♂</td>
<td>231</td>
<td>201</td>
<td>+</td>
<td>&quot; &quot; &quot; &quot; &quot;</td>
<td></td>
</tr>
<tr>
<td>2♀</td>
<td>231</td>
<td>201</td>
<td>+</td>
<td>&quot; &quot; &quot; &quot; &quot;</td>
<td></td>
</tr>
<tr>
<td>2♂</td>
<td>209</td>
<td>179</td>
<td>+</td>
<td>&quot; &quot; &quot; &quot; &quot;</td>
<td></td>
</tr>
<tr>
<td>3♀</td>
<td>191</td>
<td>161</td>
<td>+</td>
<td>&quot; &quot; &quot; &quot; &quot;</td>
<td></td>
</tr>
<tr>
<td>△</td>
<td>191</td>
<td>161</td>
<td>+</td>
<td>&quot; &quot; &quot;</td>
<td></td>
</tr>
</tbody>
</table>

Second generation animals.
Effect of Fluorine Additions on Teeth

There was no evidence when the young were taken from the mother that the incisors were faulty. In a few instances, mottled areas were seen, but this has also been occasionally seen in animals where no fluorine has been added to the diet. The females were all fertile and reared practically all their young. The males with which they were kept likewise had fluorine in their food. The animals fed the added fluorine were slightly stunted in that they never grew so large as the controls, and they were shorter and more stocky.

It was observed that the rats fed the diet of Lot 3623 developed incisors which were abnormal in color, the orange tint seen on the anterior surface of the incisors of normal rats being nearly absent. These teeth were also observed to grow into abnormal positions, the upper ones tending in nearly every case to grow backwards into a circle, finally penetrating the roof of the mouth because they were not worn down by attrition. The abnormalities of the incisors were evidently due to changes in their structure and hardness, since the lower incisors tended to wear away too easily, and the upper ones occasionally broke off, leaving a blunt end. The teeth were of especial interest to us in connection with the development of a general plan of study of the relation of the diet to dentition (18). Accordingly, we submitted the skulls of certain animals typical of the collection made by us to Dr. R. W. Bunting, of the University of Michigan, for description. His report is as follows:

In a comparison of the skulls of the rats under the fluorine treatment with those on normal diets, it is apparent that certain marked changes in dental and osseous development have been produced by even this slight modification of the normal diet. From their general appearance the bones of the experimental animals do not seem to be as good in quality as in the normal animal. The skulls appear whiter and their surfaces are manifestly more porous and lack that characteristic luster of normal cortical bone. The rami of the mandibles are somewhat thinner and less prominent than those of the controls. In the maxillae the dental arches of the fluorine rats are fully 1 mm. narrower in the molar region than those of the normal rats (Figs. 1 and 2). In the mandible of one experimental rat there is an osteoporotic affection of the alveolar process about the third molar which caused that tooth to drop out of its socket (Fig. 3).

The most notable characteristic of the fluorine rats is a marked overgrowth of the maxillary incisors, and a corresponding shortening of the mandibular incisors which elongated in a curved fashion to form an arc equivalent to the greater part of the circumference of a circle.
Fig. 1. Normal rat.

Fig. 2. Rat fed sodium fluoride.
The mandibular incisors in one rat have been so severely eroded that the exposed portions of the teeth have been reduced to a level with the gum line. These teeth in the other rat were also excessively worn down, but not to the same extent as in the former. In the latter case the lower incisors were spread widely apart so that they did not come into normal incisal occlusion with their maxillary opponents.

From even a macroscopic examination of the incisor teeth of the experimental animals it is quite apparent that they are inferior in quality to those of the normal animals. They are of a dull, opaque white color and lack the natural polish of well formed tooth substance. In certain areas they are corrugated transversely, suggesting intermittent interferences with development. These departures from normal are more apparent in the mandibular incisors, being marked by a wide separation of the teeth and an extreme friability which causes these teeth to be seriously eroded by contact with the maxillary incisors.

At first sight it might be inferred that the great overgrowth of the maxillary incisors has been caused by some stimulative action of the fluorine on the activity of the tooth formative organ. This incisal overgrowth, however, may be accounted for in another way; namely, by the lack of the natural wear which the incisors of the rat under normal conditions exert on each other in occlusion. Donaldson estimates the normal growth of the incisors at 2.5 mm. per week, which amount the adult rat must wear down by incisal attrition to maintain his teeth at the normal length. If, for any reason this incisal reduction by wear does not take place, as when the
upper and lower incisors do not occlude, or when the function of mastication is impaired, the incisors undergo a marked overgrowth quite similar to that present in the fluorine rats. In the experimental animals the mandibular incisors either spread so as to be out of contact with maxillary incisors or, if they did come into occlusion, were promptly fractured so that the maxillary incisors did not have the requisite wear to maintain their normal length. Consequently, these teeth became elongated. (Compare Figs. 4 and 5.)

The manifest inferior quality of these teeth indicates a retrograde disturbance of tooth development rather than a stimulation to overactivity.

The molars of the experimental animals have no marked differences of development from those of the normal. They have prominent cusps and well sealed sulci; they show no evidences of caries; and they differ only in that their enamel surfaces are whiter and have slightly less luster than the normal.

From the results obtained in this experiment it appears that fluorine may play an important part in dental and osseous development and that...
the administration of that substance in excess of the normal requirement may have a retrograde rather than a stimulative effect on calcification.

Nutrition investigations have dealt in most instances with the effects of deprivation, complete or partial, of some indispensable nutrient. The cause of defective structure and of low resistance to external agencies, which result in injury to the teeth, has frequently been attributed to deficiency of one kind or another in the food supply. We have, in the present study, a clear demonstration that overingestion of an element which is regularly found in both food and tissues in small amounts may exert a detrimental effect when the amount ingested is increased to but little more than certain samples of foods are known to contain. This is a positive effect of significance in bone and tooth structure.

These results of feeding small amounts of fluorine are so striking that we have undertaken to make similar studies to determine whether small amounts of lead, arsenic, tin, zinc, copper, aluminum, and other elements which are likely to be ingested in traces or in larger amounts, may adversely affect the structure of the teeth.

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