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PIGMENT ALTERATIONS AND OTHER DISTURBANCES IN RAT INCISOR ENAMEL IN CHRONIC FLUOROSIS AND IN RECOVERY

by

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In an experiment *McCollum, Simmonds, Becker & Bunting* (1925) found that rats fed with 226 p. p. m. F in their diet developed incisors with a dull opaque white colour instead of the normal orange tint. Furthermore, they observed that the incisors in certain areas were corrugated transversely. *Bergara* (1927), incorporated 50, 20, and 5 mg sodium fluoride in the daily diet of milk and white bread and found that the rat incisors lost their pigment after one and a half month. A cross striation with alternating dark and white bands was found after 2 months and 4 months.

Later in the thirties extensive studies on rats with different concentrations of fluoride in the diet were performed. In all of these studies alterations were found in the normally orange-coloured incisors. Some authors describe the alterations as "a bleaching" and others as "a lightening" in colour. Table I lists expressions used for the alterations described in the period 1925—1962.

The most detailed description of pigment alterations in the incisors of the white rat during fluoride intoxication is given by *Smith* and co-workers, *Smith & Leverton* (1934), *Smith* (1936), and *Schour & Smith* (1942). On basis of their experience with increasing amounts of fluorides in the diet *Smith & Leverton* were

Table I. *Survey of different expressions used for the alterations in the incisor enamel of rats with chronic fluorosis.*

Author	Year	Dose of F^-	NaF in diet: D in water: W	Changes of rat incisor enamel
McCollum, Simmonds, Becker & Bunting	1925	226 p. p. m. F^- NaF	D	Dull opaque white colour, certain areas corrugated transversely
Bergara	1927	50—20—5 mg NaF daily 282—129—29 mg/kg F^- daily	D	La couleur jaune rougeatre tout a fait perdu après 1 ½ mois, taches obscures et blanches formant des arcs transversaux après 2 mois et 4 mois
McClure & Mitchell	1931	0.01—0.03—0.06 % F^- NaF	D	Dull white colour
Pachaly	1932	0.12 g/kg NaF daily 54 mg/kg F^- daily	D	Streifenförmige Entfärbung
Bethke, Kick & Hill	1933	0.0045—0.009—0.0226 % F^- NaF	D	Increasing reduction in amount of pigment — gross hypoplasia
DeEds & Thomas	1933—34	12 p. p. m. F^- NaF	D	Bleaching
Smith & Leverton	1934	7—14—28—56—112—226—450 p. p. m. F^- NaF	D	Banded appearance — white dull — corrosion and attrition
Dean, Sebrell, Breaux & Elvove	1934	50—75—100—150—300 p. p. m. NaF 23—34—45—68—135 p. p. m. F^-	W	Brown striations-loss of pigment and brittle
Sutro	1935	25—50—75 mg/kg NaF daily 11—22—34 mg/kg F^- daily	W	Striped enamel
Ellis & Maynard	1936—37	8—12—14 p. p. m. F^- NaF	D	Lightening
Roholm	1939	14 p. p. m. F^- NaF	D	Stribning
Evans & Phillips	1939	10—20 p. p. m. F^- NaF	D	Bleaching
Hofmann, Schuck & Furuta	1942	0.05 % NaF 226 p. p. m. F^-	D W	Cross striation — total absence of pigment
Pindborg	1950	0.125—0.025—0.05—0.1 % NaF 56—113—226—452 p. p. m. F^-	D W	Total depigmentation — cross striation
Hasselmann & Roholt	1962	2 mg NaF daily 0.9 mg F^- daily	Stomach tube	Banded appearance

Table II. *Grading of enamel alterations in relation to concentration of F^- as sodium fluoride. Smith & Leverton, 1933.*

F^- in diet	Findings in enamel	Grading
3.5 p. p. m.	No alterations	0
7 p. p. m.	Bleaching due to alternating fine, deep and light	1+?
14 p. p. m.	orange lines	1+
28 p. p. m.	Deep and light orange lines more distinct	2+
56 p. p. m.	Orange lines alternate with colourless lines	3+
112 p. p. m.	Surface dull white	4+
226 p. p. m.	Mild corrosion and pits of enamel	5+
450 p. p. m.	Severe corrosion, loss of enamel, teeth worn to gingival level	6+

Table III. *Condition of incisors of rats receiving 0.05 % sodium fluoride for 61 days in the 6 month experiment.*

Days after begin. exp.	Condition of lower incisors	Condition of upper incisors
18	Total loss of pigment in gingival part in 50 % of rats	No alterations
33	Total loss of pigment of entire surface of all incisors	Total loss of pigment of ca. 50 % of surfaces of all incisors
41	Same condition as above	Total loss of pigment of entire surface of all incisors, except for a few incisors with 1 mm pigment incisally. Slight corrosion of surfaces
56	Beginning cross striation	Surfaces white and incisors fractured (worn?)
70	Cross striation of nearly all incisors	Incisors are fractured (worn) to gingiva

able to grade the alterations in the incisor enamel. This gradation is given in Table II in relation to the concentration of F administered as sodium fluoride.

Table II shows that a cross striation with alternating deep orange and light orange lines must be considered a symptom of a mild fluoride intoxication, while a cross striation with alternating orange and colourless lines is a symptom of a more severe fluoride intoxication. A white dull surface with absence of pigment was found to indicate a still more advanced intoxication,

and if the concentration of fluoride in the diet was further increased, corrosion of the enamel and extreme attrition of the teeth occurred.

This analysis of the course of the pathologic changes in the enamel of rat incisors is inconsistent with those of *Bergara* (1927) and *Pindborg* (1950), who claimed that a cross striation was a symptom of a more severe fluorosis than was the total absence of pigment.

In the course of an experiment set up to study the recovery processes following fluoride intoxication (*Lindemann et al.*, 1959) some observations were made, which can explain why some authors interpret cross striation as a symptom of severe fluorosis while others interpret the cross striation as a symptom of mild fluorosis. The findings concerning the enamel alterations registered in the above mentioned recovery study will be dealt with below.

MATERIAL AND METHOD

Six month recovery experiment

Forty-eight 2—2½-month-old white rats of the Wistar strain were divided into three equal groups. All animals received the same stock diet composed of dry skim-milk powder, 35 %; rye meal, 35 %; wheat bran, 11 %; dry yeast, 8 %; arachis oil, 11 %; shark-liver oil, 3 000 I. U. vitamin A per kilogram. One third of the rats received 0.05 % sodium fluoride (226 p. p. m. F^-) added to the stock diet for 61 days and were then fed the stock diet without fluoride for periods varying between 14 and 175 days. The other third of the rats received 0.05 % sodium fluoride continuously and were sacrificed simultaneously with the rats of the first group. However, some of the rats in the group receiving sodium fluoride continuously became so ill that they had to be sacrificed before the scheduled time. The last third of the rats acted as controls receiving only the stock diet. The teeth of the living rats were examined 18, 33, 41, 56, and 70 days from the beginning of the experiment. Further examination took place after the rats were sacrificed.

One year recovery experiment

Twenty-eight 2-month-old rats received 0.05 % sodium fluoride in their diet for 58 days and were then fed the stock diet without

fluoride for periods varying between 91 and 384 days. Six rats were fed the stock diet throughout 58 + 384 days. Three experimental rats died before the end of the experiment and four became so ill that they were sacrificed before the scheduled time. With a few exceptions the teeth of the living rats were examined every fortnight following withdrawal of fluoride and were examined after sacrificing.

The rats in both experiments were individually caged and were weighed once a week. The diet and tap water were available *ad libitum*. In the six months recovery experiment the amount of food consumed was computed every day and the average daily amount of fluoride was calculated.

RESULTS

Six month recovery experiment

Ingestion of fluoride. The daily fluoride intake for the 61 day period was calculated at 2.83 mg F^- for female and 3.42 mg F for male rats.

Examination of incisors of living rats. The results of the examination of the incisors of the thirty-two living rats which received 0.05 % sodium fluoride for 61 days are given in Table III which shows that the last examination took place 70 days after the experiment began. The Table includes 16 rats which after 61 days on fluoride diet had been 9 days on a fluoride-free stock diet. These rats were included because there was no visible difference between the incisors at the final examination of the living rats after 70 days.

Total loss of pigment began first in the lower incisors, and 33 days after the experiment began, the lower incisors had no pigment left (Table III). Cross striation began to occur in the lower incisors 56 days after the beginning of the experiment, and 70 days after the beginning of the experiment cross striation was predominant. Typical cross striation is seen in Fig. 1.

In the upper incisors the loss of pigment began much later than in the lower incisors (Table III). A cross striation similar to that found in the lower incisors was not found, but irregular corrosion of the surface and fracturing of the upper incisors was a predominant trait.

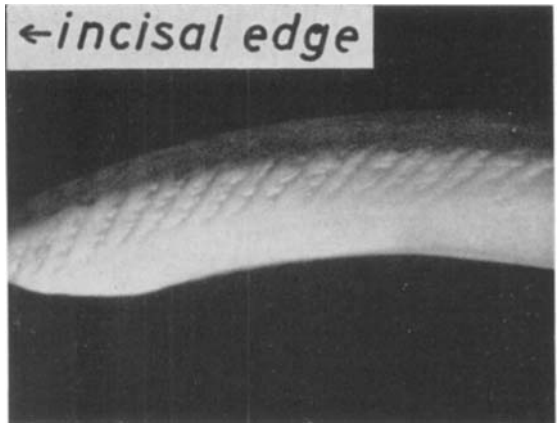

Fig. 1. Hypoplastic cross striation in a lower incisor of a rat receiving 0.05 % sodium fluoride for 117 days. Magnific. ×10.

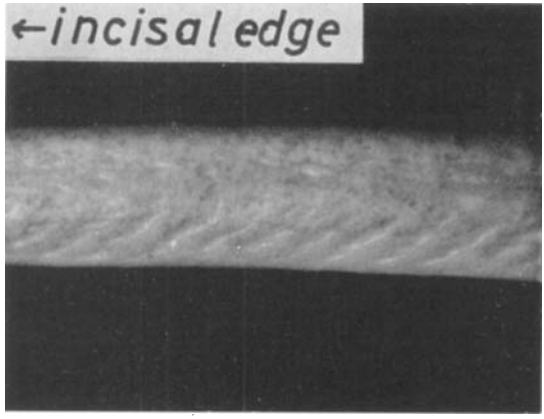

Fig. 2. Hypoplastic cross striation in a lower incisor of a rat receiving 0.05 % sodium fluoride for 89 days. The hypoplastic defects in the central part of the tooth surface are irregularly arranged. In the lateral part of the tooth surface the hypoplastic defects are regularly arranged. Magnific. ×10.

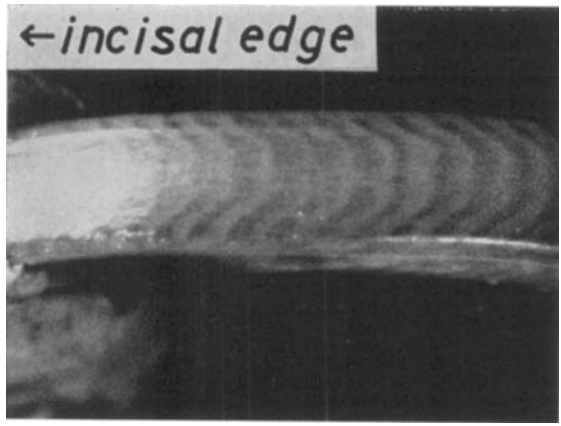

Fig. 3. Pigment cross striation in an upper incisor of a rat receiving 0.05 % sodium fluoride for 61 days followed by a recovery period of 112 days. Magnific. × 10.

Post-mortem examination of incisors

Continuous fluoride ingestion. The results of the examination are given in Table IV. The upper incisors of 10 rats were so excessively worn or fractured that further judgement was impossible. In 2 rats the attrition of the upper incisors was greater than normally seen in the upper incisors, and this was the case too in the lower incisors of 2 rats. The antagonists of incisors with attrition or fractures were elongated. Two rats had neither abnormal attrition nor elongation. Of 44 incisors available for examination, 31 had no pigment and 13 had traces of pigment. All surfaces of all incisors were rough due to hypoplastic defects. In the lower incisors these defects were arranged very regularly on the lateral enamel surfaces lending a cross striated appearance to the incisors. In the central parts of the surfaces the arrangement of the hypoplastic defects was irregular. In Figs. 1 and 2 the two types of arrangement of hypoplastic defects are illustrated. It should be noted that in the latter stages of intoxication the hypoplastic cross striation in the lower incisors tended to disappear, the surfaces now appearing rough and uneven without a special pattern of the hypoplasia. In the upper incisors no special arrangement of the hypoplastic defects was seen.

Table IV. *Condition of incisors of rats with continuous ingestion of fluoride in the 6 month experiment.*

Days of exp.	Surface condition of incisors				Abnormal attrition	Elongation
	Upper right	Upper left	Lower right	Lower left		
75 ♂	$	$	0 r c	0 r c	1+1	1—1
75 ♂	$	$	0 r c	0 r c	1+1	1—1
89 ♂	$	$	1 r c	0 r c	1+1	1—1
89 ♂	$	$	1 r c	1 r c	1+1	1—1
103 ♂	$	$	0 r c	0 r c	1+1	1—1
103 ♂	1 r	1 r	1 r c	1 r c	—	—
117 ♂	$	$	0 r c	0 r	1+1	1—1
117 ♂	$	$	1 r c	1 r c	1+1	1—1
126 ♂	$	$	0 r	0 r	1+1	1—1
131 ♂	$	$	1 r c	1 r c	1+1	1—1
131 ♂	1 r c	1 r c	0 r c	0 r c	1—1	1+1
167 ♂	0 r	0 r	0 r	0 r	1—1	1+1
168 ♂	0 r	0 r	0 r c	0 r c	1+1	1—1
173 ♂	$	$	0 r	0 r	1+1	1—1
201 ♂	0 r	0 r	0 r c	0 r c	—	—
224 ♂	0 r	0 r	0 r	0 r	1+1	1—1

0=no pigment
1=traces of pigment
2=nearly normal
3=normal
r=rough
c=cross striation
s=smoth
$=judgement impossible due to attrition
1+1 refers to both upper incisors, 1—1 to both lower incisors

Table V. *Condition of incisors of rats with 15 days to 6 months recovery period.*

Recovery period in days	Surface condition of incisors				Abnormal attrition	Elongation
	Upper right	Upper left	Lower right	Lower left		
14 ♀	$	$	0 s	0 s	1+1	1—1
14 ♀	$	$	0 r	0 r	1+1	1—1
28 ♀	$	$	0 r c	0 r c	1+1	1—1
28 ♀	0 r	0 r	0 r c	1 r c	—	—
42 ♀	2 r	2 r	2 s	1 r c	1—1	1+1
42 ♀	$	$	0 r	0 r	1+1	1—1
56 ♀	2 r c	2 r c	0 r c	2 s c	1—1	1+1
56 ♀	0 r c	0 r c	2 s c	2 s c	1—1	1+1
70 ♀	2 s c	2 s c	0 r	0 r	1+1	1—1
70 ♀	2 s c	2 s c	0 r (c)	0 r (c)	1—1	1+1
112 ♀	2 s c	—	2 s c	2 s c	+1 lost	—
112 ♀	2 s c	2 s c	0 r	0 r	1—1	1+1
140 ♀	2 s c	2 s c	2 s c	0 r	1—1	1+1
140 ♂	3 s	3 s	3 s	3 s (c)?	—	—
175 ♂	3 s	3 s	3 s	3 s	—	—
175 ♂	2 s c	2 s c	2 r c	3 s	1—1	1+1

0=no pigment
1=traces of pigment
2=nearly normal
3=normal
r=rough
c=cross striation
s=smooth
$=judgement impossible due to attrition
1+1 refers to both upper incisors, 1—1 to both lower incisors,
+1 refers to the upper left incisor

Recovery period. The results of the examination of the incisors are given in detail in Table V. Most of the upper incisors corresponding to 14, 28, and 42 days after withdrawal of fluoride were so excessively worn or fractured that further judgement was impossible. In addition, one rat had greater attrition than normal of the upper incisors and 7 rats had greater attrition than normal of the lower incisors. The antagonists of incisors with excessive attrition were elongated. In 4 rats there was neither exceptional attrition nor elongation.

The pigment of the enamel gradually reappeared as the time after withdrawal of fluoride increased. This is especially valid for the upper incisors; in the lower incisors the tendency was not so distinct, even though normal or nearly normal pigment conditions could be found.

The roughness of the surfaces disappeared as the time after withdrawal of fluoride increased. The upper incisors had perfectly smooth surfaces 70 days after withdrawal of fluoride while the lower incisors had a weaker tendency to acquire smooth surfaces.

Cross striation was found in the incisors of the majority of rats. The cross striation seen up to 56 days following withdrawal of fluoride was mostly found in connection with rough surfaces and was due to regular arrangement of hypoplastic defects. The cross striation was of the same type as shown in Fig. 1.

The cross striation observed after 56 days on stock diet and found in connection with smooth surfaces and the pigment status 2 (denoted 2 s c in Table V) was of a different type, Fig. 3. This latter cross striation was due to alternating deep orange and light orange bands over the whole surface.

One year recovery experiment

A summary of the findings concerning the surface condition of incisors is given in Table VI.

In one of two rats sacrificed 90 days after withdrawal of fluoride 2 upper incisors had smooth surfaces with pigment cross striation 64 days after withdrawal, but were found normal when the rats were sacrificed, though not all incisors in the two rats were normal at that time.

In two rats sacrificed 181 days after withdrawal of fluoride no

Table VI. *Condition of incisors of rats with 3 months to 1 year recovery period.*

Identific. no. and sex	Recovery period in days	Smooth surfaces and pigment cross striation of incisors in recovery period		All incisors normal (days)
		25 days	64 days	
247 ♀	90		2 upper	
252 ♂	90			
244 ♂	181			80
248 ♂	181			90
242 ♂	383			102
246 ♂	"	1 lower	2 upper	145
249 ♂	"		1 upper	145
254 ♂	"			145
256 ♂	"		2 upper	80
258 ♂	"			145
243 ♀	384		2 upper	145
260 ♂	"		2 upper	196
261 ♂	"		1 lower	145
262 ♂	"		2 upper	145
263 ♀	"		2 upper	384*
264 ♀	"		2 upper	301
265 ♀	"		2 upper	112
267 ♂	"		2 upper	217
268 ♂	"		2 upper	384**

* Lighter colour than normal
** One lower incisor elongated

pigment cross striation was found during the recovery period but all incisors were normal 80 and 90 days, respectively, after withdrawal of fluoride.

Among the 15 rats receiving the stock diet 383/384 days after withdrawal of fluoride, one rat had pigment cross striation in one lower incisor 25 days after withdrawal. Twenty-two incisors in 12 rats had smooth surfaces with pigment cross striation 64 days after withdrawal of fluoride and the remaining 25 incisors passed on to normal without being registered as cross striated. All incisors in 3 rats passed on to normal without visible cross striation.

The time elapsing from the cessation of fluoride feeding to when the incisors first were registered normal varied. The shortest period was 80 days, the longest 384 days. Among the 15 rats in the 383/384 day recovery period 7 had normal incisors 145 days after withdrawal of fluoride.

DISCUSSION

In the present experiments two types of cross striation in the enamel of rat incisors were found, (1) a hypoplastic cross stria-

tion that appeared later than the total loss of pigment and (2) a pigment cross striation that appeared in the recovery period some time before the enamel returned to normal pigment condition.

The finding of two types of cross striation explains why there has been controversial conceptions regarding the diagnostic significance of the cross striation.

The cross striation described by *Pindborg* (1950) and observed by him following the total loss of pigment is identical with the hypoplastic cross striation following total loss of pigment as observed in the intoxication period of the present six month experiment. The hypoplastic cross striation was probably also seen by *McCollum, Simmonds, Becker & Bunting* (1925) writing "incisors in certain areas were corrugated transversely".

The *pigment cross striation,* observed in the present recovery experiments some time before the incisors exhibited normal pigment condition, is identical with the cross striation described by *Smith & Leverton* (1933), *Smith & Schour* (1942) and *Roholm* (1939). The pigment cross striation described by the above mentioned workers was produced by low fluoride administration, that is 0.0007 % and 0.0014 % F^- as sodium fluoride in the diet. This corresponds to 0.1 mg and 0.2 mg F^- daily.

The fact that the pigment cross striation in the present experiments was observed from about 1—2 months up to six months after cessation of high fluoride administration suggests that small amounts of fluoride are released from the skeleton of the rats. This assumption is in accordance with the results of *Glock et al.* (1941) and *Savchuck & Armstrong* (1951). *Glock et al.* observed a decrease in the fluoride content in bones during a period of 14 weeks after withdrawal of 0.05 % sodium fluoride (226 p. p. m. F^-) in the diet. *Savchuck & Armstrong,* giving 20 p. p. m. F^- as sodium fluoride in the drinking water to rats for 20—40—60 days, found 150 days after terminating the fluoride regimen that the fluoride content of the incisor teeth was significantly higher in the experimental group than in the control group. They found that the fluoride elimination from the skeleton was no longer detectable at that time and interpreted the results as an intraskeletal turn-over of small amounts of fluoride.

The results of the present experiments compared with the results of all the above mentioned authors indicate that the pigment

cross striation is a symptom of a mild fluoride intoxication while the hypoplastic cross striation is a symptom of a severe fluoride intoxication.

This conclusion is not in accordance with the description of *Bergara* (1927) who gave 50, 20 and 5 mg sodium fluoride corresponding to 23, 9, and 2.3 mg F^- daily.

Bergara, however, did not calculate the actual amount of fluoride ingested in the different groups, nor did he correlate the course of the pathologic changes of the incisors to the amounts of fluoride. It is thus impossible to determine whether the loss of pigment was observed in the group receiving 50 mg sodium fluoride or in the groups receiving 20 or 5 mg sodium fluoride, as is also the case with the pigment cross striation. The present author is therefore of the opinion that no decisive importance can be attached to the description by *Bergara.*

The mechanism behind the pigment cross striation is obscure. *Hasselmann & Roholt* (1962) thought that the alternating white and orange bands observed when giving 0.9 mg F^- daily by stomach tube were due to the single administration of fluoride once in every twenty-four hours. This hypothesis is supported by the earlier findings of *Schour & Smith* (1942) giving single injections of fluoride. The fact that pigment cross striation can be produced by continuously feeding of small amounts of fluoride and the observation of pigment cross striation during the recovery period in the present experiments suggest that some other mechanism than that behind the single administration of fluoride must be present.

SUMMARY

The macroscopic pathologic changes in rat incisors during fluoride intoxication followed by recovery periods from 14 days up to one year are described. The fluoride was administered as 0.05 % sodium fluoride in the diet for 2 months.

Total loss of enamel pigment in the intoxication period was followed by a hypoplastic cross striation. During the recovery period a pigment cross striation in the enamel was observed some time before the return of normal pigment condition.

The experiments further showed that even though the intoxication was severe — 25 % of the rats did not survive in the one year

experiment — most of surviving rats exhibited macroscopically normal teeth in about 3—5 months.

RÉSUMÉ

ALTÉRATIONS PIGMENTAIRES ET AUTRES DANS L'ÉMAIL DE L'INCISIVE DU RAT PENDANT LA FLUOROSE CHRONIQUE ET PENDANT LA PÉRIODE DE RETOUR A LA NORMALE

L'auteur décrit les modifications macroscopiques pathologiques prenant place dans les incisives du rat pendant l'intoxication fluorée suivie de périodes de retour à la normale durant de 14 jours à un an. Le fluorure était administré pendant deux mois sous forme de fluorure de sodium à raison de 0,05 % dans l'alimentation.

La perte totale de pigment dans l'émail pendant la période d'intoxication a été suivie d'une striation transversale hypoplastique. Pendant la période de retour à la normale, une striation transversale pigmentaire dans l'émail a été observée quelques temps avant le retour à des conditions pigmentaires normales.

Les expériences ont de plus révélé que malgré la sévérité de l'intoxication — 25 % des rats n'ont pas survécu à l'expérience portant sur un an — la plupart des survivants présentaient des dents normales du point de vue macroscopique au bout de 3—5 mois environ.

ZUSAMMENFASSUNG

PIGMENTVERÄNDERUNGEN UND ANDERE STÖRUNGEN IN DEM SCHMELZ DER INCISIVEN VON RATTEN WÄHREND CHRONISCHER FLUORVERGIFTUNG UND EINER NACHFOLGENDEN HEILUNGSPERIODE

Die makroskopisch-pathologischen Veränderungen in den Incisiven von Ratten im Laufe einer Fluorvergiftung, die von einer Heilungsperiode von 14 Tage bis ein Jahr nachgefolgt wurde, werden beschrieben. Die Ratten wurden über 2 Monate mit 0,05 % NaF in der Kost gefüttert.

Während der Vergiftungsperiode wurde der totale Verlust des Schmelzpigmentes von einer hypoplastischen Querstreifung nachgefolgt.

In der Heilungsperiode wurden, bevor normale Pigmentverhältnisse wieder vorhanden waren, glatte Oberflächen mit Pigmentquerstreifung beobachtet.

Die Untersuchung zeigte übrigens, dass obwohl die Vergiftung schwer war — somit 25 % der Ratten die einjährige Observationsperiode nicht überlebten — die Mehrzahl der überlebenden Ratten im Laufe von 3—5 Monaten normale Pigmentverhältnisse in den Incisiven wiederhergestellt bekamen.

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